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Review

Post-Acute Sequelae of SARS-CoV2: A Narrative Review and Meta-Analysis of Individual Symptom Frequencies

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Abstract: Objective: To summarize the prevalence of PASC/Long COVID symptoms among the general population reported in published articles. This narrative review examined 21 PASC symptoms. Methods: A PubMed/manual search returned 114 articles on general PASC/Long COVID symptoms. Manuscripts were excluded if they were not research studies, didn't report symptom prevalence, or used a pediatric population. Ninety-eight studies were selected for review and 59 met criteria for inclusion. Risk of bias was assessed with the Hoy critical appraisal tool. Results: After excluding studies with high risk of bias, meta-analysis of prevalence for 21 symptom categories ranged from 2.6-28.7% in studies based on surveys to 0.3%-7.1% in studies based on EHR data. Conclusions: PASC symptom studies are limited by variability in study design and representation of the general population. Further research is needed to effectively cluster symptoms in meaningful ways that enable focused treatment.

Keywords: narrative review; long COVID; PASC

1. Introduction

1.1. Overview

It is now well-recognized that SARS-CoV-2 is associated with post-viral sequelae and these appear to be heterogeneous. The definition of post-acute sequela of SARS-CoV2 (PASC), or "Long COVID" by the lay public, is generally defined as new, recurrent, or continuous symptoms starting 3 to 4 weeks after SARS-CoV2 infection [1–4]. SARS-CoV2 has infected 671 million people world-wide as of February 2023 [5]. PASC has been reported in multiple studies from throughout the world, most of which have focused on individual symptom frequency; the primary goal of this narrative review is to summarize current literature on this topic focusing on reported prevalence of individual symptoms. Commonly reported symptoms are dyspnea, fatigue, pain, cognitive problems, and changes in or loss of smell or taste. It is likely that PASC is a heterogeneous set of syndromes, potentially with variable etiologies (e.g., initial organ injury from acute infection, viral persistence, immune dysregulation, autoimmunity, unrepaired tissue damage, dysbiosis of microbiome or virome) [6,7]. However, PASC could be a multi-system disease with a single underlying etiology. Moreover, it is possible that PASC has evolved over the course of the pandemic because of different viral strains, treatments, and vaccination rates.

1.2. Historical Perspective

Post-COVID sequela were first reported in small clinical follow-up studies published in mid to late 2020, soon after the initial wave of the COVID-19 pandemic, which were focused on post-hospital discharge cohorts. These publications were followed by outpatient studies that led to recognition that

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mild COVID cases could suffer from post-viral sequela. The Patient-Led Collaborative's high impact manuscript on more than 200 symptoms, many of which were exacerbated by physical or mental exertion or stress, produced a paradigm shift with widespread media attention. Their presentation to the US Congress ultimately lead to $1.3B in funding to study post-acute sequelae of SARS-CoV-2 The NIH-funded Researching COVID to Enhance Recovery (RECOVER) Adult Cohort (RECOVER-Adult), a longitudinal cohort study of adults with and without SARS-CoV-2 infection across 85 recruitment sites in the US, includes acute onset COVID cases with data collected during the first 5-28 days post-infection and symptom surveys every 3 months. A primary goal of this initiative is to provide prospective data on symptom frequency and patterns over time, as well as impacts on quality of life and overall physical health. RECOVER has reported PASC prevalence of 10% among acute infected participants based on symptoms reported 6 months after infection [8]. Further deep phenotyping and testing among individuals with prolonged symptoms will enhance discovery of PASC etiology(ies).

1.3. Goal of Current Review

The goal of this narrative review was to identify and synthesize the PASC symptoms most commonly reported by patients in published scientific articles and provide data to future studies to aid in better defining PASC phenotypes. The current review examined the 21 most prevalent individual PASC symptoms reported by more than one study in the included total of 59 studies.

2. Materials and Methods

2.1. Article Search Strategy

The article search was conducted on PubMed and manual review of recent systematic reviews. The specific MeSH terms and query used in the PubMed search was as follows: (Long COVID[MeSH Major Topic]) OR (PASC[MeSH Major Topic]) AND symptoms. The PubMed database was searched at least thrice monthly from October 2022 through February 2023. As of February 2023, the search returned 111 potentially eligible papers.

2.2. Eligibility Criteria

Peer-reviewed studies were considered eligible if they included at least 30 individuals with laboratory confirmed and/or clinically diagnosed COVID-19. We included studies that reported symptoms or outcomes assessed at 3 or more weeks post COVID-19 onset. Articles were excluded if they were systematic or narrative reviews, book chapters, editorials, responses, case studies, research design descriptions, or focused on institutional topics such as research management. The remaining full texts were assessed and excluded if they were meta-analyses, assessed symptoms at less than 3 weeks post-infection, addressed only acute COVID-19 symptoms, symptom outcomes were relative to a specific disease in addition to COVID-19, focused on experimental treatments, did not report prevalence data, contained no symptom data, used a pediatric sample, or in one case, a mixed adult/pediatric sample for which results were not reported separately (Figure 1). See (Table 1) for a complete overview of study characteristics. Three other eligible studies were identified through review of references of other scientific articles.

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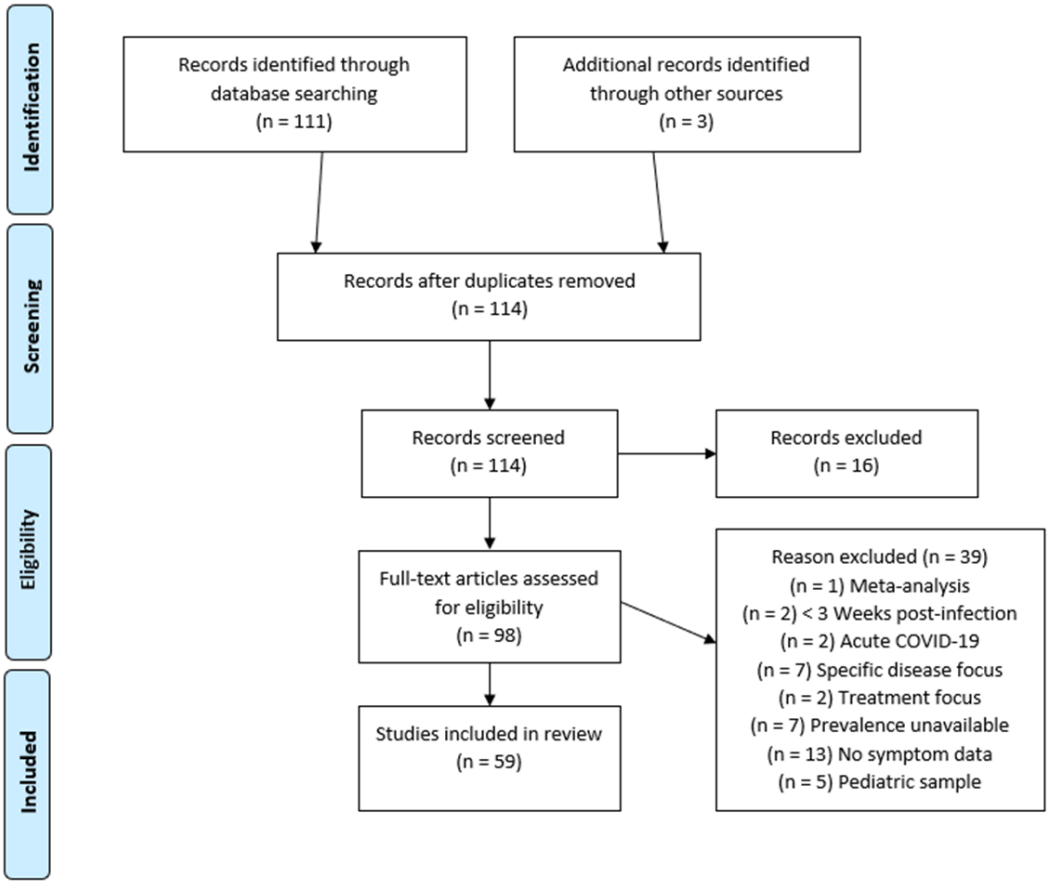

Figure 1. PRISMA Diagram.

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Table 1. Summary review table for PASC symptom studies.

Study	Publication date	Study population	Sample size/Location(s)	Top 25 symptoms (most to least common)	Time since infection or discharge (n=responders)	Exclusion criteria	Design	Case definition	Control	Matching
Anastascio et al.	Sept 2021	Patients at Eugenio Morelli Hospital (pulmonary function test, 6MWT, survey)	379 (Italy)	Dyspnea; weakness; joint or muscular pain; thoracic pain; anosmia or aguesia; depression; cough; heart palpitations; headache; sleeping disorders; hair loss; memory disorders; dizziness	4 mo. (n=379)	Previous pulmonary disease excluding ashma	Longitudinal cohort	Patients 18-80 with COVID-19 diagnosis	n/a	n/a
Arnold et al.	Dec 2020	Patients admitted with COVID-19 in Bristol (radiographs, pulmonary function testing, blood, survey)	163 (UK)	Breathlessness; fatigue; insomnia; myalgia; chest pain; cough; anosmia; arthralgia; fever; headache; abdominal pain; diarrhea; nausea	12 weeks since hospital admission (n=110)	n/a	Cohort	PCR positive or clinico-radiological diagnosis	n/a	Age-matched with population norms for survey
Baruch et al.	Nov 2022	PCR positive patients in Malta (survey)	2665 (Malta)	Shortnesss of breath; anxiety; sadness; fatigue; memory loss; cough	3-6 mo. range (n=2665)	Had COVID-19 more than once, did not have working email, asylum seekers/refugees, deceased	Cross-sectional	PCR positive in 2020, had COVID-19 only once	n/a	n/a
Becker et al.	Oct 2021	Patients hospitalized at two Swiss tertiary-care hospitals (phone interview and surveys)	126 (Switzerland)	Fatigue; concentration difficulties; shortness of breath; post-exertional malaise; joint pain; sleep disorder; dysosmia; muscle pain; anxiety; dysgeusia; chest pain/tightness; palpitations; depression; headache; paraesthesia; cough; loss of appetite/nausea; vomiting/diarrhea; skin disorders; PTSD symptoms; fever	30 (n=126) and 90 days (n=90)	Insufficient proficiency in local languages, cognitive impairment	Prospective cohort	Patients with COVID-19 admitted for inpatient care, discharged	n/a	n/a
Bellan et al.	Jan 2021	Patients at Azienda Ospedaliero-Universitaria Maggiore della Carita University Hospital (phone interview, pulmonary function and physical performance tests, psychological inventory)	COVID-19=238 (Italy)	Arthralgia; myalgia; dyspnea; ageusia; anosmia	4 mo. (n=238)	n/a	Cohort	Positive PCR or serotological test, clinical diagnosis	n/a	n/a
Blíddal et al.	June 2021	Patients in Danish Civil Registration System (online survey)	198 symptomatic (Denmark)	Fatigue; concentration or memory difficulties; shortness of breath; reduced sense of smell; headache; other; muscle and joint pain; taste loss; coughing; chest pain; sore throat; runny or stuffy nose; sneezing; diarrhea; lack of appetite; stomach pain; nausea; chills; colored sputum; fever; red runny eyes	4 weeks (n=198) and 12 weeks (n=129)	Symptoms started less than 12 weeks before survey	Cohort	Positive PCR, non-hospitalized, samples available in biobank	n/a	n/a
Blomberg et al.	Sept 2021	Patients diagnosed at testing facility in Bergen, patients hospitalized at Haukeland University Hospital or Haraldsplass Deaconess Hospital (clinic interview)	267 home-isolated patients (Norway)	Fatigue; disturbed taste/smell; concentration problems; memory problems; dyspnea; headache; dizziness; palpitations; stomach upset; cough; sleep problems; tingling in arms or fingers; fever	2 (n=267) and 6 months (n=247)	Address outside Bergen, admitted to hospital	Prospective cohort, longitudinal	Diagnosed and/or hospitalized with COVID-19	Patients' household members who were seronegative	n/a
Buttery et al.	Oct 2021	Respondents to UK national online post-COVID support survey, n=3290	3290 (UK)	Breathing problems; fatigue; joint stiffness; problems with mental abilities including anxiety and depression; sleep problems; mood changes/anxiety/depression; cough; loss of taste or smell; loss of appetite/weight loss; PTSD symptoms; nightmares or flashbacks; hair loss	4-8 weeks (n=494); 8-12 weeks (n=641); >12 weeks (n=1865)	Missing data, duplicates	Mixed-methods analysis	People who considered themselves to have long COVID	n/a	n/a
Carfì et al.	Jul 2020	Patients at Fondazione Policlinico Universitario Agostino Gemelli IRCCS (survey)	143 (Italy)	Fatigue; dyspnea; joint pain; chest pain; cough; anosmia; sicca syndrome; rhinitis; red eyes; dysguesia; headache; sputum production; lack of appetite; sore throat; vertigo; myalgia; diarrhea	Mean 60.3 days (n=143)	Refused participation, current positive test	Case series	Discharged from hospital after recovery from COVID-19, negative test at time of enrollment	n/a	n/a
Carvalho-Schneider et al.	Oct 2020	Patients at Centre Hospitalier Universitaire (EHR, phone call)	150 (France)	Other respiratory signs; flulike symptoms; anosmia/ageusia; fever; abnormal auscultation; dyspnoea/shortness of breath; diarrhea; chest pain	2 months (n=130)	Admitted to intensive care, deceased, resident of retirement/nursery home or long-term care facility, transferred to another facility, unable to answer phone questionnaire, lost to follow-up at Day 30	Case series	PCR positive	n/a	n/a
Chopra et al.	Apr 2021	Patients admitted to any of 38 hospitals in Michagin/MI-COVID 19 Initiative (EHR)	488 (USA)	Breathlessness walking up stairs; shortness of breath/chest tightness/wheezing; cough; continued loss of taste and/or smell; difficulty ambulating due to chest problems; new use of CPAP or other breathing machine while asleep; oxygen use	60 days post-discharge (n=488)	n/a	Cohort	Admitted with COVID-19, discharged, alive at 60 days	n/a	n/a
Cirulli et al.	Dec 2020	Participants in Healthy Nevada Project and Helix DNA Discovery Project (online survey); 21,359 respondents, COVID+ 357, COVID-5497, 19095 not tested	21,359 (USA)	Dry cough; difficulty breathing; anosmia; difficulty concentrating; ageusia; weak muscles; chest pain; pain deep breaths; tachycardia; heart palpitations; memory loss; confusion; headache; dizziness; notice heartbeat; acid reflux; back or joint pain; insomnia; fatigue; decreased alertness; tingling; diarrhea; tinnitus; nocturnal dyspnea; difficulty balancing; nausea	>30 days (n=357 COVID+)	Contradictory questionnaire entries, symptoms starting before 2020, diagnosis of COVID-19 despite negative test; symptoms less than 30 days	Prospective	Self-report COVID-19 positive	Self-report COVID-19 negative	n/a
Daitch et al.	Sept 2022	Multinational COVID positive patients (visit or survey)	2333 (Israel, Switzerland, Spain, Italy)	Fatigue; dyspnea; emotional distress; myalgia; memory impairment; concentration impairment; anosmia; chest pain; cough; arthralgia; headache; hair loss; palpitations	Mean 5 mo. (n=2333)	n/a	Prospective cohort	PCR positive at least 30 days before visit or interview	n/a	n/a
Daher	Oct 2020	Hospitalized patients (physical and laboratory tests, questionnaires)	33 (Germany)	Fatigue; tiredness; cough; dyspnea; angina pectoria; cognitive disorders; myalgia; headache; rhinorrhea; loss of smell; loss of taste; diarrhea; nausea; stomach pains; fever	6 weeks after discharge (n=33)	Nonsymptomatic, not hospitalized, ARDS patients who needed mechanical ventilation	Prospective	Hospitalized patients not requiring mechanical ventilation, positive PCR	n/a	n/a
Danesh et al.	Nov 2022	Patients seeking COVID-19 recovery care clinic (medical assessments)	441 (USA)	Dyspnea; brain fog; headache; anxiety; palpitations; impaired concentration; insomnia; memory loss; cough; anosmia; chest pain; depressed mood; ageusia; other neurological; dizziness; nausea; word finding difficulty; other otolaryngologic; diarrhea; other pulmonary; anorexia; confusion; paresthesia; congestion; other cardiovascular	Median 58 days (n=441)	n/a	Cohort	Laboratory-confirmed COVID 19	n/a	n/a

