# CURRENT AWARENESS BULLETIN

# LONG COVID

# May 2024

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**BACK TO TOP**

## CONTENTS

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## EPIDEMIOLOGY OF LONG COVID

**Jirmanus, L. Z., Valenti, R. M., Griest Schwartzman, E. A., Simon-Ortiz, S. A., Frey, L. I., Friedman, S. R., et al. (2024). Too many deaths, too many left behind: A people's external review of the U.S. centers for disease control and prevention's COVID-19 pandemic response. AJPM Focus, 3(4), 100207.**
The U.S. population has suffered worse health consequences owing to COVID-19 than comparable wealthy nations. COVID-19 had caused more than 1.1 million deaths in the U.S. as of May 2023 and contributed to a 3-year decline in life expectancy. A coalition of public health workers and community activists launched an external review of the Centers for Disease Control and Prevention's pandemic management from January 2021 to May 2023. The authors used a modified Delphi process to identify core pandemic management areas, which formed the basis for a survey and literature review. Their analysis yields 3 overarching shortcomings of the Centers for Disease Control and Prevention's pandemic management: (1) Centers for Disease Control and Prevention leadership downplays the serious impacts and aerosol transmission risks of COVID-19, (2) Centers for Disease Control and Prevention leadership has aligned public guidance with commercial and political interests over scientific evidence, and (3) Centers for Disease Control and Prevention guidance focuses on individual choice rather than emphasizing prevention and equity. Instead, the agency must partner with communities most impacted by the pandemic and encourage people to protect one another using layered protections to decrease COVID-19 transmission. Because emerging variants can already evade existing vaccines and treatments and Long COVID can be disabling and lacks definitive treatment, multifaceted, sustainable approaches to the COVID-19 pandemic are essential to protect people, the economy, and future generations.

**Knuppel, A., Boyd, A., Macleod, J., Chaturvedi, N., & Williams, D. M. (2024). The long COVID evidence gap in england. Lancet, 403.**

**Mandel, H., Yoo, Y., Allen, A., Abedian, S., Verzani, Z., Karlson, E., et al. (2024). Long COVID incidence in adults and children between 2020 and 2023: A real-world data study from the RECOVER initiative. Research Square.**
Estimates of post-acute sequelae of SARS-CoV-2 infection (PASC) incidence, also known as Long COVID, have varied across studies and changed over time. We estimated PASC incidence among adult and pediatric populations in three nationwide research networks of electronic health records (EHR) participating in the RECOVER Initiative using different classification algorithms (computable phenotypes). Overall, 7% of children and 8.5%-26.4% of adults developed PASC, depending on computable phenotype used. Excess incidence among SARS-CoV-2 patients was 4% in children and ranged from 4-7% among adults, representing a lower-bound incidence estimation based on two control groups - contemporary COVID-19 negative and historical patients (2019). Temporal patterns were consistent across networks, with peaks associated with introduction of new viral variants. Our findings indicate that preventing and mitigating Long COVID remains a public health priority. Examining temporal patterns and risk factors of PASC incidence informs our understanding of etiology and can improve prevention and management.

**Ramonfaur, D., Ayad, N., Liu, P. H. Z., Zhou, J., Wu, Y., Li, J., et al. (2024). The global clinical studies of long COVID. International Journal of Infectious Diseases, 107105.**
Long COVID are those who still have symptoms, signs, and conditions after the initial phase of infection of SARS-CoV-2. The incidence of long COVID varies among regions - 31% in North America, 44% in Europe, and 51% in Asia, which is challenging the healthcare system, but there is limited guideline for its treatment. With more and more nation-wide projects funded by the government such as RECOVER initiative in US and NIHR funding in UK, an increasing number of ongoing clinical trials are investigating the efficacy of diverse therapies on reversing long COVID. After searching the WHO International Clinical Trial Registry Platform, 587 clinical studies are identified as long COVID studies. Among these, 312 studies (53.2%) are testing potential therapies. Most of the long COVID trials were conducted in the United States (58 trials [18.6%]), followed by India (55 trials [17.6%]), and Spain (20 trials [6.4%]). Interventions in these clinical trials include physical exercise, rehabilitation therapy, behavioral therapy, and pharmacological therapies including herbs, paxlovid, and fluvoxamine. These trials are aiming to deal with these long COVID symptoms and signs including fatigue, decreased pulmonary function, reduce cognitive function, and others. To date, only 11 of these 312 studies have published their results that were not confirmative unfortunately. Future studies should be designed to address sleep disorders which were seldomly included in registered clinical studies. Moreover, interventions aimed at treating the underlying pathophysiology of long COVID are also necessary but currently lacking.

## PATHOPHYSIOLOGY AND MECHANISM OF LONG COVID

**Apostolou, E., & Rosen, A. (2024). Epigenetic reprograming in myalgic encephalomyelitis/chronic fatigue syndrome: A narrative of latent viruses. *Journal of Internal Medicine.***
Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a chronic disease presenting with severe fatigue, post-exertional malaise, and cognitive disturbances-among a spectrum of symptoms-that collectively render the patient housebound or bedbound. Epigenetic studies in ME/CFS collectively confirm alterations and/or malfunctions in cellular and organismal physiology associated with immune responses, cellular metabolism, cell death and proliferation, and neuronal and endothelial cell function. The sudden onset of ME/CFS follows a major stress factor that, in approximately 70% of cases, involves viral infection, and ME/CFS symptoms overlap with those of long COVID. Viruses primarily linked to ME/CFS pathology are the symbiotic herpesviruses, which follow a bivalent latent-lytic lifecycle. The complex interaction between viruses and hosts involves strategies from both sides: immune evasion and persistence by the viruses, and immune activation and viral clearance by the host. This dynamic interaction is imperative for herpesviruses that facilitate their persistence through epigenetic regulation of their own and the host genome. In the current article, we provide an overview of the epigenetic signatures demonstrated in ME/CFS and focus on the potential strategies that latent viruses-particularly Epstein-Barr virus-may employ in long-term epigenetic reprograming in ME/CFS. Epigenetic studies could aid in elucidating relevant biological pathways impacted in ME/CFS and reflect the physiological variations among the patients that stem from environmental triggers, including exogenous viruses and/or altered viral activity.

**Baig, A. M., Rosko, S., Jaeger, B., Gerlach, J., & Rausch, H. (2024). Unraveling the enigma of long COVID: Novel aspects in pathogenesis, diagnosis, and treatment protocols. *Inflammopharmacology.***
Long COVID, now unmistakably identified as a syndromic entity encompassing a complex spectrum of symptoms, demands immediate resolution of its elusive pathogenic underpinnings. The intricate interplay of diverse factors presents a complex puzzle, difficult to resolve, and thus poses a substantial challenge. As instances of long COVID manifest by repeated infections of SARS-CoV-2 and genetic predisposition, a detailed understanding in this regard is needed. This endeavor is a comprehensive exploration and analysis of the cascading pathogenetic events driven by viral persistence and replication. Beyond its morbidity, long COVID, more disabling than fatal, exacts one of the most substantial tolls on public health in contemporary times, with the potential to cripple national economies. The paper introduces a unified theory of long COVID, detailing a novel pathophysiological framework that interlinks persistent SARS-CoV-2 infection, autoimmunity, and systemic vascular pathology. We posit a model where viral reservoirs, immune dysregulation, and genetic predispositions converge to perpetuate disease. It challenges prevailing hypotheses with new evidence, suggesting innovative diagnostic and therapeutic approaches. The paper aims to shift the paradigm in long COVID research by providing an integrative perspective that encapsulates the multifaceted nature of the condition. We explain the immunological mechanisms, hypercoagulability states, and viral reservoirs in the skull that feed NeuroCOVID in patients with long COVID. Also, this study hints toward a patient approach and how to prioritize treatment sequences in long COVID patients in hospitals and clinics.

