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Review

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Review

A Comprehensive Global Review of Epidemiology, Clinical Management, Socio-Economic Impacts and National Responses of Long COVID with Future Research Directions

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Abstract: Background: Long COVID, characterized by a persistent symptom spectrum following SARS-CoV-2 infection, poses significant health, social, and economic challenges. This review aims to consolidate knowledge on its epidemiology, clinical features, and underlying mechanisms to guide global responses; **Methods:** We conducted a systematic literature review, analyzing peer-reviewed articles and reports to gather comprehensive data on long COVID's epidemiology, symptomatology, and management approaches; **Results:** Our analysis revealed a wide array of long COVID symptoms and risk factors, with notable demographic variability. The current understanding of its pathophysiology suggests a multifactorial origin yet remains partially understood. Emerging diagnostic criteria and potential therapeutic strategies were identified, highlighting advancements in long COVID management.; **Conclusion:** This review highlights the multifaceted nature of long COVID, revealing a broad spectrum of symptoms, diverse risk factors, and the complex interplay of physiological mechanisms underpinning the condition. Long COVID symptoms and disorders will continue to weigh on healthcare systems in years to come. Addressing long COVID requires a holistic management strategy that integrates clinical care, social support, and policy initiatives. The findings underscore the need for increased international cooperation in research and health planning to address the complex challenges of long COVID. There is a call for continued refinement of diagnostic and treatment modalities, emphasizing a multidisciplinary approach to manage the ongoing and evolving impacts of the condition.

Keywords: coronavirus risk factors; multisystem impact; public health response; counter measure

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1. Introduction

The COVID-19 pandemic, caused by the SARS-CoV-2 virus, has been an unprecedented disruptor since its emergence in 2020, accruing an estimated 774.6 million confirmed cases globally[1]. The World Health Organization has identified five variants of the SARS-CoV-2 virus: Alpha (α), Beta (β), Gamma (γ), Delta (δ), and Omicron. These variants exhibit differences in transmissibility, disease progression, and severity, and may significantly impact the long-term health outcomes of affected individuals. These post-infection consequences are often referred to as Post-Acute Sequelae of SARS-CoV-2 infection (PASC) or long COVID, also known as long-haul COVID [2,3]. long COVID is a complex and dynamic disease, characterized by the disappearance and recurrence of some symptoms or the emergence of new ones, with little known about the biological mechanisms triggering these symptoms, complicating the diagnosis and treatment of long COVID[4,5]. The impact of long COVID extends to significant physical, mental, and socio-economic consequences for patients [6,7].

The term "long COVID" first emerged on social media in May 2020, becoming the inaugural "infodemic" to spread across Twitter and other media platforms. It describes the phenomenon where patients exhibit symptoms for weeks or months following their initial infection with the coronavirus [8]. long COVID is a multi-systemic, potentially debilitating condition, raising concerns about permanent functional impairments [9]. In the autumn of the same year, the World Health Organization established the diagnosis for Post COVID-19 condition and assigned it the ICD-10 code U09 [10]. In October 2021, WHO members reached a consensus on the definition of Post COVID-19 condition using the Delphi technique. x This allowed for the implementation of diagnostic codes in hospitals, enabling physicians to formally diagnose patients with long COVID and record these diagnoses in electronic health records [11]. long COVID refers to individuals who continue to experience symptoms of COVID-19, persisting for at least two months and remaining unresolved three months after a suspected or confirmed infection, with no alternative diagnoses explaining these symptoms [12]. The definition of long COVID is evolving. For example the Centers for Disease Control and Prevention (CDC) in the United States defines it as a range of new, recurring, or ongoing health problems that occur four weeks or more after the initial infection, including fatigue, fever, and various symptoms affecting the respiratory system, heart, nerves, and digestive tract [13]; the National Institute for Health and Care Excellence (NICE) in the UK describes it as persistent symptoms 4 to 12 weeks after the onset of acute symptoms, or as a post-COVID syndrome if symptoms persist beyond 12 weeks [14]; the Australian Department of Health states that symptoms persisting four weeks after the initial coronavirus infection constitute long COVID [15]. In Germany, 16 medical societies have compiled guidelines for long COVID and post-COVID, defining long COVID as symptoms that persist beyond four weeks post-infection or illness, and post-COVID as symptoms that are unexplained by other means and persist or emerge anew after 12 weeks [16].

At least 65 million people worldwide have had long-term infections of COVID-19[4,8] with 23 million in the United States, 1.5 million in the United Kingdom, 1.4 million in Canada, 0.4 million in Australia, and over half of COVID-19 patients in Japan exhibiting symptoms of long COVID [9–12]. A case-control study conducted by Marra et al. (2023) among Brazilian healthcare workers revealed that up to 27% experienced long COVID after infection, with an increased risk of reinfection [13,22].

It's evident that while the incidence and implications of long COVID are increasingly documented, significant gaps persist in the comprehensive understanding of its long-term trajectory and management. This systematic review aims to address these gaps by synthesizing existing literature to evaluate the wide-ranging impact of long COVID and the efficacy of adaptive management strategies employed globally. It endeavors to provide a structured overview of the condition's symptomatic patterns, risk factors, and the socio-economic repercussions faced by affected individuals and societies. By identifying key areas lacking robust evidence and highlighting regions where knowledge is fragmented or rapidly evolving, this study seeks to elucidate a coherent narrative of long COVID's physiological mechanisms and its ripple effects across healthcare systems. Ultimately, this review intends to offer concrete insights for clinicians, researchers, and policymakers to refine approaches towards diagnosing, treating, and mitigating the multi-dimensional impacts of long COVID.

2. Materials and Methods

This systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A comprehensive search strategy was devised to capture all relevant literature pertaining to long COVID. We searched databases including PubMed, Scopus, Web of Science, and Embase from inception until December 2023, using a combination of keywords and MeSH terms related to "long COVID," "Post-Acute Sequelae SARS-CoV-2 infection (PASC)," and "chronic COVID syndrome." The inclusion criteria were peer-reviewed articles, systematic reviews, and gray literature that reported on the epidemiology, clinical manifestations, risk factors, and management strategies of long COVID. Studies were excluded if they focused on the acute phase of COVID-19, lacked specific data on long COVID, or were not in English. Two independent reviewers screened the titles and abstracts for eligibility, with any discrepancies resolved through discussion or consultation with a third reviewer (**Figure 1)**.

Data extraction was performed using a standardized form to capture information on study design, participant demographics, reported symptoms, risk factors, diagnostic criteria, therapeutic interventions, and outcomes. Quality assessment of included studies was conducted using the Newcastle-Ottawa Scale for observational studies and the Cochrane Risk of Bias tool for randomized controlled trials. The extracted data were synthesized narratively to capture the heterogeneity of the studies. The findings were organized thematically based on symptomatology, risk factors, pathophysiological hypotheses, and management strategies. Meta-analytic methods were not employed due to the anticipated variability in study designs and outcomes. This approach enabled a comprehensive summary of the current state of knowledge and identification of gaps in research on long COVID.

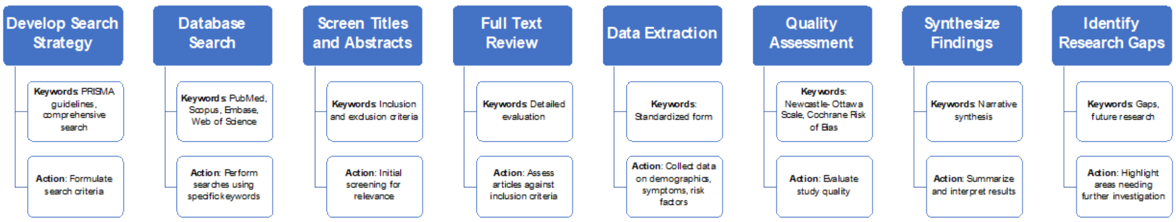

Figure 1. The framework of Long COVID comprehensive review work.

3. Results

3.1. Symptoms of Long COVID

Following the implementation of diagnostic measures, researchers have leveraged clinical data to discern the characteristics of long COVID. The researchers tracked 3,762 confirmed or suspected patients from 52 countries, all with illness durations exceeding 28 days, identifying 203 long COVID symptoms related to ten human organ systems [14,23] as shown in **Figure 2**.