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Table 1. Summary review table for PASC symptom studies, Part 2.

Study	Publication date	Study population	Sample size/Location(s)	Top 25 symptoms (most to least common)	Time since infection or discharge (n=responders)	Exclusion criteria	Design	Case definition	Control	Matching
Darcis et al.	Aug 2021	Patients hospitalized at University Hospital of Liège (survey, biological data, pulmonary function tests, CT scans of chest)	199 (Belgium)	Exertional dyspnea; fatigue; dry cough; chest pain; memory impairment; productive cough; myalgia; rhinorrhea; headaches; loss of appetite; dyspnea at rest; anosmia; ageusia; parasthesia; diarrhea; pharyngeal pain; confusion	1 mo. (n=59), 3 mo. (n=101), and 6 months (n=78)	Died before follow-up	Prospective cohort	Confirmed COVID-19 infection, discharged between Mar-Oct 2020	n/a	n/a
Davis et al.	Jul 2021	COVID-19 support groups, social media (online survey)	3762 (Global/56 countries)	Fatigue; post exertional malaise; elevated temperature; shortness of breath; tightness in chest; muscle aches; palpitations; dry cough; tachycardia; breathing difficulty normal O level; sore throat; diarrhea; chills/flushing/sweats; joint pain; pain or burning in chest; loss of appetite; nausea; skin sensations; weakness; temperature lability; night sweats; stiff neck; abdominal pain; blurred vision; extreme thirst	>6 months (n=3762)	Incomplete survey, no onset date, onset before Dec 2019 or after May 2020, ≤ 28 days of symptoms	Cohort	Confirmed (diagnosed or antibody positive) or suspected COVID-19	n/a	n/a
Dryden et al.	Sep 2022	COVID patients discharged from hospital (phone interview with ISARIC questionnaire), random sample of 241,159 eligible, 8309 invited, 3094 contacted, 2410 enrolled	2410 (South Africa)	Fatigue; shortness of breath; confusion or lack of concentration; headache; problems seeing or blurred vision; joint pain; muscle aches; chest pain; dizziness or lightheadedness; dry cough; loss of taste; abdominal pain; loss of smell; back pain or backache; cough with sputum; diarrhea; skin rash; fever; nausea or vomiting; nasal congestion or sinusitis; bleeding; loss of appetite or anorexia; body pain or body ache; seizures	3 mo. (n=1873)	Self-report that they are fully recovered or neutral about being fully recovered	Prospective observational cohort	Hospitalized patients infected with COVID-19	n/a	n/a
Elkan et al.	Aug 2021	Patients hospitalized with COVID-19 (survey)	66 (Israel)	Fatigue; myalgia; dyspnea; decreased stamina; weakness; memory and concentration impairment; headaches; hair loss; sleep disturbance; anxiety or depression	Median 9 mo. (n=66)	Could not complete questionnaire due to physical or cognitive impairment	Retrospective cross-sectional case-control	Positive PCR test, discharged from hospital	Hospitalized pneumonia patients	Age and gender
FAIR Health White	June 2021	Patients in FAIR Health database (EHR)	1,959,982 (USA)	Pain; breathing difficulties; hyperlipidemia; malaise and fatigue; hypertension; anxiety; intestinal issues; skin issues; high levels of glucose/cholesterol/BP; abnormal heart results; migraine and/or headache; GERD; sleep disorders; depression; abnormal organ tests	≥ 30 days (n=1,959,982)	Cancer (breast, colorectal, enometrial, leukemia and lymphoma, lung, prostate), chronic kidney disease, COPD, cycstic fibrosis, viral hepatitis A/B/C/D or E, HIV/AIDS, liver disease, spina bifida and other congenital anomalies of the nervous system, stroke	Case series	Diagnosed with COVID-19	n/a	n/a
Frontera et al.	July 2021	US residents Prolific.co 148,000 US residents (online survey "Prevalence of Medical Conditions among Community Dwellers")	999 survey respondents (50 US states); COVID-19=76; Prolonged symptoms=19	Anxiety; brain fog; headache; post-exertional brain fog; fatigue; depression; chest pain; joint pain; muscle aches and pains; difficulty sleeping; vision abnormalities; shortness of breath; dizziness/lightheadedness; post-exertional malaise/fatigue; persistent loss taste/smell; wheezing; irregular heart beat; cough; fever	Median = 4 mo. (n=999)	n/a	Cross-sectional	Diagnosed with COVID-19 by laboratory test or developed typical symptoms after being exposed to COVID-19	n/a	n/a
García-Abellán et al.	July 2021	Patients hospitalized with COVID-19 (phone and clinic surveys, blood and nasopharyngeal samples)	146 (Spain)	Fatigue; myalgia; dyspnea; cough; nasal congestion	2 (n=104) and 6 months (n=116)	n/a	Prospective longitudinal	Positive PCR test	n/a	n/a
Garrigues et al.	Dec 2020	Hospitalized patients at Beaujon Hospital (phone survey)	120 (France)	Fatigue; dyspnoea; memory loss; sleep disorder; attention disorder; hair loss; cough; anosmia; chest pain; aguesia	>100 days since onset (n=120)	Deceased, unreachable, bedridden, demented, non-French speaking	Cross-sectional comparative	PCR positive or chest computed tomography diagnosis, hospitalized (ward group and ICU group)	n/a	n/a
Goërtz et al.	Aug 2020	Two Facebook groups for COVID-19 patients with persistent symptoms, website panel registrants (online survey)	2113 (Netherlands, Belgium)	Fatigue; dyspnoea; chest tightness; headache; muscle pain; pain between shoulder blades; heart palpitations; cough; increased resting HR; dizziness; sore throat; pain/burning feeling in lungs; increased body temp; joint pain; burning feeling in trachea; nose cold; mucus; anosmia; hot flushes; nausea; sneezing; eye problems; aguesia; diarrhea; ear pain	>3 weeks (n=2113)	Missing data, onset before 1 Jan 2020, symptoms for <3 weeks	Prospective observational	People who considered themselves to have long COVID	n/a	n/a
Halpin et al.	July 2020	Patients at Leeds Teaching Hospitals NHS Trust who were residents of Leeds Metropolitan District (phone survey)	100 (UK)	Fatigue; breathlessness; worse usual activites; worse mobility; PTSD symptoms related to illness; worse anxiety/depression; new or worse concentration problem; voice change; worse pain/discomfort; new or worse short-term memory problem; laryngeal sensitivity; worse self-care; new bladder control problem; swallowing problem; appetite problem; communication difficulty; new bowel control problem	Mean=48 days from discharge (n=100)	No contact details, under 18, dementia, learning disability, or other cognitive or communication impairment	Screening tool evaluation	Positive PCR test during inpatient hospital admission, 4 weeks or more since discharge date, not currently inpatient	n/a	n/a
Heesakkers et al.	Jan 2022	Multicetner ICU patients (questionnaires, online or paper)	301 (Netherlands)	Weakened condition; joint stiffness; joint pain; muscle weakness; myalgia; dyspnea; tingling or numbness in limbs; lung disease; neuropathic pain; voice problems; dizziness or balance problems; hypotension or hypertension; sexual problems; skin problems; hair loss; loss of smell; loss of taste; headache; heart disease/chest pain; vision problems; loss of hearing; bowel problems; urinary problems; wound pain; pressure ulcers	1 year (n=246)	ICU admission <12 hours, life expectancy <48 hours, receiving pallative care	Exploratory prospective	Admitted to ICU with laboratory or clinical diagnosis of COVID-19	n/a	n/a
Horberg et al.	Oct 2022	Patients at Kaiser Permanente Mid-Atlantic States (EHR)	PCR positive=28,118; PCR negative matched controls=70,293 (USA)	Abdominal pain; gastrointestinal disease; nonspecific chest pain; conditions associated with dizziness or vertigo; genitourinary symptoms and ill-definited conditions; malaise and fatigue; anxiety disorders; other lower respiratory disease; mental health; cardiac dysrhymias; diabetes; other nervous system disorders; nausea and vomiting; other nutritional/endocrine/and metabolic disorders; fluid and electrolyte disorders; anosmia; respiratory failure/insufficiency/arrest	Acute/Persistent: 0-30 days; Late: 30-120 days (n's unclear)	Patients not enrolled in KPMAS 120 days post-PCR test date	Case-control	PCR positive	PCR negative	3:1 negative to positive by age, sex, testing month, service area
Horwitz et al.	Aug 2021	Patients discharged from hospital (survey)	1 mo.=152; 6 mo.=126 (USA)	Fatigue; weakness; memory changes; muscle/body ache; brain fog; difficulty sleeping; joint pain; diarrhea; lightheadedness/dizziness; numbness/tingling; headache; dry mouth; burning or pins/needles sensation; chest pain; dry eyes; palpitations; altered/loss of smell; ringing in ears; altered/loss of taste; GI; tremors; rash; nausea; hair loss; vision changes	1 (n=152) and 6 mo. (n=126)	Incomplete surveys	Prospective cohort	Hospitalized for COVID-19 at single health system who required minimum 6 1 of supplemental oxygen during admission, intact baseline functional status, discharged	n/a	n/a

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Table 1. Summary review table for PASC symptom studies, Part 3.