**Churchill, N. W., Roudaia, E., Chen, J. J., Sekuler, A., Gao, F., Masellis, M., et al. (2024). Persistent fatigue in post-acute COVID syndrome is associated with altered T1 MRI texture in subcortical structures: A preliminary investigation. *Behavioural Brain Research, 469*, 115045.**
Post-acute COVID syndrome (PACS) is a global health concern and is often associated with debilitating symptoms. Post-COVID fatigue is a particularly frequent and troubling issue, and its underlying mechanisms remain incompletely understood. One potential contributor is micropathological injury of subcortical and brainstem structures, as has been identified in other patient populations. Texture-based analysis (TA) may be used to measure such changes in anatomical MRI data. The present study develops a methodology of voxel-wise TA mapping in subcortical and brainstem regions, which is then applied to T1-weighted MRI data from a cohort of 48 individuals who had PACS (32 with and 16 without ongoing fatigue symptoms) and 15 controls who had cold and flu-like symptoms but tested negative for COVID-19. Both groups were assessed an average of 4-5 months post-infection. There were no significant differences between PACS and control groups, but significant differences were observed within the PACS groups, between those with and without fatigue symptoms. This included reduced texture energy and increased entropy, along with reduced texture correlation, cluster shade and profile in the putamen, pallidum, thalamus and brainstem. These findings provide new insights into the neurophysiological mechanisms that underlie PACS, with altered tissue texture as a potential biomarker of this debilitating condition.

**Cogliandro, V., & Bonfanti, P. (2024). Long COVID: Lights and shadows on the clinical characterization of this emerging pathology. *New Microbiologica, 47*(1), 15-27.**

More than 800 million individuals have contracted SARSCOV2 infection worldwide. It was estimated that almost 10-20% of these might suffer from Long COVID. It is a multisystemic syndrome, which negatively affects the quality of life with a significant burden of health loss compared to COVID negative individuals. Moreover, the risk of sequelae still remains high at 2 years in both nonhospitalized and hospitalized individuals. This review summarizes studies regarding long COVID and clarifies the definitions, the risk factors and the management of this syndrome. Finally, it delves into the most frequent long-term outcomes, especially postural orthostatic tachycardia syndrome" (POTS), myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), brain fog, and their therapeutical possibilities.

**Dhiman, N. R., Joshi, D., Singh, R., Gyanpuri, V., & Kumar, A. (2024). Post-COVID-19 headache- NDPH phenotype: A systematic review of case reports. *Frontiers in Pain Research, 5*, 1376506.**
**Background and objectives**: Post-acute COVID-19 syndrome or "long COVID" affects patients even after the recovery from Covid infection in various ways. Persistent headache or New Daily Persistent Headache (NDPH) is one of such symptoms. In this review, we will discuss about the case-reports of post covid-19 headache- NDPH phenotype both after and in the course of COVID-19 infection. **Methods**: Case reports/studies talked about patients having NDPH around the disease either immediately or late post COVID were included. Data was taken from the source and synthesised on a qualitative basis. **Results**: Literature search showed 3,538 articles, out of which 12 were screened as per the eligibility criteria and finally, 4 case reports on NDPH and Covid-19 were chosen for analysis from the database and by human search. All case reports justify the criteria for acceptability in quality for this systematic review. **Conclusion**: NDPH in and around Covid 19 infection is something that is currently an ingenious debated topic in the scientific community. More case studies should be written and published on the same subject so that a large systematic review could be conducted.

**Falco, P., Litewczuk, D., Di Stefano, G., Galosi, E., Leone, C., De Stefano, G., et al. (2024). Small fibre neuropathy frequently underlies the painful long-COVID syndrome. *Pain.***
**ABSTRACT**: Approximately 10% to 20% of individuals with previous SARS-CoV-2 infection may develop long-COVID syndrome, characterized by various physical and mental health issues, including pain. Previous studies suggested an association between small fibre neuropathy and pain in long-COVID cases. In this case-control study, our aim was to identify small fibre neuropathy in patients experiencing painful long-COVID syndrome. Clinical data, quantitative sensory testing, and skin biopsies were collected from 26 selected patients with painful long-COVID syndrome. We also examined 100 individuals with past COVID-19 infection, selecting 33 patients with painless long-COVID syndrome, characterized mainly by symptoms such as brain fog and fatigue, and 30 asymptomatic post-COVID-19 controls. Demographic and clinical variables were compared among these groups. Among the 26 patients with painful long-COVID syndrome, 12 had skin biopsy and/or quantitative sensory testing abnormalities compatible with small fibre neuropathy. Demographic and clinical data did not differ across patients with small fibre neuropathy, patients with painless long-COVID syndrome, and asymptomatic post-COVID-19 controls. This case-control study showed that approximately 50% of patients experiencing painful long-COVID syndrome had small fibre neuropathy. However, in our patient cohort, this specific post-COVID-19 complication was unrelated to demographic and COVID-19 clinical variables. Approximately half of our sample of patients with painful long-COVID symptoms met diagnostic criteria for small fibre neuropathy. 

**Goldenberg, D. L. (2024). How to understand the overlap of long COVID, chronic fatigue syndrome/myalgic encephalomyelitis, fibromyalgia and irritable bowel syndromes. *Seminars in Arthritis & Rheumatism, 67*, 152455.**
Long COVID should be limited to patients with multiple, persistent symptoms not related to well-defined organ damage. Once redefined, a focused review of long COVID demonstrates striking similarity to chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME), fibromyalgia (FM) and irritable bowel syndrome (IBS). Research in long COVID has revealed similar findings to those noted in CFS/ME and FM, characterized by central nervous system organ dysfunction. Long COVID, like CFS/ME, FM and IBS, is best understood as a bidirectional mind-body, neuroimmune illness.

**Lawson, C. A., Moss, A. J., Arnold, J. R., Bagot, C., Banerjee, A., Berry, C., et al. (2024). Long COVID and cardiovascular disease: A prospective cohort study. *Open Heart, 11*(1).**
**BACKGROUND**: Pre-existing cardiovascular disease (CVD) or cardiovascular risk factors have been associated with an increased risk of complications following hospitalisation with COVID-19, but their impact on the rate of recovery following discharge is not known. **OBJECTIVES**: To determine whether the rate of patient-perceived recovery following hospitalisation with COVID-19 was affected by the presence of CVD or cardiovascular risk factors. **METHODS**: In a multicentre prospective cohort study, patients were recruited following discharge from the hospital with COVID-19 undertaking two comprehensive assessments at 5 months and 12 months. Patients were stratified by the presence of either CVD or cardiovascular risk factors prior to hospitalisation with COVID-19 and compared with controls with neither. Full recovery was determined by the response to a patient-perceived evaluation of full recovery from COVID-19 in the

context of physical, physiological and cognitive determinants of health. **RESULTS**: From a total population of 2545 patients (38.8% women), 472 (18.5%) and 1355 (53.2%) had CVD or cardiovascular risk factors, respectively. Compared with controls (n=718), patients with CVD and cardiovascular risk factors were older and more likely to have had severe COVID-19. Full recovery was significantly lower at 12 months in patients with CVD (adjusted OR (aOR) 0.62, 95% CI 0.43 to 0.89) and cardiovascular risk factors (aOR 0.66, 95% CI 0.50 to 0.86). **CONCLUSION**: Patients with CVD or cardiovascular risk factors had a delayed recovery at 12 months following hospitalisation with COVID-19. Targeted interventions to reduce the impact of COVID-19 in patients with cardiovascular disease remain an unmet need.