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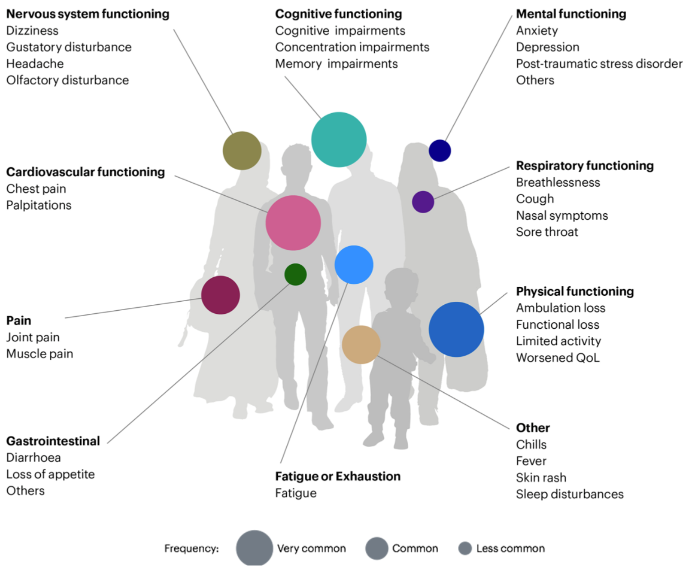

Figure 2. Some common symptoms of Long COVID. Over 200 symptoms of Long COVID have been reported in many different studies (source from: https://www.design-science.org.uk/news/visualising-long-covid).

3.1.1. Typical Symptoms of Long COVID

Typical symptoms of long COVID include fatigue, headache, body aches, shortness of breath, cognitive issues (such as brain fog), chest pain, and palpitations, with varying prevalence and severity[7,15,16]. Gutierrez-Martinez (2022) conducted a retrospective data analysis from February 2020 to May 2021, including patients with persistent symptoms after short-term hospitalization or outpatient patients who were never hospitalized and observed that individuals with brain fog exhibited a range of issues including insufficient sleep, anxiety, depression, reduced attention, and executive function impairments [17,26]. long COVID patients frequently experience autonomic dysfunction and Postural Orthostatic Tachycardia Syndrome (POTS)[18,19]. Headaches, anxiety, and depression are more prevalent among younger patients and females, while older patients are more likely to suffer from cognitive deficits and respiratory issues, and males are more prone to muscle or joint pain[20,29]. Additionally, loss of smell and taste, insomnia, and gastrointestinal problems are also occurred alongside the primary symptoms[15,16].

3.1.2. Duration of the Long COVID in the Patient

Dennis (2023) found that 59% of long COVID patients continued to exhibit organ damage one year after the initial symptoms, and 39% experienced persistent pulmonary function impairment two years later[21,30]. Baskett et al. (2022) studied the 47 most common symptoms of long COVID and found that only 7 symptoms, including accelerated heart rate, hair loss, fatigue, chest pain, shortness of breath, joint pain, and obesity, are manifest within the first year post-infection[22,31]. Jia et al. (2022) determined that the median time to initial symptom resolution are 44 days post-diagnosis, with a median duration of 214 days to resolve all symptoms [23,32]. Symptoms of COVID-19 persisting beyond 15 weeks may last for a year.

3.2. Risk Factors and Physiological Mechanisms that Trigger Long COVID

Davis et al. have posited various hypotheses regarding the pathogenesis of long COVID, including immune dysregulation, dysbiosis of the microbiome, autoimmunity, coagulation and endothelial abnormalities, and neurological dysfunction [4]. Given the widespread and nonspecific nature of long COVID, comprehending the associated risk factors and physiological mechanisms is crucial for clinicians and healthcare organizations in proficiently screening, monitoring, and treating

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patients (**Figure 3**). Furthermore, this information empowers individuals by providing them with insights into their medical history, enabling a comprehensive assessment of the risk associated with long-term COVID-19 infection for enhanced disease prevention[24–27].

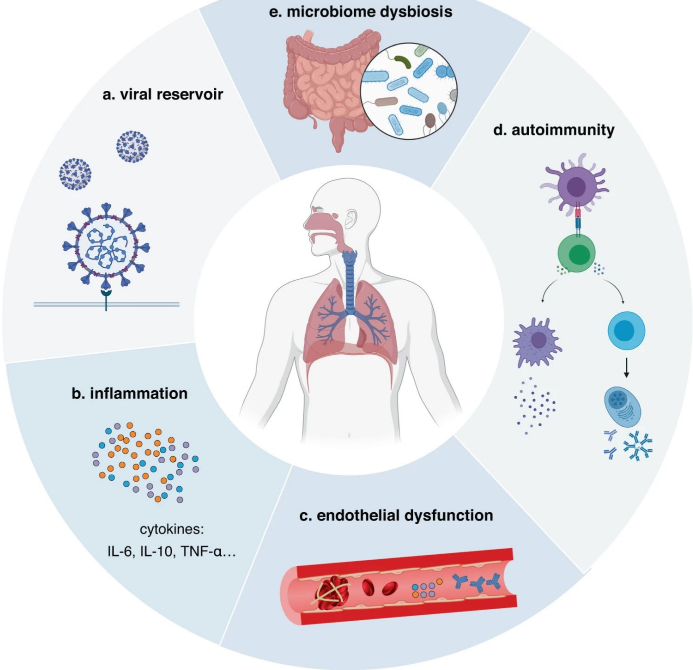

Figure 3. The potential pathophysiological mechanisms of long COVID. (source from: https://www.nature.com/articles/s41392-023-01640-z).

3.2.1. Risk Factors for Long COVID

(1) Gender, age, and pre-existing chronic conditions emerge as pivotal risk factors influencing the susceptibility to long COVID. Notably, the risk of long COVID in women is twice that of men [28,37]. Age-wise, individuals aged 60 to 79 face a 25% elevated risk compared to their younger people, escalating to a 60% higher risk for those over 80. Distinct patterns also emerge in the context of hospitalization. Patients requiring hospitalization for COVID-19 are at a substantially greater risk of developing long COVID, with the risk escalating up to 18 times. Remarkably, those necessitating invasive ventilation, such as mechanical ventilation, face an exponentially increased risk of 115 times [29][29][38]. Pre-existing health conditions play a pivotal role in long COVID diagnoses. Patients with a history of cardiovascular diseases, chronic lung diseases, kidney diseases, hypertension, diabetes, obesity, and depression before contracting COVID-19 are more predisposed to long COVID [30,39]). Additionally, individuals with rheumatic diseases, contracting the coronavirus and experiencing an heightened antibody response that triggers an immune reaction, are notably more prone to developing long COVID[31,40]. These nuanced risk factors provide critical insights for a comprehensive understanding of long COVID.

(2) Smoking, high body mass index, life stress, and psychological factors emerge as additional risk factors contributing to the complexity of long COVID. In a six-month follow-up study of discharged COVID-19 patients, researchers observed a significant correlation between high muscle atrophy and increased fatigue and muscle pain, highlighting the nuanced impact of physical health on long COVID outcomes [32,41]. A noteworthy finding indicates that women maintaining a healthy lifestyle-marked by factors such as a balanced weight, non-smoking status, regular exercise, sufficient sleep, a high-quality diet, and moderate alcohol consumption-experience a 49% reduced risk of long COVID compared to those with unhealthy lifestyles [33,42]. Furthermore, a robust association exists between the severity of long COVID and the initial severity of the COVID-19 infection [34][34][43]. Additionally, major life stressors, encompassing economic challenges, food security issues, death of close contacts, have been identified as contributors to an increased risk of long COVID [35,44].

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Psychological factors also play a pivotal role, with pre-existing distress, including towards anxiety, worry, perceived stress, and loneliness, leading to an elevated long COVID risk ranging from 32% to 46%. Additionally, these psychological factors contribute to a heightened risk of impaired daily functioning, ranging from 15% to 51% [33,42]. This comprehensive exploration sheds light on the intricate interplay between various factors and their impact on long COVID.

3.2.2. Physiological Mechanisms of Long COVID Formation

The occurrence of long COVID linked to the formation of a viral reservoir within the body subsequent to the initial infection. It triggers an overly active immune system, characterized by CD^{8+} T cell counts that can surge up to 100 times higher than normal, thereby dampening the overall immune response [36–38]. Concurrently, diminished levels of anti-nuclear envelope antibodies and the presence of pulmonary diseases contribute to the manifestation of long COVID symptoms [23,32]. Furthermore, COVID-19 infection induces immune dysfunction, resulting in nerve damage such as dysfunction of the vagus nerve and a reduction in olfactory sensory neurons, which in turn induces long COVID symptoms[39–43]. Significant differences between the circulating antibodies and other components of the immune system are noted in long COVID patients compared to other patient groups [44,53]. long COVID patients have notably lower cortisol levels, aiding in the development of related biomarkers and diagnostic and treatment methods [35,44]. Researchers utilizing a real-time deformability cytometer (RT-DC) they developed, and discovered that changes in blood cells lead to long COVID, with damaged blood cells increasing the risk of vascular blockages and pulmonary embolism [45,54].Carlo (2024) identified changes in serum proteins of long COVID patients, including the activation of the immune system's complement cascade, coagulation changes, and tissue damage, providing potential biomarkers for the diagnosis of long COVID [46,55]. Greene (2024) revealed that the integrity of brain blood vessels in long COVID patients is compromised and the leaking vessels, coupled with an overactive immune system, are a key driver of long COVID-related brain fog, assisting in the development of targeted treatments for patients[47,56].