Study	Publication date	Study population	Sample size/Location(s)	Top 25 symptoms (most to least common)	Time since infection or discharge (n=responders)	Exclusion criteria	Design	Case definition	Control	Matching
Huang et al.	Jan 2021	Patients discharged from Jin Yin-tan Hospital (surveys, physical exams, blood, pulmonary function test, chest CT, ultrasonography)	1733 (China)	Fatigue or muscle weakness; pain or discomfort; sleep difficulties; anxiety or depression; hair loss; smell disorder; palpitations; joint pain; decreased appetite; taste disorder; mobility problems; dizziness; diarrhea or vomiting; chest pain; sore throat or difficulty swallowing; skin rash; myalgia; headache; usual activity problems; personal care problems; low grade fever	Median 186 days (n=1655)	Psychosis, dementia, hospital re-admission, serious mobility issues, could not be contacted, nursing/welfare home residents, live outside Wuhan, deceased	Cohort	Laboratory diagnosis of COVID-19	n/a	n/a
Huang et al.	Nov 2022	University of California COVID Research Data Set (EHR)	1441 (USA)	Chest pain; dyspnea; anxiety; abdominal pain; cough; low back pain; fatigue; insomnia; diarrhea; joint pain; headache; nausea; tachycardia; muscle pain; alopecia; fever; heart palpitations; syncope; heartburn; dysgeusia; amnesia; skin lesions; tinnitus; sore throat or pain in throat; hypotension	0-30 days (n=1441) and 180+ days (n=227)	Hospitalized	Cohort	Patients with at least 5 year history with UC system, positive PCR test, healthcare interaction after diagnosis	n/a	n/a
Jacobson et al.	Feb 2021	Patients with COVID-19 (surveys, walk test)	118 (USA)	Fatigue; dyspnea; loss of taste/smell; myalgias; memory problems; chest pain; hair loss; cough; congestion/rhinorrhea; nausea/vomiting/diarrhea; headache; palpitations; sore throat; fever/chills	3-4 mo. (n=118)	n/a	Cohort	Positive PCR test	n/a	n/a
Kayaaslan et al.	Dec 2021	Patients with COVID-19 in Ankara City Hospital (questionnaire by phone or in clinic); 1092 invited	1007 (Turkey)	Fatigue; dyspnea; hair loss; concentration or memory deficit; myalgia; insomnia; chest pain; headache; cough; wheezing; hypersomnia; loss of weight; loss of smell; loss of taste; new anxiety; new depression; rash; nightmare; genitourinary issues; abdominal pain; constipation; diarrhea	>12 weeks (n=1007)	n/a	Prospective	Laboratory or imaging confirmation of COVID-19	n/a	n/a
Kuodi et al.	Aug 2022	Patients at Ziv Medical Centre, Padeh-Poriya Medical Centre, Galilee Medical Centre (online survey): of 79482 invitations to participate in the study, 3572 (4.5%) individuals > age 18 agreed to participate: 2447 who reported no previous SARS-CoV-2 infection and 1125 who did; excluded 174 infected individuals without vaccination status.	COVID-19=951; Control=2447 (Israel)	Fatigue; headache; weakness in arms or legs; persistent muscle pain; loss of concentration; hair loss; problem sleeping; dizziness; persistent cough; shortness of breath; loss of taste; chest pains; pins and needles sensation; palpitations; depression and anxiety; abdominal pain; problems with balance; inability to control body movement; joint pain or swelling; loss of smell; loss of appetite; pain on breathing; nausea and vomiting; constipation; erectile dysfunction	Not specified beyond "not fully recovered"	Not reporting vaccination status	Cross-sectional nested in Prospective Longitudinal Cohort Study	Self-reported previous COVID-19 infection	Self-reported no COVID-19 infection	n/a
Larsen et al.	Apr 2022	COVID support groups and social media (online survey)	Test-confirmed=1249; Test-unconfirmed=1065 (Global/34 countries)	Fatigue; Brain fog; headache; shortness of breath with exertion; body aches; palpitations; lightheadedness; tachycardia; difficulty sleeping; pre-syncope; loss of taste; loss of smell	Symptoms for >30 days, n=1249 test-confirmed and 1065 test-unconfirmed	Incomplete, symptom duration <30 days, onset before Nov 2019, age ≥65	Cross-sectional	Adults with self-suspected, clinician-diagnosed or test-confirmed COVID-19	n/a	n/a
LaVergne et al.	Jul 2021	Participants from community and hospital settings in Colorado (survey, saliva, blood, breast milk, stool)	119 (USA)	Fatigue; forgetful/absent minded; difficulty concentrating; exercise intolerance; difficulty sleeping; loss of smell; joint pain; confusion; difficulty breathing; loss of taste; change in taste; rapid heartrate; depression	25-89 days (n=56), 90-174 (days n=55), >175 days (n=42)	n/a	Case-control, longitudinal	PCR positive	PCR Negative	n/a
Liang et al.	Dec 2020	Hospitalized patients at Wuhan Union Hospital (questionnaires, laboratory tests, physical exams)	76 (China)	Chest tightness and palpitations; cough; fatigue; increased sputum; diarrhea; fever	3 mo. (n=76)	History of pulmonary resection, psychiatric or neurological disease	Prospective observational	PCR positive, discharged from hospital	n/a	n/a
Mandal et al.	Nov 2020	Patients discharged from three London hospitals (clinical assessment)	384 (UK)	Fatigue; breathlessness; cough; depression	Median 54 days (n=384)	Could not be reached, could not complete assessment	Cross-sectional	Tested positive for COVID-19	n/a	n/a
Mizrahi et al.	Nov 2022	Nationwide healthcare services members with a PCR test for COVID-19 (EHR)	COVID+=299,870; COVID-=299,870 (Israel)	Anosmia/dysgeusia; concentration/memory; weakness; dyspnea; convulsions; muscle atrophy; voice disorder; dizziness; sore throat; palpitations; arthralgia; myalgia; cough; chest pain; visual disturbances; bloody stool; tremor; headache; abdominal pain; rhinorrhea; menstruation abnormalities; skin rash; nausea/vomiting; insomnia; respiratory disorders	Single follow-up between 2nd-12th month after PCR test, n=299,870	Incomplete data, vaccinated >3 mo. before positive test, admitted to hospital with COVID 30 days after infection, patients with chronic outcomes that predated COVID infection (ever), patients with temporary outcomes that predated COVID infection (1 year)	Retrospective nationwide cohort	Positive PCR test in medical record	Negative PCR test/no previous positive PCR test	Age, sex, month of test, immune status (unvaccinated, partially vaccinated, second dose vaccine, booster)
Moreno-Perez et al.	Jan 2021	Patients at the Emergency Dept of Alicante General University Hospital (clinical exam, blood, chest x-ray, pulmonary function test, survey)	277; 141 with Post-COVID syndrome (Spain)	Fatigue; persistent dyspnea; anosmia/dysgeusia; persistent cough; myalgias/arthralgias; headache; mnesic complaints; diarrhea; skin features; visual loss; fever	77 days (follow-up n unclear)	"Severe comorbidity"	Prospective cohort	PCR or antibody positive	n/a	n/a
Munblit et al.	July 2021	Hospitalized patients at Sechenov University Hospital network (phone interview with ISARIC questionnaire)	PCR+=1358; Clinical COVID=1291 (Russia)	Chronic fatigue; respiratory; neurologic; mood and behavior changes; dermatologic	Median 218 days after discharge (PCR+ n= 1358, Clinical COVID+ n=1291)	Death, no contact info, survey not collected	Longitudinal cohort	Confirmed or suspected COVID-19	n/a	n/a
Naik et al.	Nov 2021	COVID patients discharged from hospital (phone or clinic questionnaire); 2243 invited, 1234 responded	1234 (India)	Myalgia; dyspnea; fatigue; cough; insomnia; chest pain; anxiety; mood disturbance/depression; anosmia	<1 mo. (140), 1-3 mo. (n=398), 3-6 mo. (n=264), >6 mo. (n=276)	Under 18	Longitudinal cohort	Laboratory-confirmed COVID 19	n/a	n/a
Peghin et al.	June 2021	Patients attending Infectious Disease Department (phone interview)	599 (Italy)	Fatigue; anosmia/dysgeusia; neurological disorders; rheumatological disorders; dyspnea; psychiatric disorders; hair loss; cutaneous lesions; URTI sympoms; headache; cough; GI disorders; chest pain; ocular symptoms	6 mo. (n=599)	Seronegative patients	Bidirectional prospective	Diagnosis of COVID-19	n/a	n/a

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Table 1. Summary review table for PASC symptom studies, Part 4.