**Mussabay, K., Kozhakhmetov, S., Dusmagambetov, M., Mynzhanova, A., Nurgaziyev, M., Jarmukhanov, Z., et al. (2024). Gut microbiome and cytokine profiles in post-COVID syndrome. *Viruses, 16*(5), 05 02.**
Recent studies highlight the crucial role of the gut microbiome in post-infectious complications, especially in patients recovering from severe COVID-19. Our research aimed to explore the connection between gut microbiome changes and the cytokine profile of patients with post-COVID syndrome. Using 16S rRNA amplicon sequencing, we analyzed the composition of the gut microbiome in 60 COVID-19 patients over the course of one year. We also measured the levels of serum cytokines and chemokines using the Milliplex system. Our results showed that severe SARS-CoV-2 infection cases, especially those complicated by pneumonia, induce a pro-inflammatory microbial milieu with heightened presence of Bacteroides, Faecalibacterium, and Prevotella_9. Furthermore, we found that post-COVID syndrome is characterized by a cross-correlation of various cytokines and chemokines MDC, IL-1b, Fractalkine, TNFa, FGF-2, EGF, IL-1RA, IFN-a2, IL-10, sCD40L, IL-8, Eotaxin, IL-12p40, and MIP-1b as well as a shift in the gut microbiome towards a pro-inflammatory profile. At the functional level, our analysis revealed associations with post-COVID-19 in homolactic fermentation, pentose phosphate, NAD salvage, and flavin biosynthesis. These findings highlight the intricate interplay between the gut microbiota, their metabolites, and systemic cytokines in shaping post-COVID symptoms. Unraveling the gut microbiome's role in post-infectious complications opens avenues for new treatments for those patients with prolonged symptoms.

**Olumuyide, E., Agwuegbo, C. C., & Ahmed, E. N. (2024). Exploring the heart failure connection in long COVID patients: A narrative review. *Cureus, 16*(4), e58694.**
In this narrative review, we explore the relationship between long COVID patients and their risk of developing heart failure (HF). Patients with long COVID face a heightened risk of HF, a critical cardiovascular complication linked to the prolonged effects of COVID-19. Clinical manifestations of long COVID-associated HF present diagnostic challenges, complicating patient management. Multidisciplinary care is essential to address these complexities effectively. We found that long COVID can result in various cardiovascular issues including HF. The current view is long COVID leads to HF by activating systemic inflammation by causing endothelial dysfunction, which leads to activation of the complement pathways, tissue factor pathways, and Von Willebrand factor; activation of all these factors leads to venous and arterial thrombosis, which could lead to clogging of blood vessel of the heart leading to cardiovascular complications. The association between long COVID and HF can be challenging despite being recognized as comorbidity because biomarkers are not dependable in determining whether a patient had HF before or after contracting COVID-19. Emerging therapeutic modalities offer hope for improving outcomes, but further research is needed to refine management strategies and mitigate long-term cardiovascular consequences of COVID-19.

**Ruzicka, M., Sachenbacher, S., Heimkes, F., Uebleis, A. O., Karch, S., Grosse-Wentrup, F., et al. (2024). Characterization of cognitive symptoms in post COVID-19 patients. *European Archives of Psychiatry & Clinical Neuroscience.***
Cognitive symptoms (CS) belong to the most common manifestations of the Post COVID-19 (PC) condition. We sought to objectify CS in PC patients using routine diagnostic assessments: neurocognitive testing (NCT) and brain imaging (BI). Further, we investigated possible associations of CS with patient reported outcomes (PROs), and risk factors for developing CS. Clinical data and PROs of 315 PC patients were assessed at a mean of 6 months after SARS-CoV-2 infection. 231 (73.3%) patients reported any sort of CS. Among them, 78 underwent NCT and 55 received BI. In NCT, the cognitive domains most affected were the working memory, attention, and concentration. Nonetheless, pathological thresholds were exceeded only in few cases. Neurocognitive performance did not differ significantly between patients complaining of severe (n = 26) versus non-severe (n = 52) CS. BI findings were abnormal in 8 (14.5%) cases with CS but were most likely not related to PC. Patients reporting high severity of CS scored worse in the PHQ-9, FSS, WHOQOL-BREF, were more likely to report impaired sleep, and had a higher prevalence of psychiatric diagnoses. Overall, NCT could confirm mild impairment in some but not all PC patients with CS, while BI studies were abnormal in only few cases. CS severity did not affect NCT results, but severe CS were associated with symptoms of depression (PHQ-9), fatigue (FSS), reduced quality of life (WHOQOL-BREF) and higher prevalence of psychiatric illnesses. These findings support the importance of NCT, BI, and neuro-psychological assessment in the work-up of PC patients reporting CS.

**Sadowski, J., Klaudel, T., Rombel-Bryzek, A., & Buldak, R. J. (2024). Cognitive dysfunctions in the course of SARS-CoV-2 virus infection, including NeuroCOVID, frontal syndrome and cytokine storm (review). *Biomedical Reports, 21*(1), 103.**
During the coronavirus disease 2019 (COVID-19) pandemic, cognitive impairment of varying degrees of severity began to be observed in a significant percentage of patients. The present study discussed the impact of immunological processes on structural and functional changes in the central nervous system and the related cognitive disorders. The purpose of the present review was to analyse and discuss available information from the scientific literature considering the possible relationship between severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral infection and cognitive impairment, including NeuroCOVID, frontal syndrome and cytokine storm. A systematic literature review was conducted using: Google Scholar, Elsevier and the PubMed database. When searching for materials, the following keywords were used: 'cognitive dysfunctions', 'SARS-CoV-2', 'COVID-19', 'Neuro-SARS2', 'NeuroCOVID', 'frontal syndrome', 'cytokine storm', 'Long COVID-19'. A total of 96 articles were included in the study. The analysis focused on the characteristics of each study's materials, methods, results and conclusions. SARS-CoV-2 infection may induce or influence existing cognitive disorders of various nature and severity. The influence of immunological factors related to the response against SARS-CoV-2 on the disturbance of cerebral perfusion, the functioning of nerve cells and the neuroprotective effect has been demonstrated. Particular importance is attached to the cytokine storm and the related difference between pro- and anti-inflammatory effects, oxidative stress, disturbances in the regulation of the hypothalamic-pituitary-adrenal axis and the stress response of the body.