3.3. The Social Economic Impact of Long COVID

Long COVID imposes restrictions on patients' daily activities, severely affects their ability to return to work or social life, subsequently impacting their psychological health, and causes significant economic loss to patients, their families, and society[48–50].

3.3.1. The Impact of Long COVID on Society

Previously, a national survey in the UK and found that patients treated for COVID-19 in hospitals are still not fully recovered after five months, and has limited health recovery after one year, with fewer than 3 out of 10 patients fully recovering [51,60]. The non-hospitalized patients in France experienced long COVID symptoms for up to two years, with a minority losing functional capacity for as long as 22 months [52,61]. Aburto (2022) surveyed 27 countries that had COVID-19 outbreaks and found that in 11 countries, men's life expectancy decreased by more than one year, and in 8 countries, women's life expectancy decreased by more than one year, with the largest decreases in life expectancy for men being 2.2 years in the USA and 1.7 years in Lithuania [53,62]. Severe COVID-19 has a lasting effect on memory, attention, or problem-solving abilities equivalent to aging 20 years in patients, causing persistent cognitive impairments in 50 to 70-year-old patients equivalent to a 10-point reduction in IQ [54,63]. Surveyed 1,000 Wuhan residents infected before December 2020 and found that more than half of the COVID-19 recovered has post-COVID conditions after infection of 20 months, with nearly 1/6 suffering from severe sequelae [55,64]. The cognitive effects and fatigue are the main causes for the patients to return to work, with cognitive symptoms unrelated to outward physical disability [56,65].

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3.3.2. Long COVID's Impact on the Economy

As of June 2022, data from the U.S. National Bureau of Statistics reported that over 16 million working-age Americans (aged 18 to 65) were infected by long COVID, with approximately 4 million people losing their jobs due to the disease. The resultant of losing jobs equates to an annual loss of $170 billion in wages, nearly 1% of the U.S. Gross Domestic Product (GDP) [57,66]. On December 5, 2022, data from the UK's Office for National Statistics showed that nearly 2 million people were experiencing long COVID, with their economic inactivity rate being close to ten times that of healthy individuals. A survey of a Bank of England found that labor force participation among long COVID sufferers aged 16 to 64 fell by 1.3%, and a quarter of UK companies cited long COVID as one of the main reasons for staff absenteeism [58,67]. Davis et al. (2021) found that about 20% of long COVID patients are out of work, and nearly half has reduced their working hours [14,23].

3.3.3. New Clinical Disorders and Accelerated Disease Progression

Individuals who survived acute COVID-19 may be at higher risks of developing new clinical disorders and/or accelerated disease progression of existing disorders. Higher incidences of diabetes [68–70], hypertension [71], kidney disorders [72,73] among others have been reported in individuals post COVID-19 compared to non-COVID matched controls. Worsening of disease progression of existing clinical disorders have been reported in patients with hypertension [74,75], kidney disease [76], multiple sclerosis [77–82], dementia [83–85] and other neurological conditions [84–89] post COVID-19 compared to non-COVID matched controls. We expect that there will be accelerated aging of multiorgan systems in some individuals, especially those experienced severe acute COVID-19 and/or with major pre-existing comorbidities. These new-onset disorders and accelerated disease progression are expected to result in increased healthcare burden in years to come. Identifying at-risk individuals and risk factors may encourage additional health monitoring post SARS-CoV-2 infection.

3.4. Reponses of Major Countries to Long COVID

3.4.1. Reducing the Impact of Long COVID on the Workforce through Policy Adjustments

Policy measures include ensuring better prevention and treatment options, expanding paid sick leave, improving workplace accommodations, and increasing access to disability insurance. The Americans with Disabilities Act stipulates that long COVID patients are eligible to be classified as disabled and enables to receive appropriate healthcare to regain productivity [59,90]. The UK's Equality Act considers all long COVID sufferers as disabled, entitled to support and formal protection under employment law necessary for continued work, and long COVID are recognized as an occupational disease, with entitlement to protection and compensation for infections contracted during employment [60,91].

The establishment of long COVID clinics provides patients with diagnosis, treatment, and care. As of January 2023, 477 hospitals in Tokyo, Japan, are set up clinics for post-COVID-19 sequelae. Italy offers convenience to long COVID patients through a community care network, with non-profit organizations providing remote monitoring systems, expert intervention, psychological support, and services such as neurological, respiratory, and cognitive rehabilitation post-hospitalization. Australia has also opened long COVID specialty clinics in the capital and regional centers, providing additional care for patients [61,92]. The University of Pennsylvania's School of Medicine has established a COVID Aftercare and Recovery Clinic, offering multidisciplinary assessment and treatment resources for patients recovering from COVID-19, ensuring continuity of patient care, and reducing long-term morbidity and mortality [13,62]. Hospitals in Beijing, Guangzhou, Hangzhou, Shanghai, Wuhan, Zhengzhou, and other places are already set up post-COVID infection recovery clinics or specialist joint clinics, providing patients with comprehensive diagnosis and treatment, including condition assessment, functional training, traditional Chinese medicine treatment, and psychological counseling [63,93].

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3.4.2. By Offering Government Fundings to Support Foundational Research on Long COVID

Since 2020, the Canadian Institutes of Health Research has funded $17.7 million for targeted research on post-COVID-19 sequelae. The Canadian government provided 20 million CAD for the establishment of the Canadian COVID-19 Sequelae Research Network at the beginning of 2023, to study the biological basis of the disease and its impact on clinical care, mental health, health systems, and population health, in order to formulate related plans and policies [64,94]. In 2021, the German statutory pension insurance and German social accident insurance allocated 332 million euros for health research to combat post-COVID sequelae, developing treatments for outpatient care or rehabilitation [65,95]. In 2021, the UK Research and Innovation (UKRI) and the National Institute for Health Research (NIHR) jointly funded £18.4 million for the Post-Hospitalisation COVID-19 study (PHOSP-COVID) to identify the causes of long COVID and effective treatments for patients with chronic disease symptoms [66,96]. As of May 2022, the UK government invested over £50 million in government funds to research the potential mechanisms of long COVID and symptoms such as brain fog and respiratory difficulty, testing possible treatments. In March 2022, the Japan Society for the Promotion of Science funded 300 million JPY, and the UKRI contributed £3.5 million to establish 10 collaborative research projects, focusing on the global impact of long COVID[67,97]. In February 2022, the U.S. National Institutes of Health invested $470 million to support large-scale studies on the impact of long COVID [90,97]. In August 2022, the White House released a national research action plan on long COVID, allocating $1.15 billion for research into the symptoms of long COVID and how the virus triggers these symptoms [91]. In the US, there are two major long-covid initiatives funded by the NIH (https://ncats.nih.gov/research/research-activities/n3c, https://recovercovid.org).

3.4.3. Conducting Investigation to Develop Effective Treatment Strategies for Long COVID

The over-elimination of synapses by brain immune cells aids in identifying new treatments for persistent cognitive symptoms after coronavirus infections [92,100]. Treatment of post-COVID-19 sequelae with autologous fat-derived mesenchymal stem cells is first implemented in Japan, producing positive outcomes through anti-inflammatory actions and tissue regeneration [93,94]

Mucosal antibodies can provide lasting protection against coronavirus infections Havervall (2022) found that respiratory mucosal antibodies offer durable protection; persistent mucosal antibodies produced following infection with Omicron variants BA.1 or BA.2 which reduces the risk of reinfection with BA.5 by 90% [95,103]. Yan (2023) showed that intranasal administration of platelet-rich plasma extracted from the patient's own blood treat taste loss related to long COVID [96,104].

Therapies involving certain components may be effective for certain symptomatologies. Rosmarinic acid (CA) and Carnosol (CS) found in rosemary, CA-related compounds can serve as drugs for treating coronavirus infection-related brain sequelae, penetrating the blood-brain barrier and reaching the brain parenchyma to protect nerves [97,105]. Colchicine is promising for treating long COVID, potentially reducing complications associated with long COVID [98,106]. Lithium has anti-inflammatory and neuroprotective properties, and low-dose lithium aid in the recovery of long COVID in adults[99,100]. Many effective treatments and rehabilitation methods for functional disorders are also being used in the diagnosis and treatment of long COVID [101].

Advancing the development of monitoring methods for long COVID. Fagherazzi (2022) innovatively used various devices and vocal recordings of breathing to identify COVID-related symptoms, allowing for long-term monitoring of long COVID patients and predicting the evolution of their symptoms [80]. Kovarik (2023) utilized mass spectrometry-based post-genomic analysis techniques to identify symptoms associated with long COVID [103]. Research by Kuchler (2023) et al. demonstrated that ocular blood vessels change due to persistent coronavirus symptoms; standardized ophthalmological examinations reveal whether individuals are suffering from long COVID syndrome in the future [104].