Study	Publication date	Study population	Sample size/Location(s)	Top 25 symptoms (most to least common)	Time since infection or discharge (n=responders)	Exclusion criteria	Design	Case definition	Control	Matching
Petersen et al.	Nov 2020	Patients diagnosed with COVID-19 (questionnaire, phone interview)	180 (Faroe Islands)	Fatigue; loss of smell; loss of taste; arthralgia; rhinorrhea; dyspnea; myalgia; headache; cough with expectoration; chest tightness; chills; dry cough; nausea; diarrhea; rashes; anorexia; sore throat	≥2 mo. (n=179)	n/a	Longitudinal cohort	Positive PCR test	n/a	n/a
Reese et al.	May 2022	U.S. N3C patients (EHR)/RECOVER EHR PASC: cluster analysis	N3C N=12,443,936, COVID N=2,909292, U09.9 (Long COVID) N=5645, Included in analysis N=2464	Cough; pain; fatigue; hyperglycemia; chest pain; hypoxemia; fever; myalgia; headache; insomnia; hypocalcemia; lymphopenia; asthenia; nausea; abdominal pain; vertigo; nasal congestion; diarrhea; abnormal movement; elevated ASAT; elevated creatinine; elevated ALP; thrombocytopenia; hypotension; tachycardia	≥4 weeks (n=2464)	n/a	Retrospective observational	Patients with U09.9 (Long COVID) diagnosis	n/a	n/a
Roessler et al.	Nov 2022	Insured patients (Health insurance data); COVID patients matched 1:5 with non-COVID patients	145,184 adults; 11,950 children/adolescents (Germany)	Fever; dyspnea; cough; respiratory insufficiency; throat/chest pain; hair loss; malaise/fatigue/exhaustion; dysphagia; headache	Mean = 254 days (n=145,184)	COVID-19 diagnosis without PCR, patients not continuously insured	Retrospective matched cohort study	Documented COVID-19 diagnosis with PCR detection	No COVID-19 diagnosis	1:5 by index date, age, sex and propensity score matching on preexisting medical conditions
Romero-Duarte et al.	May 2021	Patients at four Spanish hospitals (primary care records)	797 (Spain)	Dyspnea; fatigue; cough; musculoskeletal pain; diarrhea; pharyngeal symptoms; anosmia or dysgeusia; fever; anxiety symptoms; thoracic pain; abdominal pain; headache; sleep disturbances; opthalmological problems; rib pain; depressive symptoms; general malaise; UTI; muscle weakness; paraesthesia; movement disturbances; ICU-related polyneuropathy; thromboic manifestations; exanthema; arrythmia or palpitations	6 mo. (n=797)	Negative PCR	Retrospective observational	Confirmed positive PCR	n/a	n/a
Sarrafzadegan et al.	Aug 2022	Previously hospitalized patients in Isfahan urban and rural areas (questionnaires)	819 (Iran)	Joint pain or myalgia; dry cough or dyspnea; hair loss; fatigue or muscle weakness; GI disorders; mental health problems; headache; palpitations; low grade fever; dizziness; ocular problems; chest pain; skin rash/pruritus; smell disorder; body tremor or tingling; renal disorders; decreased appetite; sore throat/difficulty swallowing/sputum productions; ear problems; taste disorders; sleep difficulties	1 year (n=819)	Patients hospitalized before 10 March 2020, no PCR test, negative PCR test	Multicenter prospective cohort	Positive PCR test	n/a	n/a
Sigfrid et al.	Aug 2021	Patients hospitalized with COVID-19 (questionnaire by mail, phone, or clinic)	327 (UK)	Fatigue; breathlessness; problems sleeping; headache; limb weakness; persistent muscle pain; joint pain or swelling; dizziness/lightheadedness; problems with balance; swollen ankle; palpitations; vision problems; constipation; stomach pain; diarrhea; cough; chest pains; pain on breathing; loss of smell; persistent fevers; loss of taste; nausea/vomiting; loss of appetite; problems swallowing; skin rash	≥3 mo. (n=327)	No positive PCR test recorded	Longitudinal cohort	Patients admitted to hospital with confirmed or highly suspected COVID-19	n/a	n/a
Søraas et al.	Aug 2021	Non-hospitalized patients (online surveys)	COVID+=794; COVID-=7229 (Norway)	Fatigue; changed smell or taste; headache; nasal symptoms; dyspnea; cough; body ache/muscular pain; sore throat; abdominal pain/nausea/diarrhea; fever	3-8 mo. (n=672)	Hospitalized	Longitudinal cohort	Laboratory-confirmed COVID 19	COVID 19 negative patients	n/a
Suárez-Robles et al.	Dec 2020	Patients discharged from hospital (phone survey)	134 (Spain)	Fatigue; dyspnea; loss of weight; loss of appetite; cough; anosmia; arthritis; headaches; palpitations; dysgeusia; general malaise; dysphonia; sensitivity disorders; sputum; walking disturbances; cutaneous manifestations	90 days (n=134)	n/a	Observational descriptive	Positive PCR test	n/a	n/a
Sudre et al.	Apr 2021	Participants using Zoe COVID Symptom Study App (survey)	4182 cases/4182 controls (UK)	Fatigue; headache; palpitations/tachycardia; memory issues; tinnitus/earache; peripheral neuropathy symptoms	≥ 28 days (n=558); ≥ 8 weeks (n=189); ≥ 12 weeks (n=95)	Admitted to ICU	Prospective observational cohort	Users of the COVID Symptom Study App	Symptomatic test-negative	Age, sex, BMI
Tabacof et al.	Jan 2022	Patients at Mount Sinai post-acute COVID-19 syndrome clinic (online survey)	156 (USA)	Fatigue; brain fog; headache; sleep disturbance; dizziness; dyspnea; memory loss; palpitations; confusion; general weakness; chest pain; neuropathic pain; muscle pain; temperature dysregulation; indigestion; mood alteration; sweating; joint pain; tinnitus; nausea; tachypnoea; vision impairment; bloating; sore throat; hair loss	Median=351 days (n=156)	Incomplete survey	Cohort	PCR or antibody positive or diagnosis by medical doctor for COVID-19, diagnosis of PACS (>12 weeks of symptoms since onset)	n/a	n/a
The Writing Committee	Apr 2021	Patients hospitalized in Bicêtre Hospital (telephone assessment)	COVID+=478 (France)	Fatigue; memory difficulties; dyspnea; persistent paresthesia; mental slowness; concentration problems; weight loss > baseline; chest discomfort/pain; anorexia; anosmia; headaches; cough	4 months after discharge (n=478)	Death, persistent hospitalization, end-stage cancer, dementia, nosocomial COVID-19 infection, incidental positive result during hospital stay for another condition	Cohort	Adults patients hospitalized for COVID-19 between March 1 and May 29, 2020	n/a	n/a
Tleyjeh et al.	Dec 2021	Patients discharged from King Fahad Medical City Hospital (phone interview)	222 (Saudi Arabia)	Shortness of breath; fatigue; cough; lasting muscle/body pain; difficult concentrating; headaches; joint pain; memory impairment; insomnia; loss of appetite; chest pain; abdominal pain; nausea/vomiting; constipation; diarrhea; loss of smell; sore throat; fever; loss of taste	Median 4 mo. (n=222)	Death, still hospitalized, mental illness, did not respond	Prospective cohort	Positive PCR test	n/a	n/a
Venturelli et al.	Jan 2021	Patients discharged from Papa Giovanni XXIII Hospital (clinical assessment, blood tests, chest x-ray, electrocardiogram, full pulmonary function testing, psychological evaluation, assessment of rehabilitation needs)	767 (Italy)	Asthenia; dyspnea; palpitations; myalgia; chest pain; confusion; cough; anosmia/dysguesia; lower GI problems; fever; headache; syncope; upper GI problems	Median 81 days (n=767)	Pregnant and admitted for delivery, under 18, asymptomatic	Cohort	Admitted to or discharged from hosptial with any condition possibly related to COVID-19, then a double negative nasopharyngeal swab	n/a	n/a
Wang et al.	Sep 2020	Hospitalized patients at Tongji Hospital (hospital records, follow-up with patients/method unspecified)	131 (China)	Cough; dyspnea; pharyngeal pain; nausea; chest tightness	Follow-up at 1-2, 3-4 weeks (all n=131)	Could not be contacted	Prospective cohort	Confirmed COVID-19 cases discharged from hospital	n/a	n/a

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Table 1. Summary review table for PASC symptom studies, Part 5.

Study	Publication date	Study population	Sample size/Location(s)	Top 25 symptoms (most to least common)	Time since infection or discharge (n=responders)	Exclusion criteria	Design	Case definition	Control	Matching
Wanga et al.	Sept 2021	US nationwide CDC sample of adults (online survey)	Self-reported positive test=698; negative test=2437(USA)	Fatigue/tired/weakness; change in smell or taste; shortness of breath or breathlessness; cough; headache; problems sleeping; joint or muscle pain; cognitive dysfunction; chest pain or pressure; change in mood; post-exertional malaise; stomach pain; hair loss; diarrhea; sore throat; fever or chills; palpitations; nausea/vomiting	>4 weeks (n=698)	n/a	Retrospective observational	Positive test result	n/a	n/a
Xiong et al.	Sept 2020	Hospitalized patients at Renmin Hospital of Wuhan University (phone survey)	COVID survivors=538; residents of local area not hospitalized=184 (China)	Alopecia; fatigue; sweating; postactivity polypnoea; somnipathy; chest distress; chest pain; resting heart rate increase; arthralgia; cough; anxiety; discontinuous flushing; nonmotor polypnoea; chills; myalgia; depression; throat pain; sputum; limb edema; dizziness; dysphoria; new hypertension; feelings of inferiority	>3 mo. (n=538 COVID survivors)	Pregnant or breastfeeding, severe underlying disease, receiving invasive treatment	Longitudinal cohort	Inpatients 20-80 years old who were diagnosed with COVID-19	Residents living in urban area at same time as outbreak	n/a
Zhao et al.	Aug 2020	Hospitalized patients at 3 tertiary hospitals in Henan Province (Physical and imaging tests)	55 (China)	GI symptoms; headache; fatigue; exertional dyspnea; decreased sense of taste; cough and sputum	3 mo. (n=55)	Critical pneumonia	Retrospective cohort	Confirmed PCR positive, discharged from hospital	n/a	n/a

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2.3. PASC Symptom Categories

Symptoms were categorized into 25 different phenotypic bins in an a priori fashion based on symptoms assessed in the NIH-funded Researching COVID to Enhance Recovery (RECOVER) Adult Cohort (www.recovercovid.org), grouped by CTCAE (Common Terminology Criteria for Adverse Events) for the symptoms [9]. Any symptom that fell into one of the following categories was added to the review table (Supplemental Figure A): General symptoms included fatigue, fever, chills, sweats or flushing, post-exertional malaise; cardiac symptoms included general cardiac symptoms such as tachycardia and chest pain; respiratory symptoms included cough, shortness of breath, sleep problems; neurologic symptoms included problems thinking or concentrating, dizziness, headache, nerve problems (tremor, shaking, abnormal movements, numbness, tingling, burning, can't move part of body, seizures), and loss of or changes in smell or taste; psychiatric symptoms include mental health concerns such as depression, and anxiety; musculoskeletal symptoms included joint or muscle pain, weakness in arms or legs; gastrointestinal (GI) symptoms included abdominal pain and/or feeling full or vomiting after eating, diarrhea, constipation weight loss, dry mouth; metabolic symptoms included excessive thirst; urinary problems included incontinence, trouble passing urine or emptying bladder); dermatologic symptoms included hair loss, skin rash, hair loss; ear symptoms included hearing problems; eye symptoms included vision problems. Two symptoms, swelling of the legs and changes in skin coloration, were not reported in the top 25 symptoms of the 59 reviewed papers and were thus left out of further analyses. Two additional symptoms, dry mouth and excessive thirst, were reported in only one study. Therefore, this review used an end total of 21 phenotypic categories.

2.4. PASC Symptom Reporting

The methods used to evaluate and measure PASC symptoms were heterogeneous across the 59 studies reviewed that reported individual symptoms as prevalence (n=59). To be exhaustive in our representation of symptom data, all methods with numerical values were included and like data were grouped when possible (Table 2).

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Table 2. PASC symptom reports for all studies.