**Saito, S., Shahbaz, S., Osman, M., Redmond, D., Bozorgmehr, N., Rosychuk, R. J., et al. (2024). Diverse immunological dysregulation, chronic inflammation, and impaired erythropoiesis in long COVID patients with chronic fatigue syndrome. *Journal of Autoimmunity, 147*, 103267.**
A substantial number of patients recovering from acute SARS-CoV-2 infection present serious lingering symptoms, often referred to as long COVID (LC). However, a subset of these patients exhibits the most debilitating symptoms characterized by ongoing myalgic encephalomyelitis or chronic fatigue syndrome (ME/CFS). We specifically identified and studied ME/CFS patients from two independent LC cohorts, at least 12 months post the onset of acute disease, and compared them to the recovered group (R). ME/CFS patients had relatively increased neutrophils and monocytes but reduced lymphocytes. Selective T cell exhaustion with reduced naive but increased terminal effector T cells was observed in these patients. LC was associated with elevated levels of plasma pro-inflammatory cytokines, chemokines, Galectin-9 (Gal-9), and artemin (ARTN). A defined threshold of Gal-9 and ARTN concentrations had a strong association with LC. The expansion of immunosuppressive $CD71^+$ erythroid cells (CECs) was noted. These cells may modulate the immune response and contribute to increased ARTN concentration, which correlated with pain and cognitive impairment. Serology revealed an elevation in a variety of autoantibodies in LC. Intriguingly, we found that the frequency of $2B4^+CD160^+$ and $TIM3^+CD160^+$ $CD8^+$ T cells completely separated LC patients from the R group. Our further analyses using a multiple regression model revealed that the elevated frequency/levels of CD4 terminal effector, ARTN, CEC, Gal-9, CD8 terminal effector, and MCP1 but lower frequency/levels of TGF-beta and MAIT cells can distinguish LC from the R group. Our findings provide a new paradigm in the pathogenesis of ME/CFS to identify strategies for its prevention and treatment.

**Shankar, V., Wilhelmy, J., Curtis, E. J., Michael, B., Cervantes, L., Mallajosyula, V. A., et al. (2024). Oxidative stress is a shared characteristic of ME/CFS and long COVID. *BioRxiv : The Preprint Server for Biology*.**
More than 65 million individuals worldwide are estimated to have Long COVID (LC), a complex multisystemic condition, wherein patients of all ages report fatigue, post-exertional malaise, and other symptoms resembling myalgic encephalomyelitis / chronic fatigue syndrome (ME/CFS). With no current treatments or reliable diagnostic markers, there is an urgent need to define the molecular underpinnings of these conditions. By studying bioenergetic characteristics of peripheral blood lymphocytes in over 16 healthy controls, 15 ME/CFS, and 15 LC, we find both ME/CFS and LC donors exhibit signs of elevated oxidative stress, relative to healthy controls, especially in the memory subset. Using a combination of flow cytometry, bulk RNA-seq analysis, mass spectrometry, and systems chemistry analysis, we also observed aberrations in ROS clearance pathways including elevated glutathione levels, decreases in mitochondrial superoxide dismutase levels, and glutathione peroxidase 4 mediated lipid oxidative damage. Critically, these changes in redox pathways show striking sex-specific trends. While females diagnosed with ME/CFS exhibit higher total ROS and mitochondrial calcium levels, males with an ME/CFS diagnosis have normal ROS levels, but larger changes in lipid oxidative damage. Further analyses show that higher ROS levels correlates with hyperproliferation of T cells in females, consistent with the known role of elevated ROS levels in the initiation of proliferation. This hyperproliferation of T cells can be attenuated by metformin, suggesting this FDA-approved drug as a possible treatment, as also suggested by a recent clinical study of LC patients. Thus, we report that both ME/CFS and LC are mechanistically related and could be diagnosed with quantitative blood cell measurements. We also suggest that effective, patient tailored drugs might be discovered using standard lymphocyte stimulation assays.

**Silva-Passadouro, B., Tamasauskas, A., Khoja, O., Casson, A. J., Delis, I., Brown, C., et al. (2024). A systematic review of quantitative EEG findings in fibromyalgia, chronic fatigue syndrome and long COVID. *Clinical Neurophysiology, 163*, 209-222.**

Fibromyalgia Syndrome (FMS), Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) and Long COVID (LC) are similar multisymptom clinical syndromes but with difference in dominant symptoms in each individual. There is existing and emerging literature on possible functional alterations of the central nervous system in these conditions. This review aims to synthesise and appraise the literature on resting-state quantitative EEG (qEEG) in FMS, ME/CFS and LC, drawing on previous research on FMS and ME/CFS to help understand neuropathophysiology of the new condition LC. A systematic search of MEDLINE, Embase, CINHAL, PsycINFO and Web of Science databases for articles published between December 1994 and September 2023 was performed. Out of the initial 2510 studies identified, 17 articles were retrieved that met all the predetermined selection criteria, particularly of assessing qEEG changes in one of the three conditions compared to healthy controls. All studies scored moderate to high quality on the Newcastle-Ottawa scale. There was a general trend for decreased low-frequency EEG band activity (delta, theta, and alpha) and increased high-frequency EEG beta activity in FMS, differing to that found in ME/CFS. The limited LC studies included in this review focused mainly on cognitive impairments and showed mixed findings not consistent with patterns observed in FMS and ME/CFS. Our findings suggest different patterns of qEEG brainwave activity in FMS and ME/CFS. Further research is required to explore whether there are phenotypes within LC that have EEG signatures similar to FMS or ME/CFS. This could inform identification of reliable diagnostic markers and possible targets for neuromodulation therapies tailored to each clinical syndrome.

## SERVICE PLANNING AND DELIVERY (INC. PATHWAYS, SERVICE EVALUATIONS)

**Bramante, C. T., Beckman, K. B., Mehta, T., Karger, A. B., Odde, D. J., Tignanelli, C. J., et al. (2024). Favorable antiviral effect of metformin on severe acute respiratory syndrome coronavirus 2 viral load in a randomized, placebo-controlled clinical trial of coronavirus disease 2019. *Clinical Infectious Diseases.***

**BACKGROUND**: Metformin has antiviral activity against RNA viruses including severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The mechanism appears to be suppression of protein translation via targeting the host mechanistic target of rapamycin pathway. In the COVID-OUT randomized trial for outpatient coronavirus disease 2019 (COVID-19), metformin reduced the odds of hospitalizations/death through 28 days by 58%, of emergency department visits/hospitalizations/death through 14 days by 42%, and of long COVID through 10 months by 42%. **METHODS**: COVID-OUT was a 2 x 3 randomized, placebo-controlled, double-blind trial that assessed metformin, fluvoxamine, and ivermectin; 999 participants self-collected anterior nasal swabs on day 1 (n = 945), day 5 (n = 871), and day 10 (n = 775). Viral load was quantified using reverse-transcription quantitative polymerase chain reaction. **RESULTS**: The mean SARS-CoV-2 viral load was reduced 3.6-fold with metformin relative to placebo (-0.56 log10 copies/mL; 95% confidence interval [CI], -1.05 to -.06; P = .027). Those who received metformin were less likely to have a detectable viral load than placebo at day 5 or day 10 (odds ratio [OR], 0.72; 95% CI, .55 to .94). Viral rebound, defined as a higher viral load at day 10 than day 5, was less frequent with metformin (3.28%) than placebo (5.95%; OR, 0.68; 95% CI, .36 to 1.29). The metformin effect was consistent across subgroups and increased over time. Neither ivermectin nor fluvoxamine showed effect over placebo. **CONCLUSIONS**: In this randomized, placebo-controlled trial of outpatient treatment of SARS-CoV-2, metformin significantly reduced SARS-CoV-2 viral load, which may explain the clinical benefits in this trial. Metformin is pleiotropic with other actions that are relevant to COVID-19 pathophysiology.

