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# Neurological Factors and Gastrointestinal Health in Post-Acute COVID-19 Syndrome (PACS)

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**ABSTRACT**

Post-acute COVID-19 syndrome, often known as "long COVID," results from the global COVID-19 pandemic and is defined by the persistence of clinical symptoms long after the original infection has faded. In this study, the complex connection between mental health and gastrointestinal function in the setting of post-acute COVID-19 syndrome was explored. The study, based on clinical data and evaluations of the relevant literature, highlights the enormous effect of neurological and neuropsychiatric disorders on patients' lives. Not only do many symptoms like weariness, cognitive impairment and sleep difficulties persist long after the acute phase of the disease has gone, but they tend to worsen with time. The research also examines the incidence of depression after COVID-19 infection, looking at potential risk variables such as age, gender and inflammatory status. Individuals recuperating from COVID-19 experience heightened sensitivity to psychological distress owing to variables including isolation, financial instability and delayed schooling, highlighting the epidemic's more considerable social and economic repercussions. This investigation also sheds insight into the function of systemic inflammation and microbiota dysbiosis in post-acute COVID-19 syndrome and the intricate relationship between the gut and the brain. The study highlights the critical need for a multifaceted strategy for addressing this illness, calling for coordinated medical, psychological and social therapies. Essential components of a comprehensive plan to address the various issues faced by post-acute COVID-19 syndrome include access to healthcare services, mental health support, financial aid and possibilities for social reintegration. To improve the quality of life for people dealing with the fallout of this unprecedented global health crisis, a deeper understanding of the interplay between psychological and social factors and gastrointestinal health is required.

**KEYWORDS**

COVID-19, post-acute COVID-19 syndrome (PACS), gastrointestinal health, psychological health, white blood cells



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## INTRODUCTION

Several other clinical symptoms surfaced after the worldwide COVID-19 epidemic that persisted long after the initial infection had subsided. Post-acute COVID-19 syndrome, often known as "long COVID," is characterized by a complex interplay between the immune and gastrointestinal systems[1,2]. For those recovering from COVID-19, there is mounting evidence that psychological and social variables play a critical role in determining gastrointestinal health. The relationship between the brain and the rest of the body has always piqued the interest of scientists and medical professionals[3,4]. Recent years have seen a dramatic uptick in the acknowledgment of the importance of psychological and social considerations in the context of physical health. Multiple physiological reactions, including changes in the immune system, hormone balance and even gastrointestinal health, have been related to stress, anxiety, depression and other psychological factors. In post-acute COVID-19 syndrome[5,6], research into the interplay between emotional well-being and digestive function has become more important. This in-depth study explores the complex relationships between mental health and digestive function in the setting of post-acute COVID-19 syndrome. This study intends to provide insight into the underlying processes via which psychological moods and experiences affect the gastrointestinal well-being of persons recovering from COVID-19 by synthesizing previous research, clinical data and theoretical frameworks. In addition, this study investigates prospective therapies and therapy techniques that reduce the impact of psychological variables on GI health, thereby enhancing the quality of life for people dealing with the after effects of COVID-19. To better understand the full implications of the COVID-19 pandemic and to guide targeted interventions and support strategies for affected individuals, it is crucial to disentangle the complex relationships between psychosocial factors and gastrointestinal health[7]. Through this in-depth investigation, it is hoped that this study will contribute useful insights to the developing landscape of post-acute COVID-19 syndrome, illuminating the complex interplay between the brain and the digestive system and the long-term health issues experienced by those who have survived this unprecedented global health crisis[8].

## METHODOLOGY

A systematic and comprehensive approach was employed to identify relevant studies exploring the intricate relationship between psychosocial factors and gastrointestinal health in post-acute COVID-19 syndrome. This search strategy was conducted in three distinct steps to ensure a thorough review of the existing literature. On October 20, 2023, an initial limited search was performed across prominent databases, including Google Scholar and PubMed. The objective was to identify preliminary keywords and gain an overview of the available literature on the topic. A rigorous search strategy was implemented. Electronic databases, including PubMed, Embase and the Web of Sciences, were systematically explored. The search strategy incorporated a combination of the following keywords: "Long COVID," "long hauliers," "post-acute COVID," "chronic COVID syndrome," "late sequela COVID" and "persistent COVID." The boolean operators (AND, OR) were utilized to refine the search results.