3.4.4. Conducting Development of Vaccines in Prevention and Protection against Long COVID

Between August 2021 and June 2022, following the rollout of vaccines, referrals to the long COVID clinic in Cambridge, UK, sharply decreased by 79% [105]. Al-Aly's (2022) analysis of patients and controls in the U.S. Department of Veterans Affairs health care database showed that vaccination reduced the risk of long COVID by 15%, though this study did not include data on individuals infected with the Omicron variant [106]. Mizrahi (2023) et al. conducted a retrospective analysis of electronic medical records from the Israeli national health institution and found that vaccination reduced the risk of persistent breathing difficulties in patients with breakthrough infections [11,20]. Richard's (2023) research indicates that vaccination reduces the risk of persistent symptoms [107]. Marra's (2023) conducted as meta-analysis of literature in databases from December 2019 to June 2023 showed that the effectiveness of three vaccine doses against long COVID is 69%, while two doses is 37% effective; vaccination prior to COVID-19 infection significantly reduced long COVID cases. The next-generation vaccine GRT-R910, developed by biotechnology company Gritstone using self-amplifying mRNA (samRNA), induce a strong and lasting immune response, potentially providing broad and long-term clinical protection [108].

4. Future Adaptive Management Suggestions and Directions

Despite the expansion and acceleration of global research on long COVID, there remain significant challenges, and existing studies are not sufficient to fully improve the prognosis of long COVID patients. There is also the need to address future variants of the SARS-CoV-2 virus (Figure 4).

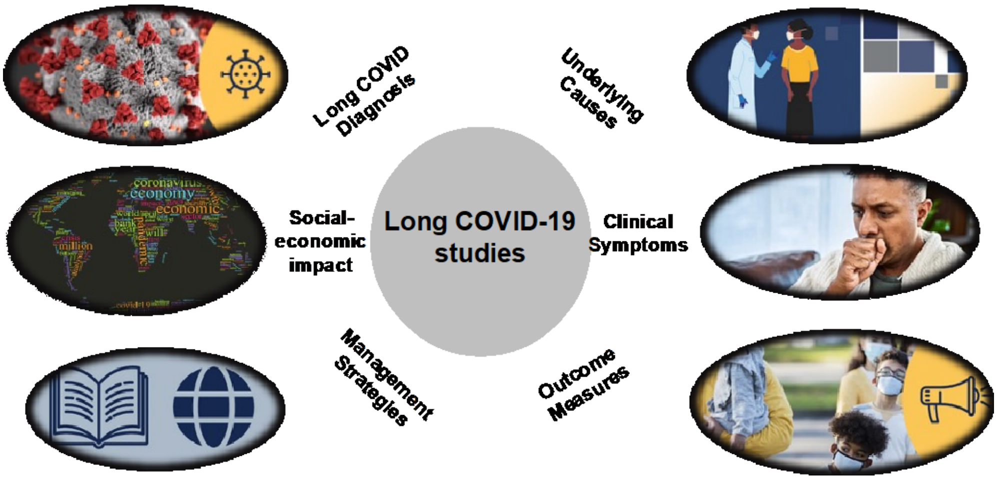

Figure 4. The framework of long COVID management.

(1) Intensify research on the mechanisms of long COVID and devise effective medical plans. The plan may involve screening for effective biomarkers to assess and predict the course of long COVID. Developing effective diagnostic and imaging tools may also be used for the safe diagnosis of long COVID. Determining the physiological mechanisms for the wide range of long COVID symptoms, designing large-scale clinical trial plans, discovering effective treatment methods, and improving the health and quality of life of long COVID patients are useful treatment plan.

(2) Within the bounds of the law, enhance multi-institutional data sharing on long COVID, implement stratified management of patients, provide effective treatments, and promote a path for full recovery. Strengthening the long COVID medical teams, reorganize healthcare resources, and invest in scientific research are also require preparing for the healthcare needs triggered by long COVID.

(3) Enhance the training and education of healthcare and research personnel, as well as public awareness may also support to minimize the risk of long COVID. Improve education about pandemics, viruses, and infection-induced diseases (such as long COVID) may ensure that people with long-term coronavirus and related diseases receive adequate care, implement effective interventions to prevent worsening prognoses. Additionally, conduct public awareness campaigns

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to inform about the risks and consequences of long COVID, and educate the public on enhancing self-prevention and monitoring are also used.

(4) Increase policy interventions to reduce the socioeconomic impact of long COVID. Conduct long COVID infection surveillance and analysis of its long-term impact on the workforce, healthcare costs, and societal and economic aspects, and develop corresponding policies and guidelines would also be useful. Optimize the organization of medical and healthcare services to ensure every patient has timely access to evidence-based and cost-effective treatment. Through population surveys, count individuals unable to work due to long COVID and establish occupational rehabilitation plans to support their re-employment and provide labor protection.

5. Limitation

The limitations of this review are primarily associated with the scope of literature analyzed and methodological constraints. Despite employing a comprehensive search strategy across multiple databases, the review was restricted to articles published in English, potentially overlooking pertinent studies in other languages that could influence the findings. Moreover, the exclusion of grey literature and unpublished studies might have introduced publication bias, favoring studies with significant results. The quality and heterogeneity of the included studies also presented challenges. Variations in study design, methodology, and quality across the papers could impact the consistency and generalizability of the review's conclusions. Additionally, due to the variability in expected outcomes, meta-analytic methods were not utilized, which may limit the capacity to quantitatively assess the effectiveness of different management strategies. Finally, the continual evolution of research on long COVID suggests that new information might emerge that was not available at the time of this review, indicating the need for ongoing research to constantly update our understanding of the condition.

6. Conclusions

This comprehensive systematic review elucidates the multifaceted nature of long COVID, revealing a broad spectrum of symptoms, diverse risk factors, and the complex interplay of physiological mechanisms underpinning the condition. The global impact of long COVID extends beyond the medical to significant socio-economic ramifications, underscoring the need for a multidisciplinary approach to management and intervention. The emergence of diagnostic criteria and therapeutic strategies marks a significant advancement in our understanding and ability to address long COVID. However, the variability in symptomatology, coupled with the evolving nature of SARS-CoV-2 and its variants, highlights the imperative for ongoing research.

The international response to long COVID, while varied, demonstrates a concerted effort to mitigate the condition's impact through clinical interventions, policy adjustments, and community support mechanisms. Nevertheless, this review identifies critical gaps in long-term management strategies and the necessity for adaptive approaches to accommodate the dynamic and persistent challenges posed by long COVID. One of the challenges is that to distinguish whether these symptoms, new disorders, and disease worsening are truly due to COVID-19 disease or are part of natural aging or have been undiagnosed. Carefully studies are needed. Future endeavors should focus on unraveling the intricate pathophysiological pathways of long COVID, developing precise diagnostic tools, and tailoring patient-centric therapeutic interventions. Furthermore, enhancing data sharing, strengthening healthcare infrastructure, and fostering public awareness are pivotal in curbing the spread and impact of long COVID. Policymakers and healthcare providers must collaborate to devise robust frameworks that address the socio-economic aspects of long COVID, ensuring comprehensive support for affected individuals and communities.

In conclusion, while significant strides have been made in understanding and managing long COVID, the journey towards fully addressing this global health challenge is ongoing. Multidisciplinary research, international cooperation, and innovative management strategies are essential in navigating the complexities of long COVID and enhancing the quality of life for those affected.