**Buchholz, S., Di Meco, E., Balkowiec-Iskra, E. Z., Sepodes, B., & Cavaleri, M. (2024). Generating clinical evidence for treatment and prevention options for long COVID. *Nature Medicine.***

***Chen*, X., Lu, C., Wang, Q., Pan, X., Zhang, Y., Wang, J., et al. (2024). Traditional, complementary and integrative medicine for fatigue post COVID-19 infection: A systematic review of randomized controlled trials. *Integrative Medicine Research, 13*(2), 101039.**

**Background**: Chronic fatigue is a predominant symptom of post COVID-19 condition, or long COVID. We aimed to evaluate the efficacy and safety of Traditional, Complementary and Integrative Medicine (TCIM) for fatigue post COVID-19 infection. **Methods**: Ten English and Chinese language databases and grey literature were searched up to 12 April 2023 for randomized controlled trials (RCTs). Cochrane "Risk of bias" (RoB) tool was applied. Evidence certainty was assessed using Grading of Recommendations Assessment, Development, and Evaluation (GRADE). Effect estimates were presented as risk ratio (RR) or mean difference (MD) with 95% confidence interval (CI). **Results**: Thirteen RCTs with 1632 participants were included. One RCT showed that Bufei Huoxue herbal capsules reduced fatigue (n=129, MD -14.90,

95%CI -24.53 to -5.27), one RCT reported that Ludangshen herbal liquid lowered fatigue (n=184, MD -1.90, 95%CI -2.38 to -1.42), and the other one RCT shown that fatigue disappearance rate was higher with Ludangshen herbal liquid (n=184, RR 4.19, 95%CI 2.06 to 8.53). Compared to traditional Chinese medicine rehabilitation (TCM-rahab) alone, one RCT showed that fatigue symptoms were lower following Qingjin Yiqi granules plus TCM-rehab (n=388, MD -0.48, 95%CI -0.50 to -0.46). Due to concerns with RoB and/or imprecision, the certainty in this evidence was low to very low. No serious adverse events was reported. **Conclusions**: Limited evidence suggests that various TCIM interventions might reduce post COVID-19 fatigue. Larger, high quality RCTs of longer duration are required to confirm these preliminary findings.

**Chou, R., Herman, E., Ahmed, A., Anderson, J., Selph, S., Dana, T., et al. (2024).** Long COVID definitions and models of care : A scoping review**.** ***Annals of Internal Medicine.***
**BACKGROUND**: Definitions of long COVID are evolving, and optimal models of care are uncertain. **PURPOSE**: To perform a scoping review on definitions of long COVID and provide an overview of care models, including a proposed framework to describe and distinguish models. **DATA SOURCES**: English-language articles from Ovid MEDLINE, PsycINFO, the Cochrane Library, SocINDEX, Scopus, Embase, and CINAHL published between January 2021 and November 2023; gray literature; and discussions with 18 key informants. **STUDY SELECTION**: Publications describing long COVID definitions or models of care, supplemented by models described by key informants. **DATA EXTRACTION**: Data were extracted by one reviewer and verified for accuracy by another reviewer. **DATA SYNTHESIS**: Of 1960 screened citations, 38 were included. Five clinical definitions of long COVID varied with regard to timing since symptom onset and the minimum duration required for diagnosis; 1 additional definition was symptom score-based. Forty-nine long COVID care models were informed by 5 key principles: a core "lead" team, multidisciplinary expertise, comprehensive access to diagnostic and therapeutic services, a patient-centered approach, and providing capacity to meet demand. Seven characteristics provided a framework for distinguishing models: home department or clinical setting, clinical lead, collocation of other specialties, primary care role, population managed, use of teleservices, and whether the model was practice- or systems-based. Using this framework, 10 representative practice-based and 3 systems-based models of care were identified. **LIMITATIONS**: Published literature often lacked key model details, data were insufficient to assess model outcomes, and there was overlap between and variability within models. **CONCLUSION**: Definitions of long COVID and care models are evolving. Research is needed to optimize models and evaluate outcomes of different models.

**Gorenshtein, A., Liba, T., Leibovitch, L., Stern, S., & Stern, Y. (2024).** Intervention modalities for brain fog caused by long-COVID: Systematic review of the literature**.** ***Neurological Sciences.***
Individuals suffering from long-COVID can present with "brain fog", which is characterized by a range of cognitive impairments, such as confusion, short-term memory loss, and difficulty concentrating. To date, several potential interventions for brain fog have been considered. Notably, no systematic review has comprehensively discussed the impact of each intervention type on brain fog symptoms. We included studies on adult (aged > 18 years) individuals with proven long- COVID brain-fog symptoms from PubMed, MEDLINE, Central, Scopus, and Embase. A search limit was set for articles published between 01/2020 and 31/12/2023. We excluded studies lacking an objective assessment of brain fog symptoms and patients with preexisting neurological diseases that affected cognition before COVID-19 infection. This review provided relevant information from 17 studies. The rehabilitation studies utilized diverse approaches, leading to a range of outcomes in terms of the effectiveness of the interventions. Six studies described noninvasive brain stimulation, and all showed improvement in cognitive ability. Three studies described hyperbaric oxygen therapy, all of which showed improvements in cognitive assessment tests and brain perfusion. Two studies showed that the use of Palmitoylethanolamide and Luteolin (PEA-LUT) improved cognitive impairment. Noninvasive brain stimulation and hyperbaric oxygen therapy showed promising results in the treatment of brain fog symptoms caused by long-COVID, with improved perfusion and cortical excitability. Furthermore, both rehabilitation strategies and PEA-LUT administration have been associated with improvements in symptoms of brain fog. Future studies should explore combinations of interventions and include longer follow-up periods to assess the long-term effects of these treatments.

**Jones, F., Domeny, A., Fish, J., Leggat, F., Patel, I., McRae, J., et al. (2024).** Using co-design methods to develop new personalised support for people living with long covid: The 'LISTEN' intervention**.** ***Health Expectations, 27*****(3), e14093**.
**INTRODUCTION**: Many Covid-19 survivors are living with unresolved, relapsing and remitting symptoms and no 'one size' of treatment is likely to be effective for everyone. Supported self-management for the varied symptoms of Long Covid (LC) is recommended by the National Institute for Health and Care Excellence in the United Kingdom. We aimed to develop a new personalised support intervention for people living with LC using a structured co-design framework to guide replication and evaluation. **METHODS**: We used the improvement methodology, Experience-Based Co-Design, in an accelerated form to harness the collective experiences of people with LC. Incorporating evidence from 'Bridges Self-Management' (Bridges) an approach in which healthcare professionals (HCPs)are trained to support knowledge, confidence and skills of individuals living with long term conditions. Co-designed resources are also central to Bridges.