**Prevalence of post COVID-19 neurological symptoms:** There was a dramatic increase in illness and deaths due to the acute coronavirus disease 2019 (COVID-19). Persistent symptoms after COVID-19 infection, also known as post-COVID-19 syndrome or COVID-19 long-haul symptoms, are a significant concern. Patients with mild, moderate and severe forms of the original COVID-19 sickness have all shown these symptoms[1,2]. Previous studies have emphasized "post-acute" or protracted COVID-19 symptoms, which remain or develop 4-12 weeks after the beginning of acute COVID-19. However, there still needs to be more in-depth data on neurological symptoms that persist or appear three months or longer after the first COVID-19 infection. Signs and symptoms that appear during or after an infection consistent with COVID-19, persist for more than 12 weeks (3 months) and cannot be explained by an alternative diagnosis" are what constitute post-COVID-19 syndrome, as defined by the National Institute for Health and Care Excellence (NICE). After a six-month (long-term) evaluation, researchers found that neurological

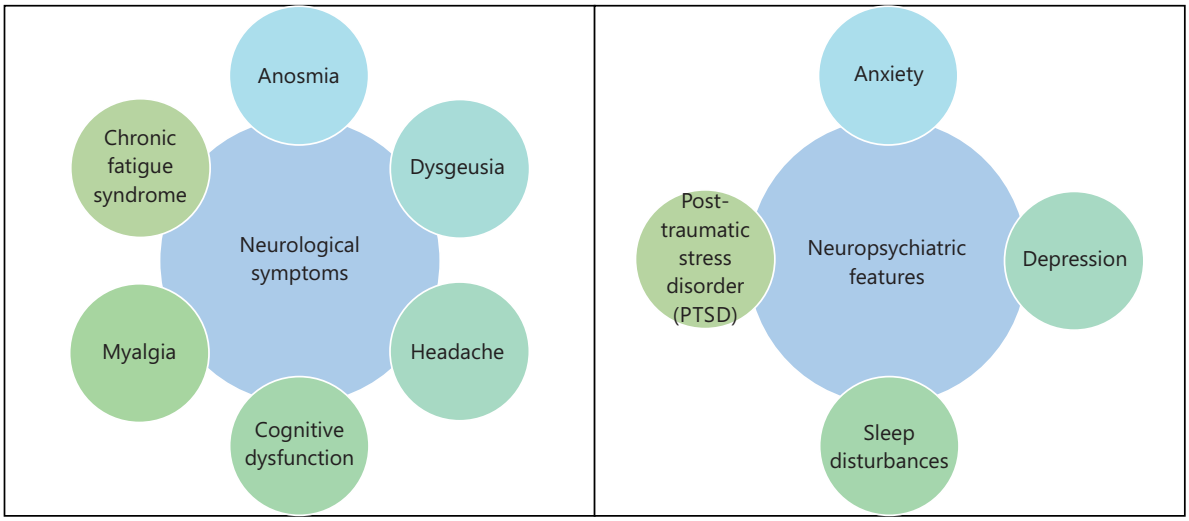


Fig. 1: Neurological and neuropsychiatric symptoms of post-COVID-19 syndrome[21-32]

and psychosocial symptoms of post-COVID-19 syndrome were more common than during the three- to six-month assessment (mid-term)[9,10]. This was the case for both short-term and long-term assessments. Between the midterm and long-term follow-up periods, there was not a significant difference (less than 5% difference) in the prevalence of anosmia[3,4], dysgeusia, myalgia, or cognitive impairment. On the other hand, the bulk of neuropsychiatric symptoms, such as anxiety and depression, were significantly higher in the long term compared to the mid-term study[11] (Fig. 1).

Neurological and psychological symptoms are prevalent three months after an acute COVID-19 infection, according to a meta-analysis of data from over 10,000 individuals taken from 18 research[12]. Nearly a third of patients reported neurological/neuropsychiatric post-COVID-19 syndrome three months after the beginning of acute COVID-19 disease, with the most common signs being fatigue, cognitive dysfunction (brain fog, memory difficulties, attention difficulty) and sleep abnormalities. Strangely, these symptoms persisted and were much more common when assessed at the mid-term (3 to 6 months) than at the long-term (6 months or more after infection) duration[13]. Consequently, post-COVID-19 syndrome is a significant and persistent public health concern for individuals globally, regardless of whether they are in a hospital or not (Table 1). Extensive variability was seen in studies that documented cognitive impairment, which includes memory issues[14]. Present study's pooled prevalence estimates are less precise than they might be due to inconsistencies in the classifications of cognitive impairment, brain fog, memory difficulties and attention disturbance[15]. Additional research should use a defined definition of "cognitive dysfunction" and use quantitative neurological testing to identify particular deficiencies (memory, spatial, sensorineural).