Author/Year	Population/Methods/Sample summary	Fatigue	Fever, chills, sweats or flushing†	Dizziness	Post-exertional malaise	Sleep problems	Weakness in arms or legs	Headache	Joint/muscle pain†	Loss of or change in smell or taste†	Shortness of breath	Persistant cough †	Cardiac symptoms including chest pain†	GI symptoms including abdominal pain†	Urinary symptoms	Mental health concerns†	Nerve problems, seizures†	Problems thinking or concentrating	Skin rash	Hair loss	Vision problems	Hearing problems	Dry mouth	Excessive thirst
Anastacio et al. 2021	Previously hospitalized and non-hospitalized patients (pulmonary function test, 6MWT, survey), n=379	n/a	n/a	2.4%	n/a	4.2%	n/a	5.3%	13.7%	10.3%	42.7%	6.1%	6.1%	n/a	n/a	8.2%	n/a	n/a	n/a	3.2%	n/a	n/a	n/a	n/a
Arnold et al. 2020*	Previously hospitalized patients (radiographs, pulmonary function testing, blood, survey), n=163	39.0%	2.0%	n/a	n/a	26.0%	n/a	2.0%	5.0%	11.0%	39.0%	11.0%	12.0%	2.0%	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Baruch et al. 2022	Previously hospitalized and non-hospitalized patients (survey), n=2665	9.7%	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	14.2%	5.3%	n/a	n/a	n/a	11.0%	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Becker et al. 2021	Previously hospitalized patients (phone interview and surveys), n=90	46.0%	2.0%	n/a	20.0%	17.0%	n/a	9.0%	18.0%	16.0%	21.0%	7.0%	12.0%	6.0%	n/a	13.0%	8.0%	31.0%	n/a	n/a	n/a	n/a	n/a	n/a
Bellan et al. 2021	Previously hospitalized patients (phone interview, pulmonary function and physical performance tests, psychological inventory), n=238	n/a	n/a	n/a	n/a	n/a	n/a	n/a	5.9%	5.0%	5.5%	2.5%	0.4%	1.3%	n/a	n/a	5.9%	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Blíddal et al. 2021*	Non-hospitalized patients in Danish Civil Registration System (online survey), n=198	16.0%	1.0%	n/a	n/a	n/a	n/a	6.5%	5.5%	7.5%	12.0%	4.5%	n/a	2.3%	n/a	n/a	n/a	13.0%	n/a	n/a	n/a	n/a	n/a	n/a
Blomberg et al. 2021	Home isolated or hospitalized patients (clinic interview), n=247	30.0%	2.0%	10.0%	n/a	5.0%	n/a	11.0%	n/a	27.0%	15.0%	6.0%	6.0%	6.0%	n/a	n/a	4.0%	19.0%	n/a	n/a	n/a	n/a	n/a	n/a
Buttery et al. 2021	Respondents to UK national online post-COVID support survey, n=3290 enrolled, n=1865 at 12 weeks.	84.1%	n/a	n/a	n/a	47.6%	n/a	n/a	52.8%	26.2%	91.5%	40.3%	n/a	n/a	n/a	45.1%	n/a	50.9%	n/a	13.3%	n/a	n/a	n/a	n/a
Carfì et al. 2020*	Previously hospitalized patients (survey), n=143	55.0%	n/a	n/a	n/a	n/a	n/a	9.0%	n/a	15.0%	42.0%	17.0%	21.0%	2.0%	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Carvalho-Schneider et al. 2020	Previously hospitalized and non-hospitalized patients (EHR, phone call), n=150 enrolled, n=130 at 2 months	n/a	0.0%	n/a	n/a	n/a	n/a	n/a	16.3%	22.7%	7.7%	n/a	13.1%	11.5%	n/a	n/a	n/a	n/a	11.5%	n/a	n/a	n/a	n/a	n/a
Chopra et al. 2021	Previously hospitalized patients/MI-COVID 19 Initiative (EHR), n=488	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	13.1%	16.6%	15.4%	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Cirulli et al. 2020*	Participants in Healthy Nevada Project and Helix DNA Discovery Project (online survey); 21,359 respondents, COVID+ 357, COVID-5497, 19095 not tested, n=21359	4.0%	n/a	5.0%	n/a	4.0%	n/a	5.0%	5.0%	10.0%	n/a	10.0%	6.0%	4.0%	n/a	n/a	4.0%	8.0%	n/a	n/a	n/a	3.0%	n/a	n/a
Daitch et al. 2022	Patients at COVID-19 recovery clinics (visit or survey), n=2333	39.0%	n/a	n/a	n/a	n/a	n/a	6.8%	n/a	15.5%	28.0%	11.4%	11.8%	n/a	n/a	n/a	n/a	19.1%	n/a	5.3%	n/a	n/a	n/a	n/a
Daher et al. 2020	Previously hospitalized patients (physical and laboratory tests, questionnaires), n=33	45.0%	3.0%	n/a	n/a	n/a	n/a	15.0%	15.0%	12.0%	33.0%	33.0%	n/a	9.0%	n/a	n/a	n/a	18.0%	n/a	n/a	n/a	n/a	n/a	n/a
Danesh et al. 2022	Patients seeking COVID-19 recovery care clinic (medical assessments), n=441	n/a	n/a	3.4%	n/a	15.6%	n/a	19.3%	n/a	14.1%	63.7%	26.9%	17.2%	5.9%	n/a	11.6%	2.3%	20.2%	n/a	n/a	2.0%	1.1%	n/a	n/a
Darcis et al. 2021	Previously hospitalized patients (survey, biological data, pulmonary function tests, CT scans of chest), n=199 enrolled, n=78 at 6 month follow-up	32.0%	n/a	n/a	n/a	n/a	n/a	1.0%	n/a	1.0%	1.0%	9.0%	5.0%	1.0%	n/a	n/a	1.0%	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Davis 2021	COVID-19 support groups, social media (online survey), n=3762	97.0%	56.0%	n/a	88.0%	n/a	n/a	n/a	70.0%	n/a	77.0%	66.0%	67.0%	60.0%	n/a	n/a	n/a	n/a	n/a	n/a	36.0%	n/a	n/a	36.0%
Dryden et al. 2022	Previously hospitalized patients (phone interview), 3 month follow-up, n=2410 surveyed, n=1873 responders at 3 months	50.3%	1.5%	6.2%	n/a	n/a	n/a	13.8%	9.3%	2.7%	23.4%	4.2%	7.0%	2.3%	n/a	n/a	n/a	17.5%	1.9%	n/a	10.1%	n/a	n/a	n/a
Elkan et al. 2021*	Previously hospitalized patients (survey), n=66	27.0%	n/a	n/a	n/a	8.0%	n/a	8.0%	n/a	n/a	11.0%	n/a	n/a	n/a	n/a	7.0%	n/a	n/a	n/a	8.0%	n/a	n/a	n/a	n/a
FAIR Health White 2021*	Previously hospitalized and non-hospitalized patients in FAIR Health database (EHR), n=1,959,982	2.9%	n/a	n/a	n/a	1.3%	n/a	1.6%	5.1%	n/a	n/a	n/a	n/a	2.2%	n/a	2.3%	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Frontera et al. 2021	US community research platform (online survey), n=999 respondents; COVID-19=76; Prolonged symptoms=19	42.0%	11.0%	26.0%	26.0%	32.0%	n/a	47.0%	37.0%	21.0%	26.0%	16.0%	37.0%	n/a	n/a	53.0%	n/a	47.0%	n/a	n/a	26.0%	n/a	n/a	n/a
García-Abellán et al. 2021	Previously hospitalized patients (phone and clinic surveys, blood and nasopharyngeal samples), n=146	10.3%	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	4.3%	4.3%	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Garrigues et al. 2020	Previously hospitalized patients (phone survey), n=120	55.0%	n/a	n/a	n/a	n/a	n/a	n/a	n/a	13.3%	41.7%	16.7%	10.8%	n/a	n/a	n/a	n/a	n/a	n/a	20.0%	n/a	n/a	n/a	n/a
Goërtz et al. 2020	Two Facebook groups for COVID-19 patients with persistent symptoms, website panel registrants (online survey), n=2113	87.0%	22.0%	27.0%	n/a	n/a	n/a	38.0%	66.7%	13.0%	71.0%	29.0%	32.0%	41.1%	n/a	n/a	n/a	n/a	n/a	n/a	25.7%	n/a	n/a	n/a
Halpin et al. 2020	Previously hospitalized patients (phone survey), n=100	64.0%	n/a	n/a	n/a	n/a	n/a	n/a	19.0%	n/a	50.0%	n/a	n/a	n/a	n/a	31.0%	n/a	22.0%	n/a	n/a	n/a	n/a	n/a	n/a
Heesakkers et al. 2022	Previously hospitalized patients (questionnaires, online or paper), n=301 surveyed, n=246 responders at 1 year	n/a	n/a	11.5%	n/a	n/a	n/a	5.3%	25.5%	6.9%	20.8%	n/a	5.3%	3.7%	3.3%	n/a	20.6%	n/a	n/a	7.0%	4.9%	4.1%	n/a	n/a

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Table 2. PASC symptom reports for all studies, Part 2.

Author/Year	Population/Methods/Sample summary	Fatigue	Fever, chills, sweats or flushing†	Dizziness	Post-exertional malaise	Sleep problems	Weakness in arms or legs	Headache	Joint/muscle pain†	Loss of or change in smell or taste†	Shortness of breath	Persistant cough †	Cardiac symptoms including chest pain†	GI symptoms including abdominal pain†	Urinary symptoms	Mental health concerns†	Nerve problems, seizures†	Problems thinking or concentrating	Skin rash	Hair loss	Vision problems	Hearing problems	Dry mouth	Excessive thirst
Horberg et al. 2022	Previously hospitalized and non-hospitalized patients (EHR), PCR positive=28,118; PCR negative matched controls=70,293	1.4%	n/a	1.7%	n/a	n/a	n/a	n/a	n/a	0.3%	1.1%	n/a	1.7%	1.8%	1.5%	1.1%	1.8%	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Horwitz et al. 2021	Previously hospitalized patients (survey), 1 mo. n=152, 6 mo. n =126	85.0%	n/a	29.0%	n/a	35.0%	n/a	26.0%	33.0%	15.0%	n/a	n/a	21.0%	33.0%	n/a	n/a	28.0%	37.0%	9.0%	7.0%	3.0%	12.0%	25.0%	n/a
Huang et al. 2021	Previously hospitalized patients (surveys, physical exams, blood, pulmonary function test, chest CT, ultrasonography), n=1733	63.0%	<1%	6.0%	n/a	26.0%	n/a	2.0%	9.0%	11.0%	n/a	n/a	9.0%	5.0%	n/a	23.0%	n/a	n/a	3.0%	22.0%	n/a	n/a	n/a	n/a
Huang et al. 2022*	Non-hospitalized patients (EHR), n=1407	9.0%	3.0%	n/a	n/a	7.0%	n/a	12.0%	4.0%	n/a	16.0%	7.0%	13.0%	12.0%	n/a	8.0%	1.0%	n/a	n/a	1.0%	1.0%	2.0%	n/a	n/a
Jacobson et al. 2021	Previously hospitalized and non-hospitalized patients (surveys, walk test), n=118	30.8%	0.9%	n/a	n/a	n/a	n/a	6.0%	n/a	21.4%	26.5%	8.5%	13.7%	6.8%	n/a	n/a	n/a	n/a	n/a	12.0%	n/a	n/a	n/a	n/a
Kayaaslan et al. 2021	Previously hospitalized and non-hospitalized patients (questionnaire by phone or in clinic); 1092 invited, n=1007	24.3%	n/a	n/a	n/a	n/a	n/a	5.7%	n/a	3.1%	20.5%	4.5%	5.8%	0.4%	0.8%	1.5%	n/a	16.2%	1.0%	16.5%	n/a	n/a	n/a	n/a
Kuodi et al. 2022	Previously hospitalized and non-hospitalized patients (online survey), COVID-19=951; Control=2447	21.9%	n/a	7.8%	n/a	8.9%	13.5%	20.0%	10.3%	6.6%	7.2%	7.4%	6.4%	6.0%	n/a	5.8%	6.3%	9.5%	n/a	9.3%	n/a	n/a	n/a	n/a
Larsen et al. 2022	COVID support groups and social media (online survey), Test-confirmed=1249; Test-unconfirmed=1065	89.4%	n/a	68.6%	n/a	65.4%	n/a	77.9%	n/a	61.3%	n/a	n/a	65.0%	n/a	n/a	n/a	n/a	81.3%	n/a	n/a	n/a	n/a	n/a	n/a
LaVergne et al. 2021*	Previously hospitalized and non-hospitalized patients (survey, saliva, blood, breast milk, stool), n=119	23.0%	n/a	n/a	n/a	18.0%	n/a	n/a	18.0%	17.0%	n/a	n/a	5.0%	n/a	n/a	18.0%	n/a	18.0%	n/a	n/a	n/a	n/a	n/a	n/a
Liang et al. 2020	Previously hospitalized patients (questionnaires, laboratory tests, physical exams), n=76	60.0%	20.0%	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	60.0%	62.0%	26.0%	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Mandal et al. 2020	Previously hospitalized patients (clinical assessment), n=384	69.0%	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	53.0%	34.0%	n/a	n/a	n/a	15.0%	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Mizrahi et al. 2022*	Non-hospitalized patients (EHR), n=299,870	n/a	n/a	0.9%	n/a	0.02%	2.5%	2.1%	0.9%	0.3%	2.0%	2.9%	2%	3.4%	n/a	0.5%	0.5%	0.3%	0.8%	0.7%	0.3%	0.4%	n/a	n/a
Moreno-Perez et al. 2021	Previously hospitalized and non-hospitalized patients (clinical exam, blood, chest x-ray, pulmonary function test, survey), n=277	34.8%	<1%	n/a	n/a	n/a	n/a	17.8%	n/a	21.4%	34.4%	21.3%	n/a	10.5%	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Munblit et al. 2021	Previously hospitalized patients (phone interview with ISARIC questionnaire), PCR+=1358; Clinical COVID=1291	21.2%	n/a	n/a	n/a	7.0%	n/a	n/a	n/a	n/a	14.5%	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	7.6%	7.1%	n/a	n/a
Naik et al. 2021	Previously hospitalized and non-hospitalized patients (phone or clinic questionnaire); n=1234	5.5%	n/a	n/a	n/a	n/a	n/a	n/a	n/a	0.2%	6.1%	2.1%	1.2%	n/a	n/a	0.6%	n/a	1.2%	n/a	n/a	n/a	n/a	n/a	n/a
Peghin et al. 2021	Previously hospitalized and non-hospitalized patients (phone interview), n=599 in study, n=596 in Table 3 frequency table	13.1%	n/a	n/a	n/a	n/a	n/a	2.7%	n/a	10.4%	6.0%	2.0%	0.8%	1.5%	n/a	n/a	n/a	n/a	n/a	3.7%	n/a	n/a	n/a	n/a
Petersen et al. 2020*	Non-hospitalized patients (questionnaire, phone interview), n=180	23.0%	4.0%	n/a	n/a	n/a	n/a	7.0%	n/a	23.0%	9.0%	5.0%	n/a	3.0%	n/a	n/a	n/a	n/a	2.0%	n/a	n/a	n/a	n/a	n/a
Reese et al. 2022	Previously hospitalized and non-hospitalized patients (EHR)/RECOVER PASC N3C N=12,443,936, COVID N=2,909292, U09.9 (Long COVID) N=5645, Included in analysis N=2464	30.9%	12.3%	3.7%	n/a	5.6%	n/a	8.3%	43.9%	n/a	28.0%	61.8%	3.1%	3.7%	n/a	n/a	1.3%	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Roessler et al. 2022	Previously hospitalized and non-hospitalized patients (Health insurance data); COVID patients matched 1:5 with non-COVID patients, 145,184 adults	4.3%	1.2%	n/a	n/a	n/a	n/a	4.1%	n/a	1.2%	4.4%	3.0%	3.5%	n/a	n/a	n/a	n/a	n/a	n/a	1.4%	n/a	n/a	n/a	n/a
Romero-Duarte et al. 2021	Previously hospitalized patients (EHR, phone), n=797	22.1%	7.0%	n/a	n/a	4.9%	n/a	5.3%	15.3%	7.2%	n/a	19.2%	3.1%	10.3%	n/a	6.8%	3.4%	n/a	3.1%	n/a	4.6%	n/a	n/a	n/a
Sarrafzadegan et al. 2022	Previously hospitalized patients (questionnaires), n=819	11.7%	3.7%	3.2%	n/a	0.2%	n/a	5.7%	19.7%	1.3%	18.7%	18.7%	5.1%	7.1%	n/a	n/a	1.3%	n/a	2.2%	14.7%	2.7%	1.1%	n/a	n/a
Sigfrid et al. 2021*	Previously hospitalized patients (questionnaire by mail, phone, or clinic), n=327	83.0%	15.0%	36.0%	n/a	42.0%	37.0%	38.0%	36.0%	16.0%	54.0%	17.0%	25.0%	20.0%	n/a	n/a	n/a	n/a	14.0%	n/a	20.0%	n/a	n/a	n/a
Søraas et al. 2021	Non-hospitalized patients (online surveys), COVID+=794, n=676 at 3 months; COVID-=7229	23.0%	3.0%	n/a	n/a	n/a	n/a	13.0%	8.0%	14.0%	10.0%	8.0%	n/a	6.0%	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Suárez-Robles et al. 2020	Previously hospitalized patients (phone survey), n=134	54.5%	n/a	n/a	n/a	n/a	n/a	24.6%	n/a	26.1%	40.3%	26.1%	21.6%	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Sudre et al. 2020	Participants using Zoe COVID Symptom Study App (survey): 4182 COVID cases, 4182 matched non-COVID controls	97.7%	n/a	n/a	n/a	n/a	n/a	91.2%	n/a	n/a	n/a	n/a	6.1%	n/a	n/a	n/a	2.0%	n/a	n/a	n/a	n/a	3.6%	n/a	n/a
Tabacof et al. 2022*	Patients at COVID-19 syndrome clinic (online survey), n=156	82.0%	29.0%	54.0%	n/a	59.0%	n/a	60.0%	33.0%	n/a	53.0%	n/a	44.0%	n/a	n/a	30.0%	n/a	67.0%	n/a	19.0%	25.0%	27.0%	n/a	n/a