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References

1. Available online: https://covid19.who.int/ (accessed on 16, March, 2023).
2. Logue, J.K.; Franko, N.M.; McCulloch, D.J.; McDonald, D.; Magedson, A.; Wolf, C.R.; Chu, H.Y. Sequelae in adults at 6 months after COVID-19 infection. JAMA network open 2021, 4, e210830-e210830.
3. Trihandini, I.; Muhtar, M. The effect of long-haul COVID-19 toward domains of the health-related quality of life among recovered hospitalized patients. Frontiers in Public Health 2023, 11, 1068127.
4. Davis, H.E.; McCorkell, L.; Vogel, J.M.; Topol, E.J. Long COVID: major findings, mechanisms and recommendations. Nature Reviews Microbiology 2023, 21, 133-146, doi:10.1038/s41579-022-00846-2.
5. Iwasaki, A.; Putrino, D. Why we need a deeper understanding of the pathophysiology of long COVID. The Lancet Infectious Diseases 2023, 23, 393-395.
6. Natarajan, A.; Shetty, A.; Delanerolle, G.; Zeng, Y.; Zhang, Y.; Raymont, V.; Rathod, S.; Halabi, S.; Elliot, K.; Shi, J.Q. A systematic review and meta-analysis of long COVID symptoms. Systematic reviews 2023, 12, 88.
7. Bowyer, R.C.; Huggins, C.; Toms, R.; Shaw, R.J.; Hou, B.; Thompson, E.J.; Kwong, A.S.; Williams, D.M.; Kibble, M.; Ploubidis, G.B. Characterising patterns of COVID-19 and long COVID symptoms: evidence from nine UK longitudinal studies. European journal of epidemiology 2023, 38, 199-210.
8. Chen, C.; Haupert, S.R.; Zimmermann, L.; Shi, X.; Fritsche, L.G.; Mukherjee, B. Global Prevalence of Post-Coronavirus Disease 2019 (COVID-19) Condition or Long COVID: A Meta-Analysis and Systematic Review. J. Infect. Dis. 2022, 226, 1593-1607, doi:10.1093/infdis/jiac136
9. Imoto, W.; Yamada, K.; Kawai, R.; Imai, T.; Kawamoto, K.; Uji, M.; Kanda, H.; Takada, M.; Ohno, Y.; Ohtani, H.; et al. A cross-sectional, multicenter survey of the prevalence and risk factors for Long COVID. Sci Rep 2022, 12, 22413, doi:10.1038/s41598-022-25398-6
10. Damant, R.W.; Rourke, L.; Cui, Y.; Lam, G.Y.; Smith, M.P.; Fuhr, D.P.; Tay, J.K.; Varughese, R.A.; Laratta, C.R.; Lau, A.; et al. Reliability and validity of the post COVID-19 condition stigma questionnaire: A prospective cohort study. EClinicalMedicine 2023, 55, 101755, doi:10.1016/j.eclinm.2022.101755
11. Mizrahi, B.; Sudry, T.; Flaks-Manov, N.; Yehezkelli, Y.; Kalkstein, N.; Akiva, P.; Ekka-Zohar, A.; Ben David, S.S.; Lerner, U.; Bivas-Benita, M.; et al. Long covid outcomes at one year after mild SARS-CoV-2 infection: nationwide cohort study. BMJ 2023, 380, e072529, doi:10.1136/bmj-2022-072529.
12. Wang, S.; Li, Y.; Yue, Y.; Yuan, C.; Kang, J.H.; Chavarro, J.E.; Bhupathiraju, S.N.; Roberts, A.L. Adherence to Healthy Lifestyle Prior to Infection and Risk of Post-COVID-19 Condition. JAMA Intern Med 2023, 183, 232-241, doi:10.1001/jamainternmed.2022.6555.
13. Marra, A.R.; Sampaio, V.S.; Ozahata, M.C.; Lopes, R.; Brito, A.F.; Bragatte, M.; Kalil, J.; Miraglia, J.L.; Malheiro, D.T.; Guozhang, Y.; et al. Risk factors for long coronavirus disease 2019 (long COVID) among healthcare personnel, Brazil, 2020-2022. Infect. Control Hosp. Epidemiol. 2023, 1-7, doi:10.1017/ice.2023.95
14. Davis, H.E.; Assaf, G.S.; McCorkell, L.; Wei, H.; Low, R.J.; Re'em, Y.; Redfield, S.; Austin, J.P.; Akrami, A. Characterizing long COVID in an international cohort: 7 months of symptoms and their impact. EClinicalMedicine 2021, 38, 101019,
15. Iqbal, A.; Iqbal, K.; Ali, S.A.; Azim, D.; Farid, E.; Baig, M.D.; Arif, T.B.; Raza, M. The COVID-19 sequelae: a cross-sectional evaluation of post-recovery symptoms and the need for rehabilitation of COVID-19 survivors. Cureus 2021, 13.

Preprints.org (www.preprints.org) | NOT PEER-REVIEWED | Posted: 26 April 2024 doi:10.20944/preprints202404.1755.v1

16. Mandal, S.; Barnett, J.; Brill, S.E.; Brown, J.S.; Denneny, E.K.; Hare, S.S.; Heightman, M.; Hillman, T.E.; Jacob, J.; Jarvis, H.C. 'Long-COVID': a cross-sectional study of persisting symptoms, biomarker and imaging abnormalities following hospitalisation for COVID-19. Thorax 2021, 76, 396-398.
17. Gutierrez-Martinez, L.; Karten, J.; Kritzer, M.D.; Josephy-Hernandez, S.; Kim, D.; Newhouse, A.; Pasinski, M.; Praschan, N.; Razafsha, M.; Rubin, D.B.; et al. Post-Acute Sequelae of SARS-CoV-2 Infection: A Descriptive Clinical Study. J. Neuropsychiatry Clin. Neurosci. 2022, 34, 393-405, doi:10.1176/appi.neuropsych.21070193
18. Mallick, D.; Goyal, L.; Chourasia, P.; Zapata, M.R.; Yashi, K.; Surani, S. COVID-19 induced postural orthostatic tachycardia syndrome (POTS): a review. Cureus 2023, 15.
19. Reis Carneiro, D.; Rocha, I.; Habek, M.; Helbok, R.; Sellner, J.; Struhal, W.; Wenning, G.; Fanciulli, A. Clinical presentation and management strategies of cardiovascular autonomic dysfunction following a COVID-19 infection–A systematic review. European journal of neurology 2023, 30, 1528-1539.
20. Landry, M.; Bornstein, S.; Nagaraj, N.; Sardon, G.A., Jr.; Castel, A.; Vyas, A.; McDonnell, K.; Agneshwar, M.; Wilkinson, A.; Goldman, L. Postacute Sequelae of SARS-CoV-2 in University Setting. Emerg. Infect. Dis. 2023, 29, 519-527, doi:10.3201/eid2903.221522
21. Dennis, A.; Cuthbertson, D.J.; Wootton, D.; Crooks, M.; Gabbay, M.; Eichert, N.; Mouchti, S.; Pansini, M.; Roca-Fernandez, A.; Thomaides-Brears, H.; et al. Multi-organ impairment and long COVID: a 1-year prospective, longitudinal cohort study. J. R. Soc. Med. 2023, 116, 97-112, doi:10.1177/01410768231154703
22. Baskett, W.I.; Qureshi, A.I.; Shyu, D.; Armer, J.M.; Shyu, C.-R. COVID-Specific Long-term Sequelae in Comparison to Common Viral Respiratory Infections: An Analysis of 17 487 Infected Adult Patients. Open Forum Infectious Diseases 2022, 10, doi:10.1093/ofid/ofac683.
23. Jia, X.; Cao, S.; Lee, A.S.; Manohar, M.; Sindher, S.B.; Ahuja, N.; Artandi, M.; Blish, C.A.; Blomkalns, A.L.; Chang, I.; et al. Anti-nucleocapsid antibody levels and pulmonary comorbid conditions are linked to post-COVID-19 syndrome. JCI Insight 2022, 7, e156713, doi:10.1172/jci.insight.156713.
24. Matta, J.; Wiernik, E.; Robineau, O.; Carrat, F.; Touvier, M.; Severi, G.; de Lamballerie, X.; Blanché, H.; Deleuze, J.-F.; Gouraud, C. Association of self-reported COVID-19 infection and SARS-CoV-2 serology test results with persistent physical symptoms among French adults during the COVID-19 pandemic. JAMA internal medicine 2022, 182, 19-25.
25. Moreno-Pérez, O.; Merino, E.; Leon-Ramirez, J.-M.; Andres, M.; Ramos, J.M.; Arenas-Jiménez, J.; Asensio, S.; Sanchez, R.; Ruiz-Torregrosa, P.; Galan, I. Post-acute COVID-19 syndrome. Incidence and risk factors: A Mediterranean cohort study. Journal of Infection 2021, 82, 378-383.
26. Augustin, M.; Schommers, P.; Stecher, M.; Dewald, F.; Gieselmann, L.; Gruell, H.; Horn, C.; Vanshylla, K.; Di Cristanziano, V.; Osebold, L. Post-COVID syndrome in non-hospitalised patients with COVID-19: a longitudinal prospective cohort study. The Lancet Regional Health–Europe 2021, 6.
27. Cabrera Martimbianco, A.L.; Pacheco, R.L.; Bagattini, Â.M.; Riera, R. Frequency, signs and symptoms, and criteria adopted for long COVID-19: A systematic review. International journal of clinical practice 2021, 75, e14357.
28. Nabavi, N. Long covid: How to define it and how to manage it. BMJ 2020, 370, m3489, doi:10.1136/bmj.m3489
29. Available online: https://www.umu.se/en/news/research-to-spread-light-on-long-covid-uncertainties_11713455/ (accessed on 2023-01-26).
30. Song, Z.; Giuriato, M. Demographic And Clinical Factors Associated With Long COVID. Health Aff. (Millwood) 2023, 42, 433-442, doi:10.1377/hlthaff.2022.00991
31. Herman, J.D.; Atyeo, C.; Zur, Y.; Cook, C.E.; Patel, N.J.; Vanni, K.M.; Kowalski, E.N.; Qian, G.; Srivatsan, S.; Shadick, N.A.; et al. Humoral immunity to an endemic coronavirus is associated with postacute sequelae of COVID-19 in individuals with rheumatic diseases. Sci. Transl. Med. 2023, 15, eadf6598, doi:10.1126/scitranslmed.adf6598
32. Gil, S.; de Oliveira Júnior, G.N.; Sarti, F.M.; Filho, W.J.; Longobardi, I.; Turri, J.A.O.; Shinjo, S.K.; Ferriolli, E.; Avelino-Silva, T.J.; Busse, A.L.; et al. Acute Muscle Mass Loss Predicts Long-Term Fatigue, Myalgia, and Health Care Costs in COVID-19 Survivors. Journal of the American Medical Directors Association 2023, 24, 10-16, doi:https://doi.org/10.1016/j.jamda.2022.11.013.
33. Wang, S.; Quan, L.; Chavarro, J.E.; Slopen, N.; Kubzansky, L.D.; Koenen, K.C.; Kang, J.H.; Weisskopf, M.G.; Branch-Elliman, W.; Roberts, A.L. Associations of Depression, Anxiety, Worry, Perceived Stress, and

Preprints.org (www.preprints.org) | NOT PEER-REVIEWED | Posted: 26 April 2024 doi:10.20944/preprints202404.1755.v1

Loneliness Prior to Infection With Risk of Post-COVID-19 Conditions. JAMA Psychiatry 2022, 79, 1081-1091, doi:10.1001/jamapsychiatry.2022.2640.