Adults who self-identified as living with or recovered from LC, from England or Wales, aged 18 years and over were recruited, and HCPs, with experience of supporting people with LC. Participants took part in a series of small co-design group meetings and larger mixed meetings to agree priorities, core principles and generate resources and intervention content. **RESULTS**: People with LC (n = 28), and HCPs (n = 9) supported co-design of a book (hard-copy and digital form) to be used in 1:1 support sessions with a trained HCP. Co-design stages prioritised stories about physical symptoms first, and psychological and social challenges which followed, nonlinear journeys and reconceptualising stability as progress, rich descriptions of strategies and links to reputable advice and support for navigating healthcare services. Co-design enabled formulation of eight core intervention principles which underpinned the training and language used by HCPs and fidelity assessments. **CONCLUSION**: We have developed a new personalised support intervention, with core principles to be used in one-to-one sessions delivered by trained HCPs, with a new co-designed book as a prompt to build personalised strategies and plans using narratives, ideas, and solutions from other people with LC. Effectiveness and cost effectiveness of the 'LISTEN' intervention will be evaluated in a randomised controlled trial set within the context of the updated Framework for Developing and Evaluating Complex Interventions. **PATIENT AND PUBLIC CONTRIBUTION**: The LISTEN Public and Patient Involvement (PPI) group comprised seven people living with LC. They all contributed to the design of this study and five members were part of a larger co-design community described in this paper. They have contributed to this paper by interpreting stages of intervention design and analysis of results. Three members of our PPI group are co-authors of this paper.

**Krumholz, H. M., Sawano, M., Bhattacharjee, B., Caraballo, C., Khera, R., Li, S., et al. (2024). The PAX LC trial: A decentralized, phase 2, randomized, double-blind study of nirmatrelvir/ritonavir compared with placebo/ritonavir for long COVID. *American Journal of Medicine.***
**INTRODUCTION**: Individuals with long COVID lack evidence-based treatments and have difficulty participating in traditional site-based trials. Our digital, decentralized trial investigates the efficacy and safety of nirmatrelvir/ritonavir, targeting viral persistence as a potential cause of long COVID. **METHODS**: The PAX LC trial (NCT05668091) is a Phase 2, 1:1 randomized, double-blind, superiority, placebo-controlled trial in 100 community-dwelling, highly symptomatic adult participants with long COVID residing in the 48 contiguous US states to determine the efficacy, safety, and tolerability of 15 days of nirmatrelvir/ritonavir compared with placebo/ritonavir. Participants are recruited via patient groups, cultural ambassadors, and social media platforms. Medical records are reviewed through a platform facilitating participant-mediated data acquisition from electronic health records nationwide. During the drug treatment, participants complete daily digital diaries using a web-based application. Blood draws for eligibility and safety assessments are conducted at or near participants' homes. The study drug is shipped directly to participants' homes. The primary endpoint is the PROMIS-29 Physical Health Summary Score difference between baseline and Day 28, evaluated by a mixed model repeated measure analysis. Secondary endpoints include PROMIS-29 (Mental Health Summary Score and all items), Modified GSQ-30 with supplemental symptoms questionnaire, COVID Core Outcome Measures for Recovery, EQ-5D-5L (Utility Score and all items), PGIS 1 and 2, PGIC 1 and 2, and healthcare utilization. The trial incorporates immunophenotyping to identify long COVID biomarkers and treatment responders. **CONCLUSION**: The PAX LC trial uses a novel decentralized design and a participant-centric approach to test a 15-day regimen of nirmatrelvir/ritonavir for long COVID.

**Marcella, M., Luca, C., Nicoletta, B., Elisa, Z., & Francesca, L. F. (2024). Heart rate variability modulation through slow paced breathing in healthcare workers with long-COVID: A case-control study. *American Journal of Medicine.***
**BACKGROUND**: Long-COVID is a syndrome persisting 12+ weeks after COVID-19 infection, impacting life and work ability. Autonomic nervous system imbalance has been hypothesised as the cause. This study aims to investigate cardiovascular autonomic function in health care workers (HCWs) with Long-COVID and the effectiveness of slow paced breathing SPB on autonomic modulation. **METHODS**: From 1st December 2022 to 31th March 2023, 6655 HCWs of the University Hospitals of Trieste (Northeast Italy) were asked to participate the study by company-email. Inclusion/exclusion criteria were assessed. Global health status and psychosomatic disorders were evaluated through validated questionnaires. Heart rate variability was assessed by finger-photoplethysmography during spontaneous breathing (SB) and SPB, which stimulate vagal response. Long-COVID-HCWs (G1) were contrasted with never infected (G2) and fully recovered COVID-19 workers (G3). **RESULTS**: 126 HCWs were evaluated. The. 58 Long-COVID were assessed at a median time since COVID-19 of 419.5 days (IQR 269-730) and had significantly more psychosomatic symptoms and lower detectability of spontaneous systolic pressure oscillation at 0.1 Hz (Mayer wave - baroreflex arc) during SB compared to 53 never-infected and 14 fully-recovered HCWs (19%, 42% and 40%, respectively, p=0.027). During SPB, the increase in this parameter was close to controls (91.2%, 100% and 100%, respectively, p=0.09). No other differences in HRV parameters were found among groups. **CONCLUSIONS**: Resting vascular modulation was reduced in Long-COVID, while during SPB baroreflex sensitivity effectively improved. Long-term studies are needed to evaluate whether multiple sessions of breathing exercises can restore basal vascular reactivity and reduce cardiovascular risk in these patients.

**Naik, H., Cooke, E., Boulter, T., Dyer, R., Bone, J. N., Tsai, M., et al. (2024). Low-dose naltrexone for post-COVID fatigue syndrome: A study protocol for a double-blind, randomised trial in british columbia. *BMJ Open, 14*(5), e085272.**
**INTRODUCTION**: A significant proportion of individuals suffering from post COVID-19 condition (PCC, also known as long COVID) can present with persistent, disabling fatigue similar to myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) and post-viral fatigue syndromes. There remains no clear pharmacological therapy for patients with this subtype of PCC, which can be referred to as post-COVID fatigue syndrome (PCFS). A low dose of the opioid antagonist naltrexone (ie, low-dose naltrexone (LDN)) has emerged as an off-label treatment for treating fatigue and other symptoms in PCC. However, only small, non-controlled studies have assessed LDN in PCC, so randomised trials are urgently required. **METHODS AND ANALYSIS**: A prospective, randomised, double-blind, parallel arm, placebo-controlled phase II trial will be performed to assess the efficacy of LDN for improving fatigue in PCFS. The trial will be decentralised and open to eligible individuals throughout the Canadian province of British Columbia (BC). Participants will be recruited through the province-wide Post-COVID-19 Interdisciplinary Clinical Care Network (PC-ICCN) and research volunteer platform (REACH BC). Eligible participants will be 19-69 years old, have had a confirmed or physician-suspected SARS-CoV-2 infection at least 3 months prior and meet clinical criteria for PCFS adapted from the Institute of Medicine ME/CFS criteria. Individuals who are taking opioid medications, have a history of ME/CFS prior to COVID-19 or history of significant liver disease will be excluded. Participants will be randomised to an LDN intervention arm (n=80) or placebo arm (n=80). Participants in each arm will be prescribed identical capsules starting at 1 mg daily and follow a prespecified schedule for up-titration to 4.5 mg daily or the maximum tolerated dose. The trial will be conducted over 16 weeks, with assessments at baseline, 6, 12 and 16 weeks. The primary outcome will be fatigue severity at 16 weeks evaluated by the Fatigue Severity Scale. Secondary outcomes will include pain Visual Analogue Scale score, overall symptom severity as measured by the Patient Phenotyping Questionnaire Short Form, 7-day step count and health-related quality of life measured by the EuroQol 5-Dimension questionnaire.