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Table 2. PASC symptom reports for all studies, Part 3.

Author/Year	Population/Methods/Sample summary	Fatigue	Fever, chills, sweats or flushing†	Dizziness	Post-exertional malaise	Sleep problems	Weakness in arms or legs	Headache	Joint/muscle pain†	Loss of or change in smell or taste†	Shortness of breath	Persistant cough †	Cardiac symptoms including chest pain†	GI symptoms including abdominal pain†	Urinary symptoms	Mental health concerns†	Nerve problems, seizures†	Problems thinking or concentrating	Skin rash	Hair loss	Vision problems	Hearing problems	Dry mouth	Excessive thirst
The Writing Committee 2021	Previously hospitalized patients (telephone assessment), n=478	31.1%	n/a	n/a	n/a	n/a	n/a	5.5%	8.1%	6.0%	16.3%	5.0%	n/a	n/a	n/a	n/a	12.1%	10.0%	n/a	n/a	n/a	n/a	n/a	n/a
Tleyjeh et al. 2021*	Previously hospitalized patients (phone interview), n=222	30.0%	2.0%	n/a	n/a	5.0%	n/a	8.0%	8.0%	2.0%	40.0%	27.5%	4.0%	3.0%	n/a	n/a	n/a	8.0%	n/a	n/a	n/a	n/a	n/a	n/a
Venturelli et al. 2021	Previously hospitalized patients (clinical assessment, blood tests, chest x-ray, electrocardiogram, full pulmonary function testing, psychological evaluation, assessment of rehabilitation needs), n=767	n/a	0.5%	0.1%	n/a	n/a	n/a	0.5%	n/a	3.4%	22.6%	3.0%	3.9%	0.7%	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Wang et al. 2020	Previously hospitalized patients (hospital records, follow-up with patients/method unspecified), n=131	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	1.5%	9.2%	n/a	0.8%	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Wanga et al. 2021	Previously hospitalized and non-hospitalized (online survey), Self-reported positive test=698; negative test=2437	34.2%	7.5%	n/a	n/a	18.1%	n/a	20.9%	16.9%	26.2%	23.6%	22.0%	11.0%	8.0%	n/a	10.1%	n/a	15.5%	n/a	8.5%	n/a	n/a	n/a	n/a
Xiong et al. 2020	Previously hospitalized patients (phone survey), COVID survivors=538; residents of local area not hospitalized=184	28.3%	23.8%	2.6%	n/a	17.7%	n/a	n/a	n/a	n/a	n/a	7.1%	12.3%	n/a	n/a	6.5%	n/a	n/a	n/a	28.6%	n/a	n/a	n/a	n/a
Zhao et al. 2020	Previously hospitalized (Physical and imaging tests), n=55	16.4%	n/a	n/a	n/a	n/a	n/a	18.2%	n/a	4.0%	n/a	1.8%	n/a	30.9%	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a

* Indicates study values were visually estimated from graph or figure.

† Highest frequencies included for categories with multiple symptoms reported

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2.5. Risk of Bias Assessment

The included studies were assessed for risk of bias using the Hoy et al. [10] critical appraisal tool for prevalence studies. The critical appraisal checklist for studies reporting prevalence consists of nine topics: (a) target population representativeness (b) sample frame suitability, (c) sampling method appropriateness, (d) likelihood of non-response bias (e) direct data collection from subjects, (f) usage of valid methods for identification of the condition, (g) use of valid, reliable study instrument to measure parameter of interest (h) same mode of data collection for all subjects, and (i) adequate response rate. Each study was assessed across each of these areas, with results reported as Yes, No, or Unclear. Studies were assigned an overall score, reflecting the number of questions with a Yes response.

2.6. Statistical Methods

Sample sizes and populations in each paper are summarized in (Table 1). Frequencies were summarized across studies using random-effects meta-analyses. Where available, exact number of events and total number of respondents for each symptom was included in the meta-analyses For studies that only report proportions, number of events were estimated by multiplying number of respondents by proportion with event and rounding up. Studies were grouped in three ways, by type of study (EHR, survey, Long Covid), risk of bias (low, medium, high) and hospitalization of respondents (hospitalized only versus non-hospitalized and mixed). Comparisons of proportion within each symptom category were done using a fixed-effects model using the "metafor" package in R (Supplemental Figure B) [11]. All analyses were performed using R.

3. Results

3.1. Population Characteristics

The global population was surveyed thanks in part to authors' efforts to include COVID support groups and social media groups in an online survey across 34 countries [12]. Study populations were reported from around the world including the USA, UK, Italy, Malta, South Africa, Netherlands, Belgium, China, Turkey, Switzerland, Denmark, Norway, France, Israel, Spain, Germany, Belgium, Russia, India, Faroe Islands, Iran, and Saudi Arabia. Twenty-one of the studies included had a COVID-19 patient sample size >950, with the largest sample at nearly 2 million [13]. The most common reasons for patients to be excluded from analyses were incomplete follow-up data, cognitive or neuropsychiatric conditions that prevented participation, death, current COVID-19 infection, and chronic or severe illness unrelated to/predating the COVID infection (Table 1).

3.2. Study Designs and Case Definitions

Study designs varied in the reviewed papers and included cohort (prospective, retrospective, and longitudinal), COVID case-uninfected control, cross-sectional, case series, and diverse combinations thereof. Many studies required clinical diagnosis via laboratory confirmation of a past COVID-19 infection such as a positive PCR-test. However, we also included survey studies that relied on self-reports of COVID-19 infection. Control groups were not commonly present (n=8/59 or 14% of reviewed studies included controls) but usually identified patients as COVID negative via formal laboratory testing, although self-reports of negative infection status were sometime used for inclusion (Table 1).

3.3. Definitions of PASC

Definitions varied for PASC in terms of length of time necessary for symptoms to persist or emerge. The lower ends of post-infection follow-up times started at just over 3 weeks [14,15]. Remaining studies investigated symptoms from 30+ days onward, even up to 1 year after the initial COVID-19 infection, hospital admission, or hospital discharge (Table 1). Several studies also utilized

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multiple time points for comparison [15–27]. Definitions of symptom-based phenotypes were also diverse across studies. Most included symptom checklists without assessment of PASC symptom severity.

3.4. Most Common Symptoms Reported across 59 Studies

Due to the focus on utility in this review, article symptom lists were capped at 25 with priority given to the most common symptoms [8]. Of note, a handful of studies reported highly comprehensive lists of PASC symptoms at 39 [13], 58 [28], 68 [21], and 203 [29]. The general symptoms that patients experienced most often, and that were reported by at least two of the studies reviewed, were: respiratory problems such as shortness of breath, fatigue, pain of various kinds, cognitive problems such as brain fog, changes in or loss of smell or taste, weakness, mental health issues such as anxiety and depression, cardiac symptoms such as palpitations or chest pain, hair loss, fever/chills, sleep problems, gastrointestinal symptoms, and flu-like symptoms. Symptoms reported by patients but not repeatedly captured in the selected studies included hyperlipidemia, post-exertional malaise, worse performance at usual activities, neurological disorders and unintentional weight loss (Supplemental Figure C).

3.5. Data Collection Methods

Three studies utilized electronic health records (EHR) to create comprehensive data sets of COVID cases and uninfected controls [19,30,31]. Three used EHR data on COVID cases only [13,20,32]. Four studies conducted national or community surveys among self-reported COVID test positive cases and COVID test negative controls [18,33–35]. One study utilized a COVID Symptom Study app, for which 4,223,955 adults registered from the UK (88.2%), US (7.3%), and Sweden (4.5%); in this study, a small subset (<0.1%) reported prospective data on symptoms after 28 days [27]. Seven studies were limited to populations with reported Long COVID symptoms. Four studies conducted surveys using social media and online outreach to support groups for individuals with post-COVID symptoms [12,14,18,29]. Two studies surveyed patients visiting local clinics for Long COVID symptoms [28,36]. One study relied on EHR data and used the Long COVID ICD-10 code to identify the cohort [37].

Davis and colleagues from the Patient-Led Research Collaborative conducted an online survey that was distributed via COVID-19 support groups and social media to patients from 56 countries with symptoms lasting >28 days, and onset prior to June 2020 [29]. They estimated the prevalence of 203 symptoms among 3762 respondents. The most common symptoms were fatigue, post-exertional malaise, and cognitive dysfunction, with 85.9% of participants experiencing relapses triggered by physical or mental activity, and stress. Buttery et. al. studied survey responses from a UK online post-COVID-19 support and information hub, completed ≥4 weeks after onset of symptoms [18]. Goertz et al. studied 21,113 members of Facebook groups for COVID patients with persistent symptoms in The Netherlands and Belgium [14]. Larsen et. al. studied an online survey of 2,314 adults with PASC recruited through long COVID support groups and social media channels between October 2020 and August 2021 for 53 symptoms including autonomic symptoms assessed with COMPASS-31 [12]. Tabacof et al. conducted a survey of 156 patients attending Mount Sinai's PASC clinic [36]. Danesh et al. conducted interviews of 441 patients from an integrated health system multispecialty telemedicine-based consultation service for post-COVID patients [28].

Multiple studies conducted post-discharge surveys by telephone or email with COVID infected inpatients who were recently hospitalized [15–17,21–26,36,38–67]. Five of these studies also included either follow-up surveys [22,56] or EHR data [19,31,37] from hospitalized and non-hospitalized COVID patients, while three studies focused only on non-hospitalized COVID patients using surveys [52,60] or EHR data [30]. For this review and meta-anaylsis, we limited the data extracted from manuscripts to PASC symptoms.

We classified study design into 3 categories: 1) "EHR" studies that included data on COVID cases and/or uninfected controls; 2) "Survey" studies of general population groups, COVID patients post-hospitalization/or post-outpatient infections; and 3) "Long COVID" survey studies of patients

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attending Long COVID clinics or that used social media and outreach to survey Long COVID support groups, or EHR data on COVID cases specifically using Long COVID ICD-10 codes.