34. Fischer, A.; Zhang, L.; Elbeji, A.; Wilmes, P.; Oustric, P.; Staub, T.; Nazarov, P.V.; Ollert, M.; Fagherazzi, G. Long COVID Symptomatology After 12 Months and Its Impact on Quality of Life According to Initial Coronavirus Disease 2019 Disease Severity. Open Forum Infect Dis 2022, 9, ofac397, doi:10.1093/ofid/ofac397
35. Klein, J.; Wood, J.; Jaycox, J.; Dhodapkar, R.M.; Lu, P.; Gehlhausen, J.R.; Tabachnikova, A.; Greene, K.; Tabacof, L.; Malik, A.A.; et al. Distinguishing features of Long COVID identified through immune profiling. Nature 2023, doi: 10.1038/s41586-41023-06651-y, doi:10.1038/s41586-023-06651-y
36. Hopkins, F.R.; Govender, M.; Svanberg, C.; Nordgren, J.; Waller, H.; Nilsdotter-Augustinsson, A.; Henningsson, A.J.; Hagbom, M.; Sjowall, J.; Nystrom, S.; et al. Major alterations to monocyte and dendritic cell subsets lasting more than 6 months after hospitalization for COVID-19. Front Immunol 2022, 13, 1082912, doi:10.3389/fimmu.2022.1082912
37. Littlefield, K.M.; Watson, R.O.; Schneider, J.M.; Neff, C.P.; Yamada, E.; Zhang, M.; Campbell, T.B.; Falta, M.T.; Jolley, S.E.; Fontenot, A.P.; et al. SARS-CoV-2-specific T cells associate with inflammation and reduced lung function in pulmonary post-acute sequalae of SARS-CoV-2. PLoS Pathog. 2022, 18, e1010359, doi:10.1371/journal.ppat.1010359
38. Wisk, L.E.; Gottlieb, M.A.; Spatz, E.S.; Yu, H.; Wang, R.C.; Slovis, B.H.; Saydah, S.; Plumb, I.D.; O'Laughlin, K.N.; Montoy, J.C.C.; et al. Association of Initial SARS-CoV-2 Test Positivity With Patient-Reported Well-being 3 Months After a Symptomatic Illness. JAMA Netw Open 2022, 5, e2244486, doi:10.1001/jamanetworkopen.2022.44486.
39. Astin, R.; Banerjee, A.; Baker, M.R.; Dani, M.; Ford, E.; Hull, J.H.; Lim, P.B.; McNarry, M.; Morten, K.; O'Sullivan, O.; et al. Long COVID: mechanisms, risk factors and recovery. Exp. Physiol. 2023, 108, 12-27, doi:10.1113/EP090802
40. Badran, B.W.; Huffman, S.M.; Dancy, M.; Austelle, C.W.; Bikson, M.; Kautz, S.A.; George, M.S. A pilot randomized controlled trial of supervised, at-home, self-administered transcutaneous auricular vagus nerve stimulation (taVNS) to manage long COVID symptoms. Res Sq 2022, doi:10.21203/rs.3.rs-1716096/v1
41. Badran, B.W.; Huffman, S.M.; Dancy, M.; Austelle, C.W.; Bikson, M.; Kautz, S.A.; George, M.S. A pilot randomized controlled trial of supervised, at-home, self-administered transcutaneous auricular vagus nerve stimulation (taVNS) to manage long COVID symptoms. Bioelectron Med 2022, 8, 13, doi:10.1186/s42234-022-00094-y
42. Colzato, L.S.; Elmers, J.; Beste, C.; Hommel, B. A Prospect to Ameliorate Affective Symptoms and to Enhance Cognition in Long COVID Using Auricular Transcutaneous Vagus Nerve Stimulation. J Clin Med 2023, 12, doi:10.3390/jcm12031198
43. Oaklander, A.L.; Mills, A.J.; Kelley, M.; Toran, L.S.; Smith, B.; Dalakas, M.C.; Nath, A. Peripheral Neuropathy Evaluations of Patients With Prolonged Long COVID. Neurol Neuroimmunol Neuroinflamm 2022, 9, doi:10.1212/NXI.0000000000001146
44. Klein, J.; Wood, J.; Jaycox, J.; Dhodapkar, R.M.; Lu, P.; Gehlhausen, J.R.; Tabachnikova, A.; Greene, K.; Tabacof, L.; Malik, A.A.; et al. Distinguishing features of Long COVID identified through immune profiling. Nature 2023, doi:10.1038/s41586-023-06651-y
45. Kubankova, M.; Hohberger, B.; Hoffmanns, J.; Furst, J.; Herrmann, M.; Guck, J.; Krater, M. Physical phenotype of blood cells is altered in COVID-19. Biophys. J. 2021, 120, 2838-2847, doi:10.1016/j.bpj.2021.05.025
46. Cervia-Hasler, C.; Brüningk, S.C.; Hoch, T.; Fan, B.; Muzio, G.; Thompson, R.C.; Ceglarek, L.; Meledin, R.; Westermann, P.; Emmenegger, M.; et al. Persistent complement dysregulation with signs of thromboinflammation in active Long Covid. Science 2024, 383, eadg7942, doi:doi:10.1126/science.adg7942.
47. Greene, C.; Connolly, R.; Brennan, D.; Laffan, A.; O'Keeffe, E.; Zaporojan, L.; O'Callaghan, J.; Thomson, B.; Connolly, E.; Argue, R.; et al. Blood–brain barrier disruption and sustained systemic inflammation in individuals with long COVID-associated cognitive impairment. Nature Neuroscience 2024, doi:10.1038/s41593-024-01576-9.
48. Saladino, V.; Algeri, D.; Auriemma, V. The psychological and social impact of Covid-19: new perspectives of well-being. Frontiers in psychology 2020, 11, 577684.
49. Ali, I.; Alharbi, O.M. COVID-19: Disease, management, treatment, and social impact. Science of the total Environment 2020, 728, 138861.

Preprints.org (www.preprints.org) | NOT PEER-REVIEWED | Posted: 26 April 2024 doi:10.20944/preprints202404.1755.v1