**Palacio, A., Bast, E., Klimas, N., & Tamariz, L. (2024). Lessons learned in implementing a multidisciplinary long COVID clinic. *American Journal of Medicine.***
The diagnosis and treatment of long COVID patients is challenging. Our aim is to share lessons learned using a multidisciplinary approach within the Veterans Affairs system. Our long COVID clinic is based in primary care but has imbedded rehabilitations specialists, nutrition. whole health and different specialists within internal medicine. We conduct an extensive work-up to evaluate the presence of end-organ damage, ongoing inflammation and dysautonomia. Our treatments are based on the prior experience that the VA system has on chronic fatigue syndrome and gulf war illness.

**Spiesshoefer, J., Regmi, B., Senol, M., Jorn, B., Gorol, O., Elfeturi, M., et al. (2024). Potential diaphragm muscle weakness-related dyspnea persists two years after COVID-19 and could be improved by inspiratory muscle training: Results of an observational and an interventional trial. *American Journal of Respiratory & Critical Care Medicine.***
**RATIONALE**: Diaphragm muscle weakness might underly persistent exertional dyspnea despite normal lung/cardiac function in individuals previously hospitalized for acute COVID-19 illness. **OBJECTIVES**: Firstly, to determine the persistence and pathophysiological nature of diaphragm muscle weakness and its association with exertional dyspnea two years after hospitalization for COVID-19, and secondly to investigate the impact of inspiratory muscle training (IMT) on diaphragm and inspiratory muscle weakness and exertional dyspnea in individuals with long COVID. **METHODS**: ~2 years after hospitalization for COVID-19, 30 individuals (11 female, median age 58 [interquartile range (IQR) 51-63] years) underwent comprehensive (invasive) respiratory muscle assessment and evaluation of dyspnea. Eighteen with persistent diaphragm muscle weakness and exertional dyspnea were randomized to 6 weeks of IMT or sham training; assessments were repeated immediately after and 6 weeks after IMT completion. The primary endpoint was change in inspiratory muscle fatiguability immediately after IMT. **RESULTS**: At median 31 [IQR 23-32] months after hospitalization, 21/30 individuals reported relevant persistent exertional dyspnea. Diaphragm muscle weakness on exertion and reduced diaphragm cortical activation were potentially related to exertional dyspnea. Compared with sham control, IMT improved diaphragm and inspiratory muscle function (sniff transdiaphragmatic pressure 83 [IQR 75-91] vs. 100 [IQR 81-113] cmH2O; p=0.02), inspiratory muscle fatiguability (time to task failure 365 [IQR 284-701] vs. 983 [IQR 551-1494] sec; p=0.05), diaphragm voluntary activation index (79 [IQR 63-92] vs 89 [IQR 75-94]%; p=0.03), and dyspnea (Borg score 7 [IQR 5.5-8] vs. 6 [IQR 4-7]; p=0.03); improvements persisted for 6 weeks after IMT completion. **CONCLUSIONS**: This study is the first to identify a potential treatment for persisting exertional dyspnea in long COVID, and provide a possible pathophysiological explanation for the treatment benefit.

**Sunkersing, D., Ramasawmy, M., Alwan, N. A., Clutterbuck, D., Mu, Y., Horstmanshof, K., et al. (2024). What is current care for people with long COVID in england? A qualitative interview study. *BMJ Open, 14*(5), e080967.**

**OBJECTIVE**: To investigate current care for people with Long COVID in England. **DESIGN**: In-depth, semistructured interviews with people living with Long COVID and Long COVID healthcare professionals; data analysed using thematic analysis. **SETTING**: National Health Service England post-COVID-19 services in six clinics from November 2022 to July 2023. **PARTICIPANTS**: 15 healthcare professionals and 21 people living with Long COVID currently attending or discharged (18 female; 3 male). **RESULTS**: Health professionals and people with lived experience highlighted the multifaceted nature of Long COVID, including its varied symptoms, its impact on people's lives and the complexity involved in managing this condition. These impacts encompass physical, social, mental and environmental dimensions. People with Long COVID reported barriers in accessing primary care, as well as negative general practitioner consultations where they felt unheard or invalidated, though some positive interactions were also noted. Peer support or support systems proved highly valuable and beneficial for individuals, aiding their recovery and well-being. Post-COVID-19 services were viewed as spaces where overlooked voices found validation, offering more than medical expertise. Despite initial challenges, healthcare providers' increasing expertise in diagnosing and treating Long COVID has helped refine care approaches for this condition. **CONCLUSION**: Long COVID care in England is not uniform across all locations. Effective communication, specialised expertise and comprehensive support systems are crucial. A patient-centred approach considering the unique complexities of Long COVID, including physical, mental health, social and environmental aspects is needed. Sustained access to post-COVID-19 services is imperative, with success dependent on offering continuous rehabilitation beyond rapid recovery, acknowledging the condition's enduring impacts and complexities.

**Torres, F., Shedd, C., Kaza, V., Bollineni, S., Banga, A., Mohanka, M. R., et al. (2024). Outpatient management of post-COVID syndrome - single center experience. *Heart & Lung, 67*, 137-143.**
**BACKGROUND**: COVID patients continue to experience unremitting symptoms that extend far beyond the initial illness. While there is rapid accumulation of data on acute COVID treatment in hospitalized patients, little is known regarding post-COVID management. **OBJECTIVES**: To describe our center's experience treating post-COVID sub-syndromes encountered in Post-COVID Lung Clinic. **METHODS**: We retrospectively reviewed data on 98 post-COVID patients evaluated in our clinic between 07/01/2020-12/31/2022. We encountered three distinct post-COVID subtypes: 1) respiratory complaints associated with increased O2 requirements and abnormal CT findings (post-COVID interstitial lung disease [ILD]), 2) respiratory complaints associated with tachycardia (post-COVID dyspnea-tachycardia syndrome [DTS]). Post-COVID ILD patients (n = 28) received steroids in combination with cell cycle inhibitor (mycophenolate mofetil-MMF). Post-COVID DTS patients (n = 16) were treated with metoprolol. 3) A third, undifferentiated group presented with mild respiratory complaints and normal spirometry (n = 17) and was followed in clinic without initiation of a specific treatment. **RESULTS**: In treated post-COVID ILD patients, mean oxygen requirements at rest (1.96 +/- 1.79 L/NC) decreased to 0.89 +/- 1.29 L/NC at 6 months follow-up, p = 0.005. In patients with post-COVID DTS, mean heart rate at rest decreased (98 +/- 15 bpm to 79 +/- 11 bpm) at 6 months follow-up, p = 0.023. 60 % of patients reported an improvement in exertional dyspnea. **CONCLUSIONS**: Our descriptive study presents a single center outpatient COVID-19 clinic experience. We encountered 3 post-COVID sub-syndromes and describe their treatments: post-COVID interstitial lung disease [ILD] treated with a novel regimen of MMF and steroids, post COVID dyspnea-tachycardia syndrome [DTS] treated with metoprolol, and a third subgroup with mild undifferentiated symptoms without specific treatment.