The denominator for calculating frequency varied and was based on the specific population studied. For example, the population included for symptom frequency in Long COVID studies were limited to people with PASC symptoms, patients seen in long COVID clinics, or patients with Long COVID ICD-10 codes in EHR [12,14,18,29,36,37], whereas studies classified as "Survey" aimed to assess frequency among populations that included people with no PASC symptoms at all. For the 59 studies that reported prevalence, averaged PASC symptom frequencies for 21 of the phenotypic symptom categories are presented in (Figure 2), stratified into Long COVID, Survey, and EHR groups. Two symptoms, dry mouth and excessive thirst, were reported in one study each and were excluded from the meta-analyses; thus 21 symptoms were included in the final meta-analyses. Marked differences were observed in symptom prevalence across the three different study design groups (Long COVID (n=7), EHR (n=6), Survey (n=46), (Figure 2) where the highest frequencies were observed in studies that only included respondents with Long COVID symptoms [12,14,18,29], patients seen at Long COVID clinics [28,36], or with EHR Codes for Long COVID [37]. Across studies stratified by risk of bias (Figure 3), eleven categories were reported across all groups (fatigue, fever/sweats, dizziness, sleep problems, headache, joint/muscle pain, loss of or change in smell or taste, shortness of breath, persistent cough, cardiac symptoms, GI symptoms, mental health concerns, nerve problems, problems thinking or concentrating, hair loss, hearing problems). These symptoms were among the most commonly reported across studies as noted in (Supplemental Figure C).

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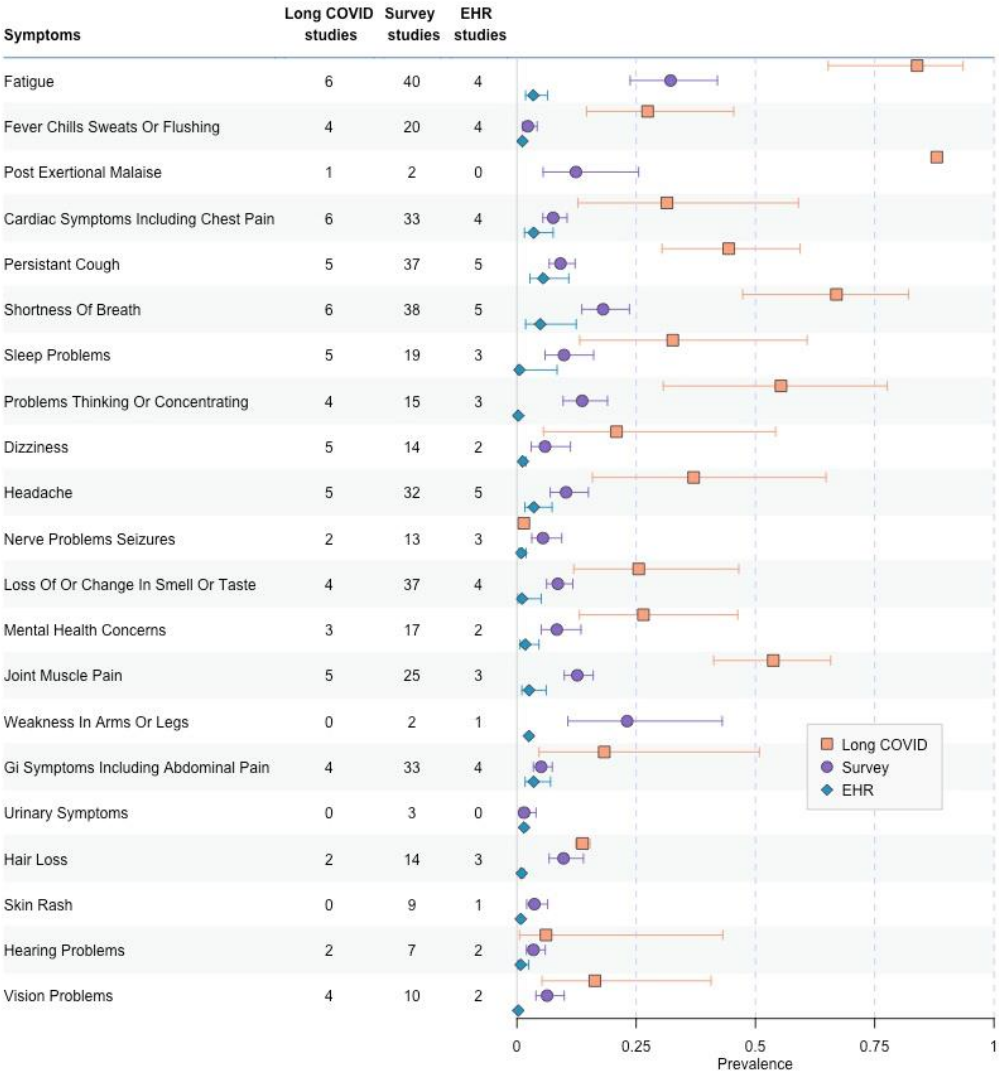

Figure 2. PASC symptom frequencies (n=59 studies) according to three study design groups: Long COVID, Survey and EHR studies. Bars around the means indicate 95% CI.

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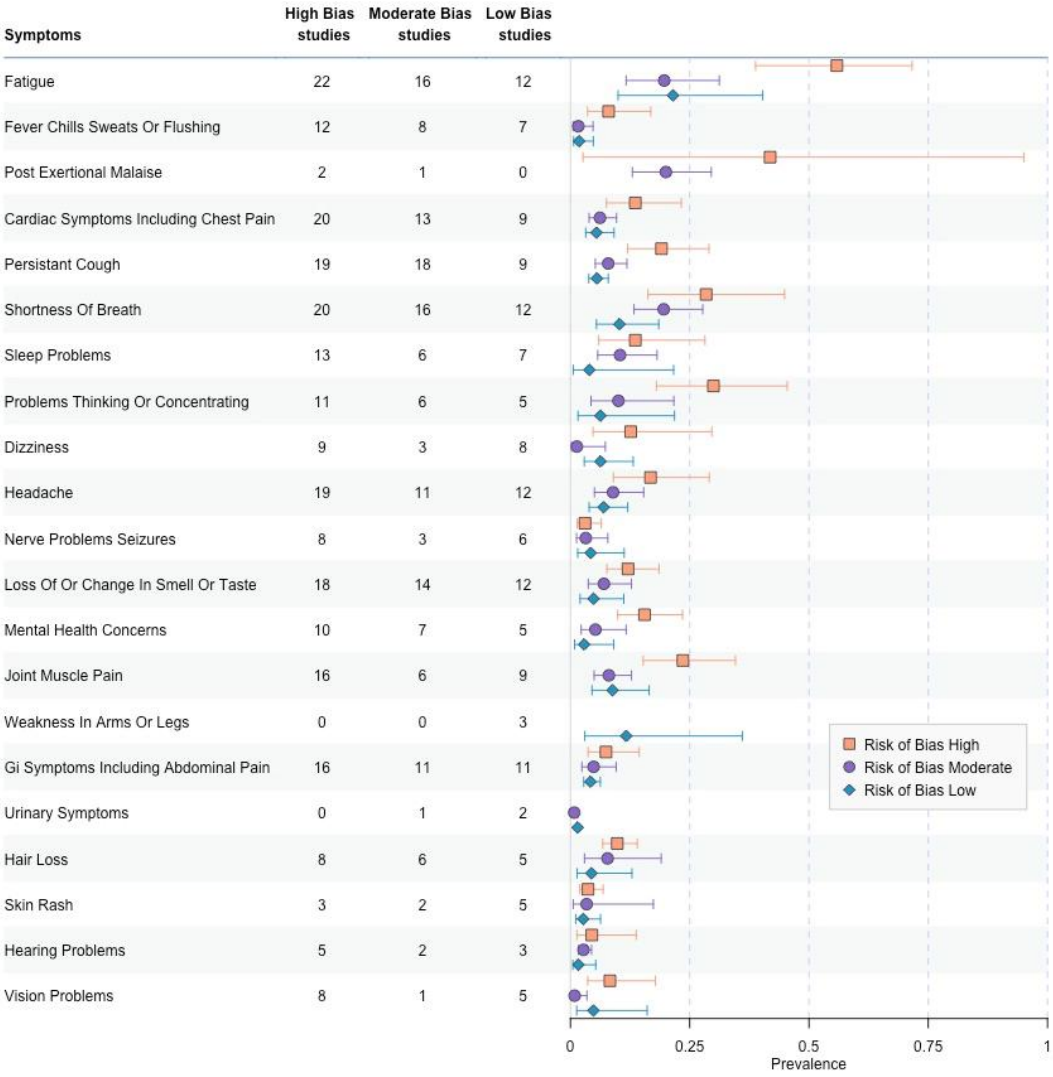

Figure 3. PASC symptom frequency across High, Moderate, Low risk of bias groups. Bars around the means indicate 95% CI.

3.6. Risk of Bias Comparisons

Using the Hoy [10] critical appraisal tool, 25 studies were classified as high risk of bias, 19 as moderate risk of bias, 15 as low risk of bias. Comparing symptom prevalence across three risk of bias categories demonstrated differences in results across high risk of bias studies (largest difference seen for fatigue, post exertional malaise, cardiac symptoms including chest pain, persistent cough, problems thinking or concentrating, dizziness, headache, mental health concerns, joint or muscle pain) with less variation comparing moderate risk of bias studies to low risk of bias studies. The highest variation between studies was seen in the high risk of bias studies (Figure 3)**.** High risk of bias studies included those with small sample size that did not reflect the general population characteristics in a country, studies with low response rates suggesting selection bias, and studies without general population data on symptom prevalence. Since the primary goal of this meta-analysis was to summarize the prevalence of PASC symptoms among the general population, all Long COVID studies were classified as high risk of bias.

3.7. Low-to Moderate Risk fo Bias, EHR Versus Survey Collection

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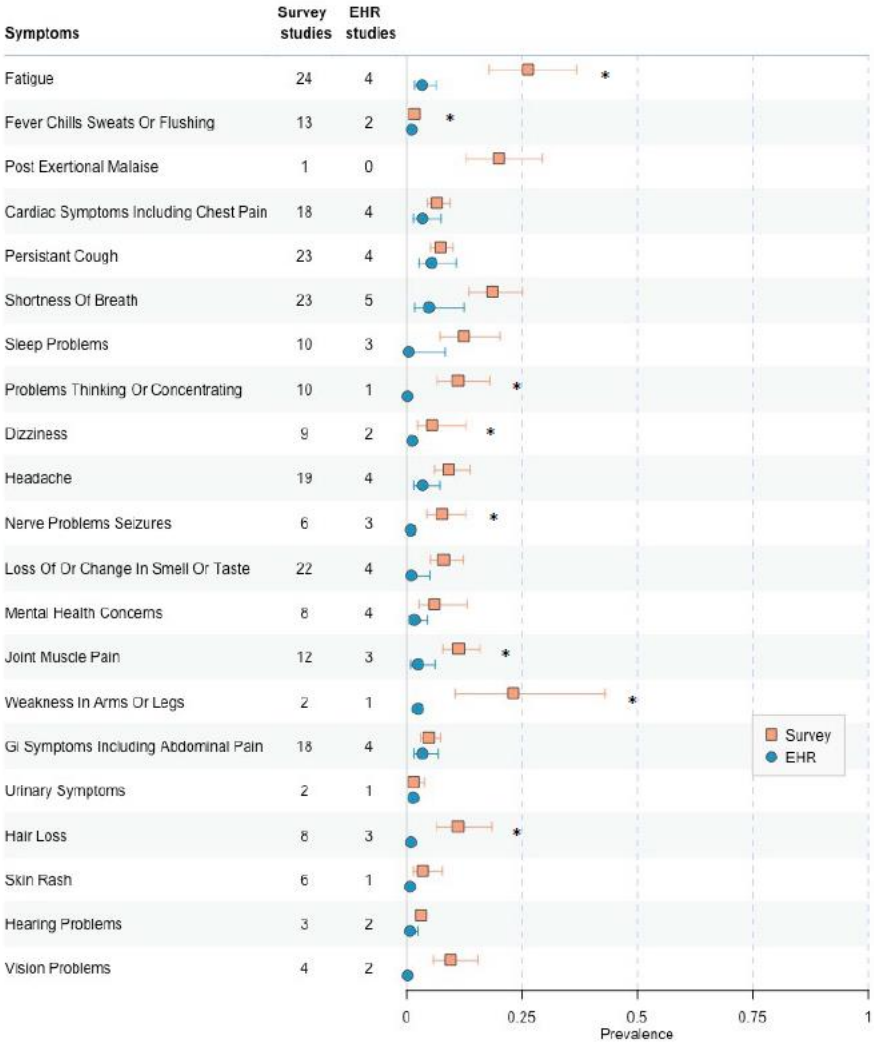
Among the low- and moderate-risk of bias studies, PASC symptoms were compared between the EHR and survey studies (Figure 4a). Twenty-seven studies were classified as surveys, while five were classified as EHR studies. A higher prevalence was recorded across 20 of 21 symptoms when evaluated with the survey compared to that of the EHR. Eight of those symptoms were found to have a statistically significant difference including fatigue, problems thinking of concentrating, and weakness in arms or legs. The prevalence across the two study designs were relatively similar for certain symptoms including cardiac/chest pain, GI/abdominal pain, and persistent cough.