50. Long, E.; Patterson, S.; Maxwell, K.; Blake, C.; Pérez, R.B.; Lewis, R.; McCann, M.; Riddell, J.; Skivington, K.; Wilson-Lowe, R. COVID-19 pandemic and its impact on social relationships and health. J Epidemiol Community Health 2022, 76, 128-132.
51. Evans, R.A.; McAuley, H.; Harrison, E.M.; Shikotra, A.; Singapuri, A.; Sereno, M.; Elneima, O.; Docherty, A.B.; Lone, N.I.; Leavy, O.C.; et al. Physical, cognitive, and mental health impacts of COVID-19 after hospitalisation (PHOSP-COVID): a UK multicentre, prospective cohort study. Lancet Respir Med 2021, 9, 1275-1287, doi:10.1016/S2213-2600(21)00383-0.
52. Van Wambeke, E.; Bezler, C.; Kasprowicz, A.M.; Charles, A.L.; Andres, E.; Geny, B. Two-Years Follow-Up of Symptoms and Return to Work in Complex Post-COVID-19 Patients. J Clin Med 2023, 12, doi:10.3390/jcm12030741
53. Aburto, J.M.; Scholey, J.; Kashnitsky, I.; Zhang, L.; Rahal, C.; Missov, T.I.; Mills, M.C.; Dowd, J.B.; Kashyap, R. Quantifying impacts of the COVID-19 pandemic through life-expectancy losses: a population-level study of 29 countries. Int. J. Epidemiol. 2022, 51, 63-74, doi:10.1093/ije/dyab207
54. Hampshire, A.; Chatfield, D.A.; Mphil, A.M.; Jolly, A.; Trender, W.; Hellyer, P.J.; Giovane, M.D.; Newcombe, V.F.J.; Outtrim, J.G.; Warne, B.; et al. Multivariate profile and acute-phase correlates of cognitive deficits in a COVID-19 hospitalised cohort. eClinicalMedicine 2022, 47, doi:10.1016/j.eclinm.2022.101417.
55. Zhao, Y.; Shi, L.; Jiang, Z.; Zeng, N.; Mei, H.; Lu, Y.; Yang, J.; Jin, F.; Ni, S.; Wu, S.; et al. The phenotype and prediction of long-term physical, mental and cognitive COVID-19 sequelae 20 months after recovery, a community-based cohort study in China. Mol. Psychiatry 2023, 28, 1793-1801, doi:10.1038/s41380-023-01951-1
56. Suran, M. Long COVID Linked With Unemployment in New Analysis. JAMA 2023, 329, 701-702, doi:10.1001/jama.2023.015710.1001/jama.2023.0157.
57. Available online: https://www.weforum.org/agenda/2022/08/long-covid-work-economy-united-states-health (accessed on Aug 30, 2022).
58. Available online: https://www.bankofengland.co.uk/speech/2022/may/michael-saunders-speech-at-the-resolution-foundation-event (accessed on 09 May 2022).
59. Available online: https://www.hhs.gov/civil-rights/for-providers/civil-rights-covid19/guidance-long-covid-disability/index.html#footnote3_25o93ze (accessed on July 26, 2021).
60. Hussain, Z.; Rizvi, L.J.; Sheikh, H. The Equality Act (2010)-pre-and post-pandemic historic development on equality and discrimination issues for employers: review of literature. International Journal of Law and Management 2022, 64, 168-183.
61. Available online: https://www.sydney.edu.au/news-opinion/news/2022/06/30/long-covid-presents-a-major-health-challenge-how-can-australia-b.html (accessed on 30 June 2022).
62. Available online: https://www.pennmedicine.org/for-health-care-professionals/for-physicians/covid-information/post-covid19-assessment-and-recovery-clinic-at-penn (accessed on
63. Available online: http://news.china.com.cn/2023-01/13/content_85058563.html (accessed on 2023-01-13).
64. Available online: https://www.canada.ca/en/public-health/news/2022/12/government-of-canada-welcomes-task-force-report-on-post-covid-19-condition.html (accessed on December 14, 2022).
65. Gandjour, A. Long COVID: Costs for the German economy and health care and pension system. BMC Health Services Research 2023, 23, 1-7.
66. Available online: https://www.ukri.org/news/18-5-million-to-tackle-long-covid-in-the-community/ (accessed on 18 February 2021).
67. Available online: https://www.ukri.org/news/uk-japanese-collaboration-to-address-covid-19-challenges/ (accessed on 30 March 2022).
68. Lu, J.Y.; Wilson, J.; Hou, W.; Fleysher, R.; Herold, B.C.; Herold, K.C.; Duong, T.Q. Incidence of new-onset in-hospital and persistent diabetes in COVID-19 patients: comparison with influenza. EBioMedicine 2023, 90, 104487, doi:10.1016/j.ebiom.2023.104487.
69. Xu, A.Y.; Wang, S.H.; Duong, T.Q. Patients with prediabetes are at greater risk of developing diabetes 5 months postacute SARS-CoV-2 infection: a retrospective cohort study. BMJ Open Diabetes Res Care 2023, 11, e003257, doi:10.1136/bmjdrc-2022-003257.
70. Xie, Y.; Al-Aly, Z. Risks and burdens of incident diabetes in long COVID: a cohort study. Lancet Diabetes Endocrinol 2022, doi:10.1016/S2213-8587(22)00044-4.

Preprints.org (www.preprints.org) | NOT PEER-REVIEWED | Posted: 26 April 2024 doi:10.20944/preprints202404.1755.v1

71. Zhang, V.; Fisher, M.; Hou, W.; Zhang, L.; Duong, T.Q. Incidence of New-Onset Hypertension Post-COVID-19: Comparison With Influenza. Hypertension 2023, 80, 2135-2148, doi:10.1161/HYPERTENSIONAHA.123.21174.
72. Lu, J.Y.; Boparai, M.S.; Shi, C.; Henninger, E.M.; Rangareddy, M.; Veeraraghavan, S.; Mirhaji, P.; Fisher, M.C.; Duong, T.Q. Long-term outcomes of COVID-19 survivors with hospital AKI: association with time to recovery from AKI. Nephrol Dial Transplant 2023, doi:10.1093/ndt/gfad020.
73. Zhang, Y.; Zhao, Y.; Wang, J.; Zheng, X.; Xu, D.; Lv, J.; Yang, L. Long-term renal outcomes of patients with COVID-19: a meta-analysis of observational studies. J Nephrol 2023, 36, 2441-2456, doi:10.1007/s40620-023-01731-8.
74. Zhang, S.; Zhou, X.; Chen, Y.; Wang, L.; Zhu, B.; Jiang, Y.; Bu, P.; Liu, W.; Li, D.; Li, Y.; et al. Changes in Home Blood Pressure Monitored Among Elderly Patients With Hypertension During the COVID-19 Outbreak: A Longitudinal Study in China Leveraging a Smartphone-Based Application. Circ Cardiovasc Qual Outcomes 2021, 14, e007098, doi:10.1161/CIRCOUTCOMES.120.007098.
75. Gotanda, H.; Liyanage-Don, N.; Moran, A.E.; Krousel-Wood, M.; Green, J.B.; Zhang, Y.; Nuckols, T.K. Changes in Blood Pressure Outcomes Among Hypertensive Individuals During the COVID-19 Pandemic: A Time Series Analysis in Three US Healthcare Organizations. Hypertension 2022, 79, 2733-2742, doi:10.1161/HYPERTENSIONAHA.122.19861.
76. Bouwmans, P.; Malahe, S.R.K.; Messchendorp, A.L.; Vart, P.; Imhof, C.; Sanders, J.F.; Gansevoort, R.T.; de Vries, A.P.J.; Abrahams, A.C.; Bemelman, F.J.; et al. Post COVID-19 condition imposes significant burden in patients with advanced chronic kidney disease: A nested case-control study. Int J Infect Dis 2024, 142, 106990, doi:10.1016/j.ijid.2024.106990.
77. Etemadifar, M.; Abhari, A.P.; Nouri, H.; Salari, M.; Maleki, S.; Amin, A.; Sedaghat, N. Does COVID-19 increase the long-term relapsing-remitting multiple sclerosis clinical activity? A cohort study. BMC Neurol 2022, 22, 64, doi:10.1186/s12883-022-02590-9.
78. Etemadifar, M.; Sedaghat, N.; Aghababaee, A.; Kargaran, P.K.; Maracy, M.R.; Ganjalikhani-Hakemi, M.; Rayani, M.; Abhari, A.P.; Khorvash, R.; Salari, M.; et al. COVID-19 and the Risk of Relapse in Multiple Sclerosis Patients: A Fight with No Bystander Effect? Mult Scler Relat Disord 2021, 51, 102915, doi:10.1016/j.msard.2021.102915.
79. Montini, F.; Nozzolillo, A.; Tedone, N.; Mistri, D.; Rancoita, P.M.; Zanetta, C.; Mandelli, A.; Furlan, R.; Moiola, L.; Martinelli, V.; et al. COVID-19 has no impact on disease activity, progression and cognitive performance in people with multiple sclerosis: a 2-year study. J Neurol Neurosurg Psychiatry 2023, doi:10.1136/jnnp-2023-332073.
80. Andersen, M.L.; Zegers, F.D.; Jolving, L.R.; Knudsen, T.; Stenager, E.; Norgard, B.M. Patients with multiple sclerosis: COVID-19 related disease activity and hospitalisations based on a nationwide cohort study. Mult Scler Relat Disord 2023, 79, 105031, doi:10.1016/j.msard.2023.105031.
81. Conway, S.E.; Healy, B.C.; Zurawski, J.; Severson, C.; Kaplan, T.; Stazzone, L.; Galetta, K.; Chitnis, T.; Houtchens, M.K. COVID-19 severity is associated with worsened neurological outcomes in multiple sclerosis and related disorders. Mult Scler Relat Disord 2022, 63, 103946, doi:10.1016/j.msard.2022.103946.
82. Hadidchi, R.; Wang, S.H.; Rezko, D.; Henry, S.; Coyle, P.K.; Duong, T.Q. SARS-CoV-2 infection increases long-term multiple sclerosis disease activity and all-cause mortality in an underserved inner-city population. Mult Scler Relat Disord 2024, 86, 105613, doi:10.1016/j.msard.2024.105613.
83. Brown, E.E.; Kumar, S.; Rajji, T.K.; Pollock, B.G.; Mulsant, B.H. Anticipating and Mitigating the Impact of the COVID-19 Pandemic on Alzheimer's Disease and Related Dementias. Am J Geriatr Psychiatry 2020, 28, 712-721, doi:10.1016/j.jagp.2020.04.010.
84. Coolen, T.; Lolli, V.; Sadeghi, N.; Rovai, A.; Trotta, N.; Taccone, F.S.; Creteur, J.; Henrard, S.; Goffard, J.C.; Dewitte, O.; et al. Early postmortem brain MRI findings in COVID-19 non-survivors. Neurology 2020, 95, e2016-e2027, doi:10.1212/WNL.0000000000010116.
85. Boruah, A.P.; Thakur, K.T.; Gadani, S.P.; Kothari, K.U.; Chomba, M.; Guekht, A.; Heydari, K.; Hoo, F.K.; Hwang, S.; Michael, B.D.; et al. Pre-existing neurological conditions and COVID-19 co-infection: Data from systematic reviews, meta-analyses, and scoping reviews. J Neurol Sci 2023, 455, 120858, doi:10.1016/j.jns.2023.120858.
86. Eligulashvili, A.; Gordon, M.; Lee, J.S.; Lee, J.; Mehrotra-Varma, S.; Mehrotra-Varma, J.; Hsu, K.; Hilliard, I.; Lee, K.; Li, A.; et al. Long-term outcomes of hospitalized patients with SARS-CoV-2/COVID-19 with and