**Zheng, Z. S., Simonian, N., Wang, J., & Rosario, E. R. (2024). Transcutaneous vagus nerve stimulation improves long COVID symptoms in a female cohort: A pilot study. *Frontiers in Neurology [Electronic Resource], 15*, 1393371.**
**Background**: Long COVID, also known as Post-COVID-19 syndrome, is characterized by multisystemic symptoms that persists for weeks to years beyond acute infection. It disproportionately affects women and those with pre-existing anxiety/depression, conditions more prevalent in females. The vagus nerve, with its extensive innervation and regulation of critical bodily functions, has become a focal point for therapeutic interventions. Transcutaneous vagus nerve stimulation (t-VNS) has emerged as a promising non-invasive treatment for COVID-19 conditions. **Methods**: This pilot study assessed the efficacy of t-VNS in 24 female Long COVID patients (45.8 +/- 11.7 years old; 20.2 +/- 7.1 months since infection), who underwent a 10-day t-VNS intervention at home (30 min/session, twice a day). Cognition was considered the primary outcome, with anxiety, depression, sleep, fatigue, and smell as secondary outcomes. Outcomes were measured at baseline, post-intervention, and 1-month follow-up. **Results**: Significant improvements were observed in various cognitive functions, anxiety, depression, and sleep at post-intervention, with benefits remaining or progressing at 1-month follow-up. Improvements in fatigue were delayed, reaching statistical significance at 1-month follow-up compared to baseline. No significant changes were noted in olfactory performance. **Conclusion**: This pilot study provides preliminary evidence supporting the potential of t-VNS as a therapeutic intervention for female Long COVID patients. The encouraging results justify further rigorous investigation through larger, randomized controlled trials to confirm the efficacy of t-VNS, assess its generalizability to male cohorts, and explore biological markers to inform personalized treatment approaches. Our findings support the allocation of resources to conduct such trials and advance the understanding of t-VNS as a potential treatment for Long COVID.

## PSYCHO-SOCIAL IMPACTS OF LONG COVID (INC. WORK, EDUCATION, QOL)

**Burton-Fisher, W., & Gordon, K. (2024). Holding the hope? therapist and client perspectives on long COVID recovery: A Q-methodology. *British Journal of Health Psychology.***

**PURPOSE**: Long COVID is a global health concern which has debilitating effects on the individual experiencing it. In the United Kingdom, psychological therapies are being offered to people with long COVID, although the evidence for these therapies is yet to be demonstrated. This research aimed to understand how therapists and clients define and understand recovery from long COVID, and use hope theory to interpret the results. **METHODS**: An online Q-methodology was employed, where participants sorted a range of statements pertaining to long COVID recovery based on their level of agreement with them. These arranged statements (Q-sorts) were collated and factor analysed to explore and compare underlying perspectives. **RESULTS**: Sixteen participants were recruited for the study, including eleven clients, four IAPT therapists and one therapist working in the broader long COVID pathway. A four-factor model is reported, including (1) Psychological Pathways to Recovery, (2) Social Context and Agency, (3) Physiological Goals of Recovery and (4) Personal Meaning Making. All IAPT therapists loaded onto the psychological pathways factor, whereas the remaining participants shared more diverse perspectives. **CONCLUSIONS**: The belief that long COVID recovery was possible, taken as an indicator of hopefulness, was rated highest for Factor 1, Psychological Pathways to Recovery, and Factor 3, Physiological Recovery Goals. This suggested that having a clear definition of recovery, or clear guidance on how to intervene, promoted hopefulness and, theoretically, well-being. However, clients reported experiences of being invalidated and disbelieved by health professionals, with psychological explanations sometimes being experienced as dismissive and invalidating. Clinical implications and future research directions are discussed.

**Kalinowski, J., Hintz, E. A., & Izeogu, C. (2024). The untapped power of "we don't know": Epistemological humility in the era of COVID-19. *Journal of Patient Experience, 11*.**

The SARS-CoV-2 (COVID-19) pandemic introduced many challenges and nuances that have transformed medical practice and research. The uncertainty caused by COVID-19 led to inevitable challenges to patient-provider relationships. The ever-changing landscape of COVID-19 research and policy proved to be challenging for the medical community and patients. These challenges also exacerbated long-standing issues regarding patient-provider communication and trust. On the other hand, these challenges gave voice to a burgeoning patient advocacy community. Through social media, advocacy and patient organizing, patients harnessed their power and organized over challenges relating to COVID-19 fears and concerns, ramifications of "Long COVID," and much more. During this unprecedented pandemic, there was a realization that the science and research surrounding COVID-19 is evolving and that there may be a benefit to embracing the dynamic nature of research and the scientific process. We propose that providers and the medical community should consider epistemological humility, which acknowledges insufficiencies related to the state of medical knowledge with a sense of understanding and respect for not having all of the answers. We argue that there is untapped potential in saying, "We don't know" and explaining why. There is an implicit culture that providers should be responsible for knowing everything and solving every problem. Epistemological humility challenges this culture, and inherently gives credence and voice to patient perspectives. We assert that epistemological humility is necessity when addressing contemporary health challenges such as COVID-19.

**Sanal-Hayes, N. E. M., Mclaughlin, M., Hayes, L. D., Berry, E. C. J., & Sculthorpe, N. F. (2024). Examining well-being and cognitive function in people with long covid and ME/CFS, and age-matched healthy controls: A case-case-control study. *American Journal of Medicine.***

**PURPOSE**: Well-being and cognitive function had not previously been compared between people with long COVID and people with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS). Therefore, this study examined well-being and cognitive function in people with long COVID (~16 months illness duration; n= 17) and ME/CFS (~16 years illness duration; n=24), versus age-matched healthy controls (n=16). **METHODS**: Well-being was examined using several questionnaires, namely the Health Visual Analogue Scale (VAS), Fatigue Severity Scale (FSS), Post-exertional malaise (PEM), Pittsburgh Sleep Quality Index (PSQI), European Quality of Life-5 Domains (EQ-5D), MRC Dyspnoea, Self-Efficacy (SELTC), The Edinburgh Neurosymptoms Questionnaire (ENS), General Anxiety Disorder 7 (GAD-7), and Patient Health Questionnaire 9 (PHQ-9). Cognitive function was examined using Single Digit Modalities Test (SDMT), Stroop test, and Trails A and B. These were delivered via a mobile application (app) built specifically for this remote data collection. **RESULTS**: The main findings of the present investigation were that people with ME/CFS and people with long COVID were generally comparable on all well-being and cognitive function measures, but self-reported worse values for pain, fatigue, Post-exertional malaise, sleep quality, general well-being in relation to mobility, usual activities, self-care, breathlessness, neurological symptoms, self-efficacy, and other well-being such as anxiety and depression, compared to controls. There was no effect of group for cognitive function measures. **CONCLUSIONS**: These data suggest that both

people with long COVID and people with ME/CFS have similar impairment on well-being measures examined herein. Therefore, interventions that target well-being of people with ME/CFS and long COVID are required.

### NEW/UPDATED GUIDELINES, POLICIES AND REPORTS

**ME Association, An Incomplete Picture: Understanding the Burden of Long Covid, May 2024**
This report, supported by Pfizer and created by Economist Impact, investigates the burden of long Covid globally and in eight countries of focus, analysing the societal, economic and health system challenges posed by this disease. The report examines national priorities and guidelines and the local healthcare system's response to long Covid and emphasises the need for multidisciplinary, patient-centred care provision and integrated policy frameworks to address long Covid. By researching the complexities of long Covid, this report serves as a resource for healthcare professionals, policymakers and stakeholders seeking to understand and address the multifaceted implications of this condition.

**AHRQ, Long Covid Models of Care, April 2024**
The Agency for Healthcare Research and Quality (AHRQ) published a Technical Brief summarizing definitions of long COVID and describing what is known about long COVID models of care. The brief includes models currently in use, promising approaches, advantages and disadvantages of models in different populations and settings, barriers and facilitators to implementation, access and equity issues, and needed research.

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