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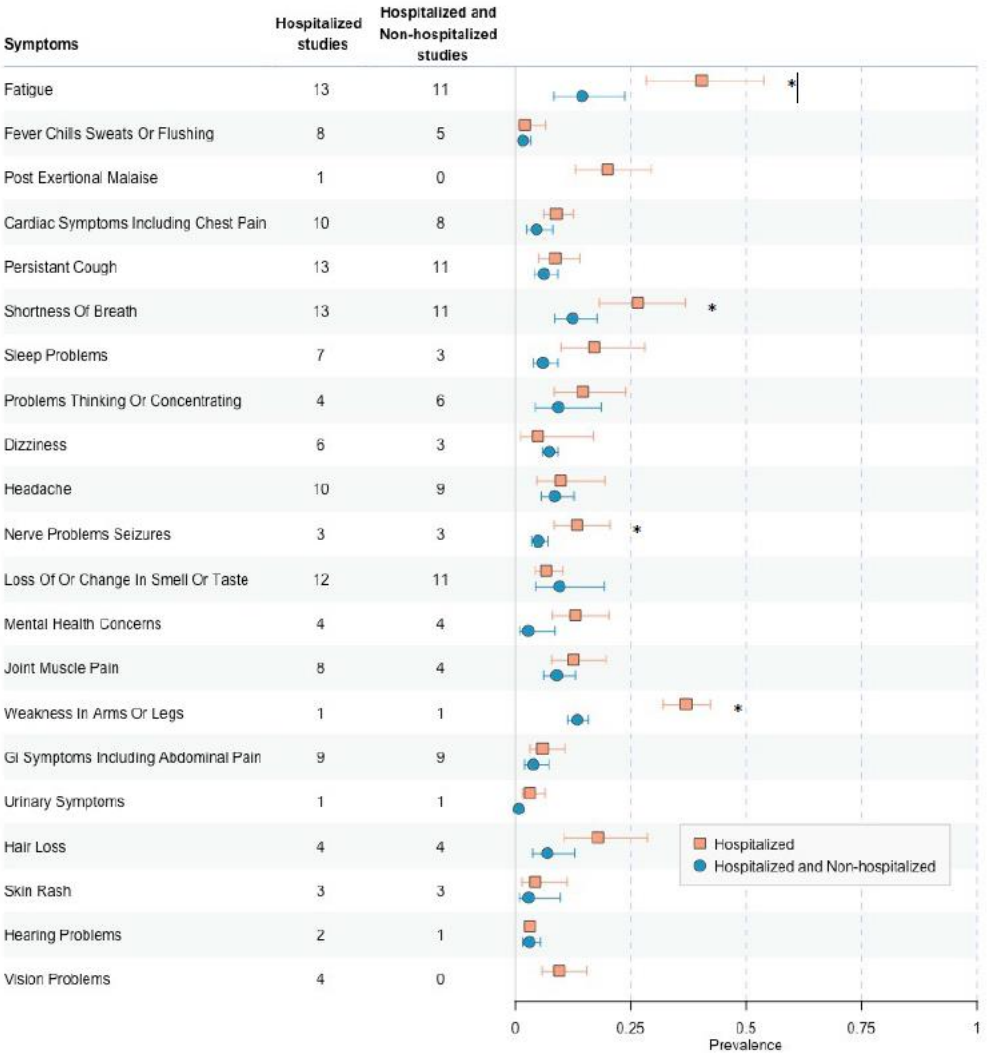

Figure 4. a. PASC symptom prevalence Limited to Moderate or Low Risk of Bias Studies Stratified by EHR or Survey Data. Bars around the means indicate 95% CI. An asterisk indicates a statistically significant comparison of proportion for a given symptom category after multiple hypothesis correction ($p < 0.0024$) **Figure 4b**. PASC symptom prevalence in Moderate or Low Risk of Bias Studies Stratified by Hospitalized or Mixed Studies with Hospitalized and Non-Hospitalized Survey Data. Bars around the means indicate 95% CI. An asterisk indicates a statistically significant comparison of proportion for a given symptom category after multiple hypothesis correction ($p < 0.0024$).

3.8. Low-to Moderate Risk of Bias, Hospitalized Versus Hospitalized and Non-Hospitalized among Survey Studies

Among the low- and moderate-risk of bias survey studies, PASC symptoms were then compared between studies including patients who were hospitalized at the time of the incident COVID-19 event versus studies from non-hospitalized patients, and mixed studies of hospitalized and non-hospitalized patients. Sixteen studies were from patients exclusively hospitalized with COVID-19 versus 11 studies that were from a non-hospitalized and mixed studies. 20 of 21 PASC symptoms had a higher prevalence among the hospitalized group. Only dizziness had a higher prevalence among the non-hospitalized and mixed studies (Figure 4b). Four of the symptoms were found to have a statisically significant difference. See (Supplemental Figure D) for a visual summary of meta-analysis groupings.

4. Discussion

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In 59 studies of symptoms lasting more than 3 weeks after acute COVID infection, we found wide ranges of symptom frequencies, variable categories of symptoms included, and marked variation in study design. Most studies to date have focused largely on individual symptom prevalence but are limited by lack of controls and retrospective data. The current review examined the most prevalent PASC symptoms in 59 scientific articles as fitted to a 21-symptom phenotype grid. Individual symptom prevalence varied widely depending on study design with lower prevalence in studies based on EHR to moderate prevalence through surveys conducted by outreach to general population samples, infected inpatients after hospital discharge, or mixed studies of hospitalized and non-hospitalized outpatients to highest symptom prevalence reported from surveys on recorded in the EHR of individuals with suspected Long COVID. After excluding studies with high risk of bias, meta-analysis of symptom prevalence for 21 symptom categories ranged widely from 2.6-28.7% in studies based on surveys to 0.3%-7.1% in studies based on EHRs. The challenges with varied study design include potential biases resulting in under-ascertainment of symptoms in EHR studies to including symptom frequencies only among individuals with suspected Long COVID that do not reflect general population prevalence.

EHR studies demonstrated the lowest prevalence rates for PASC symptoms, shortness of breath, fatigue, pain, cognitive problems, changes in smell and/or taste compared to other methods with some symptoms not available in EHR data. The challenges in survey design include assuring a representative sample of the general population. Many of the studies that surveyed hospitalized patients or mixed hospitalized and non-hospitalized outpatients used smaller populations and were classified as high risk of bias. Some large studies that surveyed general population samples with low response rates, thus raising the issue of representativeness of responders, were also rated as high risk of bias. For studies that assessed symptoms only among individuals with suspected Long COVID (Long COVID clinics, diagnosis code, Long COVID support groups/social media), prevalence data demonstrates much higher symptom rates The most striking of these are post-exertional malaise (88%) and fatigue (80%), followed by shortness of breath (55%), cognitive problems (53%), changes in smell and/or taste (26%), joint/muscle pain (42%), and fever/chills/sweats (36%), illustrating the burden of symptoms among people with Long COVID symptoms.

Differences in data collection methods across the studies can affect how prevalence is reported. Potential biases in symptom assessment in EHR data include absence of diagnosis codes for many symptoms, incomplete symptom assessment or documentation by providers, potential limited access to care by vulnerable patients, and lack of full data on individuals who receive care outside the EHR system. Many of these limitations could result in underestimates of symptom prevalence. This may contribute to the lower frequencies reported in EHR studies. Conversely, survey studies could be impacted by response bias whereby symptomatic individuals are more likely to respond than asymptomatic individuals. Surveys among individuals seeking resources for Long COVID, such as in specialty clinics or social media support groups, are most likely to exhibit selection bias. The very high prevalence among support groups and Long COVID clinics implies that their symptoms may have been more likely to be severe or disruptive to their quality of life. Nevertheless, symptom prevalence data amongst the moderate and low risk of bias studies supports substantial prevalence of symptoms across a wide array of organ systems and suggests that PASC/Long COVID is a multi-system disorder.

While EHR and survey studies each can have their own biases, this meta-analysis identifies which of the PASC symptoms have similar measurements between study designs. For example, chest pain, GI pain, and persistent cough were all detected with similar prevalence in the EHR and survey studies. This would suggest that future PASC studies that use EHR should expect the prevalence of these specific symptoms to be more accurate. However, the prevalence of fatigue, post-exertional malaise, and weakness in arms and legs were significantly different between the EHR and the survey studies. Therefore, these symptoms may not be as reliably measured. Given that collecting prospective or retrospective data from EHR's can be easier and less expensive than setting up a survey study, future PASC studies could rely on the EHR to track symptoms such as chest pain and

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gastrointestinal discomfort in PASC. However, they should consider alternative ways to measure symptoms like fatigue and post-exertional malaise.

In addition, it has already been observed that a longer recovery course is expected in patients requiring hospitalization or prolonged stays in the hospital [41,45,68]. While this meta-analysis validates increased prevalence of PASC among hospitalized patients, it provides further insight into exactly how these differences manifest across the various PASC symptoms. Interestingly, for certain symptoms such as headaches, nerve problems/seizures, and changes in smell, no statistically significant difference was observed between the two cohorts. While these data suggest the severity of the acute COVID-19 episode may directly lead to increased prevalence of fatigue, weakness, and shortness of breath in the subsequent recovery phase, an alternative mechanism (auto-immune response, persistent viral reservoir) may explain why that difference is not as significant for PASC symptoms like headache and changes in smell. These findings may also prepare health care providers for what to expect with patients depending on their acute COVID-19 level of severity.

Other limitations to the published studies include incomplete symptom lists in some studies and lack of control groups to assess frequency of symptoms in a representative uninfected group. Many of these PASC symptoms, taken individually, are non-specific, prevalent in the population, vary widely, and overlap with many other conditions. The heterogeneity of symptoms suggests that PASC is a set of syndromes with variable etiologies [6,7]. Because of the substantial short- and long-term effects of PASC, including impacts on quality of life, healthcare costs, and economic productivity [69], it is imperative to better characterize PASC, and PASC sub-phenotypes, in a prospective design with uniform data collection from a diverse group of uninfected and infected participants as the RECOVER Initiative intends to do.

We acknowledge that PASC symptoms—especially considering the introduction of vaccinations, virus variants, and pre-existing conditions—are difficult to fully capture and describe. A comprehensive overview of symptom phenotypes was attempted in this review, however, 200+ symptoms have been reported post-COVID. Knowledge of PASC is still evolving. Another challenge in this review was reliability of self-reports compared to EHR, for example, and wide variation in the quality of symptom reporting. Occasionally, values had to be visually estimated from graphs and figures when exact numbers were not provided. We have attempted to summarize extant research in a way that is helpful for clinicians, the patient community, and researchers alike while keeping these caveats in mind.

The striking variability in symptom prevalence across studies of PASC/Long COVID illustrates the challenge with defining criteria for this novel, multi-system condition. Studies to date have focused largely on individual symptom prevalence but some are limited by lack of controls, small sample size, potentially biased study designs. Symptom prevalence ranges widely, with lowest prevalence in EHR studies and higher prevalence in Survey studies, as illustrated by a range of 1-8% in EHR studies versus 2-28% in Survey studies in the low to moderate risk of bias studies. When limiting the study population to only participants who report Long COVID, the prevalence is much higher, reflecting a change in the denominator for prevalence calculations and a different study question, namely: “what is the prevalence of symptoms among participants who have any long term symptoms after SARS-CoV-2 infection?” rather than “what is the prevalence among a population infected with SARS-CoV-2”. The challenges are that many of these symptoms, taken individually, can be common in the population regardless of COVID infection. PASC symptoms are also heterogeneous and overlap with many other conditions. Major questions remain about the effect of vaccination status, the role of viral variants, the role of COVID therapies, comorbidities, social determinants of health, and clinical risk factors on the development of PASC/Long COVID to enable studies on the underlying pathobiology of individual symptoms and clusters of symptoms. Further research into PASC phenotypes is needed to effectively cluster symptoms in meaningful ways that enable focused pathobiology studies and clinical trials.

Supplementary Materials: The following supporting information can be downloaded at: www.mdpi.com/xxx/s1, Figure S1: A. Symptom Categories; Figure S2: Meta Analysis; Figure S3: Top 3 Most Prevalent Symptoms (n = 59 studies); Figure S4: Meta-Analysis Categories.

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