Preprints.org (www.preprints.org) | NOT PEER-REVIEWED | Posted: 26 April 2024 doi:10.20944/preprints202404.1755.v1

without neurological involvement: 3-year follow-up assessment. PLoS Med 2024, 21, e1004263, doi:10.1371/journal.pmed.1004263.
87. Li, H.; Qian, J.; Wang, Y.; Wang, J.; Mi, X.; Qu, L.; Song, N.; Xie, J. Potential convergence of olfactory dysfunction in Parkinson's disease and COVID-19: The role of neuroinflammation. Ageing Res Rev 2024, 97, 102288.
88. Bougea, A.; Georgakopoulou, V.E.; Palkopoulou, M.; Efthymiopoulou, E.; Angelopoulou, E.; Spandidos, D.A.; Zikos, P. New-onset non-motor symptoms in patients with Parkinson's disease and post-COVID-19 syndrome: A prospective cross-sectional study. Med Int (Lond) 2023, 3, 23, doi:10.3892/mi.2023.83.
89. Weiss, M.; Gutzeit, J.; Appel, K.S.; Bahmer, T.; Beutel, M.; Deckert, J.; Fricke, J.; Hanss, S.; Hettich-Damm, N.; Heuschmann, P.U.; et al. Depression and fatigue six months post-COVID-19 disease are associated with overlapping symptom constellations: A prospective, multi-center, population-based cohort study. J Affect Disord 2024, 352, 296-305, doi:10.1016/j.jad.2024.02.041.
90. Available online: https://news.cuanschutz.edu/cctsi/nationwide-study-of-long-covid-to-launch-at-university-of-colorado-anschutz-medical-campus (accessed on February 7, 2022).
91. National Research Action Plan on Long COVID. Available online: (accessed on August 2022).
92. Samudyata; Oliveira, A.O.; Malwade, S.; Rufino de Sousa, N.; Goparaju, S.K.; Gracias, J.; Orhan, F.; Steponaviciute, L.; Schalling, M.; Sheridan, S.D.; et al. SARS-CoV-2 promotes microglial synapse elimination in human brain organoids. Mol. Psychiatry 2022, 27, 3939-3950, doi:10.1038/s41380-022-01786-2
93. Adult Stem Cell Therapy for COVID-19 Sequelae Begins in Japan for the First Time in the World.
94. Ra, J.C.; Shin, I.S.; Kim, S.H.; Kang, S.K.; Kang, B.C.; Lee, H.Y.; Kim, Y.J.; Jo, J.Y.; Yoon, E.J.; Choi, H.J.; et al. Safety of intravenous infusion of human adipose tissue-derived mesenchymal stem cells in animals and humans. Stem Cells Dev. 2011, 20, 1297-1308, doi:10.1089/scd.2010.0466
95. Havervall, S.; Marking, U.; Svensson, J.; Greilert-Norin, N.; Bacchus, P.; Nilsson, P.; Hober, S.; Gordon, M.; Blom, K.; Klingstrom, J.; et al. Anti-Spike Mucosal IgA Protection against SARS-CoV-2 Omicron Infection. N. Engl. J. Med. 2022, 387, 1333-1336, doi:10.1056/NEJMc2209651
96. Yan, C.H.; Jang, S.S.; Lin, H.C.; Ma, Y.; Khanwalkar, A.R.; Thai, A.; Patel, Z.M. Use of platelet-rich plasma for COVID-19-related olfactory loss: a randomized controlled trial. Int Forum Allergy Rhinol 2023, 13, 989-997, doi:10.1002/alr.23116
97. Satoh, T.; Trudler, D.; Oh, C.K.; Lipton, S.A. Potential Therapeutic Use of the Rosemary Diterpene Carnosic Acid for Alzheimer's Disease, Parkinson's Disease, and Long-COVID through NRF2 Activation to Counteract the NLRP3 Inflammasome. Antioxidants (Basel) 2022, 11, doi:10.3390/antiox11010124
98. Jha, V. Colchicine to Reduce Coronavirus Disease-19 Related Inflammation and Cardiovascular complications in High-Risk Patients Post-Acute Infection With SARS-COV. 2021.
99. Could low-dose lithium treat long COVID? UB launches clinical trial to find out. Available online: https://www.buffalo.edu/news/releases/2023/01/002.html (accessed on January 6, 2023).
100. Effect of Lithium Therapy on Long COVID Symptoms. Available online: https://www.clinicaltrials.gov/ct2/show/NCT05618587?term=Guttuso&cond=Long+COVID&draw=2&rank=1 (accessed on November 16, 2022).
101. Saunders, C.; Sperling, S.; Bendstrup, E. A new paradigm is needed to explain long COVID. Lancet Respir Med 2023, 11, e12-e13, doi:10.1016/S2213-2600(22)00501-X
102. Fagherazzi, G.; Zhang, L.; Elbeji, A.; Higa, E.; Despotovic, V.; Ollert, M.; Aguayo, G.A.; Nazarov, P.V.; Fischer, A. A voice-based biomarker for monitoring symptom resolution in adults with COVID-19: Findings from the prospective Predi-COVID cohort study. PLOS Digit Health 2022, 1, e0000112, doi:10.1371/journal.pdig.0000112
103. Kovarik, J.J.; Bileck, A.; Hagn, G.; Meier-Menches, S.M.; Frey, T.; Kaempf, A.; Hollenstein, M.; Shoumariyeh, T.; Skos, L.; Reiter, B.; et al. A multi-omics based anti-inflammatory immune signature characterizes long COVID-19 syndrome. iScience 2023, 26, 105717, doi:https://doi.org/10.1016/j.isci.2022.105717.
104. Kuchler, T.; Gunthner, R.; Ribeiro, A.; Hausinger, R.; Streese, L.; Wohnl, A.; Kesseler, V.; Negele, J.; Assali, T.; Carbajo-Lozoya, J.; et al. Persistent endothelial dysfunction in post-COVID-19 syndrome and its associations with symptom severity and chronic inflammation. Angiogenesis 2023, 26, 547-563, doi:10.1007/s10456-023-09885-6

Preprints.org (www.preprints.org) | NOT PEER-REVIEWED | Posted: 26 April 2024 doi:10.20944/preprints202404.1755.v1

105. Krishna, B.A.; Metaxaki, M.; Wills, M.R.; Sithole, N. Reduced Incidence of Long Coronavirus Disease Referrals to the Cambridge University Teaching Hospital Long Coronavirus Disease Clinic. Clin. Infect. Dis. 2023, 76, 738-740, doi:10.1093/cid/ciac630
106. Al-Aly, Z.; Bowe, B.; Xie, Y. Long COVID after breakthrough SARS-CoV-2 infection. Nat. Med. 2022, 28, 1461-1467, doi:10.1038/s41591-022-01840-0.
107. Richard, S.A.; Pollett, S.D.; Fries, A.C.; Berjohn, C.M.; Maves, R.C.; Lalani, T.; Smith, A.G.; Mody, R.M.; Ganesan, A.; Colombo, R.E.; et al. Persistent COVID-19 Symptoms at 6 Months After Onset and the Role of Vaccination Before or After SARS-CoV-2 Infection. JAMA Netw Open 2023, 6, e2251360, doi:10.1001/jamanetworkopen.2022.51360
108. Palmer, C.D.; Scallan, C.D.; Kraemer Tardif, L.D.; Kachura, M.A.; Rappaport, A.R.; Koralek, D.O.; Uriel, A.; Gitlin, L.; Klein, J.; Davis, M.J.; et al. GRT-R910: a self-amplifying mRNA SARS-CoV-2 vaccine boosts immunity for >/=6 months in previously-vaccinated older adults. Nat. Commun. 2023, 14, 3274, doi:10.1038/s41467-023-39053-9

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