Despite being prevalent neurological indications of acute COVID-19, another research found that anosmia, dysgeusia and headache often resolved by post-COVID-19. A retrospective study of 3,737 patients found that 68% regained their sense of smell and 73% their sense of taste after six weeks of symptom start among those who had anosmia and/or dysgeusia during acute COVID-19. However, the percentage of patients who had recovered dropped after three months, reaching a plateau after around 20 weeks. Similarly[16], current data shows that anosmia and dysgeusia are often just short-term symptoms of COVID-19 and do not persist or arise for the first time in most patients after 3 months. Notably, the sample of patients exhibited an increase in the occurrence of symptoms such as anxiety, sadness, brain fog, tiredness and sleeplessness during the mid-term to long-term follow-up. This suggests that these symptoms may emerge rather than persist post-infection[17]. However, it's important to consider that (1) Inconsistent definitions of 'cognitive dysfunction' may have artificially inflated findings at both time

Table 1: Longitudinal effects of COVID-19: Clinical markers for monitoring, stratified by degree of participation[33]

| Level of involvement | Clinical indicators |
|---|---|
| Psychological, neuropsychiatric and cognitive | Anxiety, depression, dysphoria, panic attacks, hallucinations, paranoia, anorexia, insomnia/sleep apnea, post-traumatic stress disorder and obsessive-compulsive disorder, neurocognitive impairment, memory disorder, attention disorder, brain fog, psychiatric morbidity and incoherent thoughts-confusion/disorientation |
| Gastrointestinal | Abdominal pain, digestive disorder, gastroesophageal reflux, vomiting, constipation, diarrhea, ulcer and liver damage |
| Dermatological | Hair loss, skin peeling, dermatography, petechiae, swelling and discoloration of extremities, COVID toes and red spots on feet |
| Cardiovascular | New hypertension, myocarditis, arrhythmia, tachycardia, bradycardia, palpitations, pericardial effusion, diastolic dysfunction, swollen veins and stroke |
| Respiratory and pulmonary | Pulmonary embolism, pulmonary infarcts, pulmonary fibrosis, altered spirometry, thoracic abnormalities, pulmonary hypertension, impaired lung function, dyspnea/polypnea and wheezing |
| Immune and endocrine | Diabetes mellitus and severe allergic reaction |
| Gynecologic and urologic | Bladder control problems and menstrual problems |
| Ears, nose and throat and ophthalmologic | Sinusitis, hyposmia, anosmia, hypogeusia, dysgeusia, hearing loss and phonophobia |
| Musculoskeletal functionality | Arthralgia, myalgia, tiredness and poor walking performance |

points and (2) The prevalence of symptoms common in the general population, even in the absence of COVID-19 (such as headache and fatigue), is likely overstated, especially in the long term. This is due to the insufficient data available for calculating uncertainties associated with the prevalence of mid- to long-term symptoms[18]. Large retrospective cohort studies that followed patients for an extended period of time still indicate comparable tendencies in the neuropsychiatric and neurological symptoms documented here. There may be both biological and psychological causes for chronic symptoms[19]. Long-term retention of SARS-CoV-2 RNA in brain tissue, for instance, may exacerbate neuronal death. In addition, the infiltration of innate immune cells due to blood-brain barrier failure may elongate neuro-inflammation. Post-infection neuropsychiatric symptoms, notably insomnia, have strong ties to factors such as social isolation, incarceration, trauma during acute infection and chronic exhaustion[20].

**Prevalence of post COVID-19 depressive symptoms:** The neurocognitive impairment that was seen throughout the acute phase of the COVID-19 study did not act as a mediator of depression. In post-COVID-19 syndrome, however, depressive symptoms substantially affected neurocognitive performance. A group of COVID-19 patients with no neurological difficulties served as a control for another group of COVID-19 patients who experienced neurological complications throughout their hospital stay[34]. After 6.7 months had passed since the beginning of the neurological symptoms, there was no discernible difference in the depression levels of the 2 groups. Patients with depression were shown to tend to perform worse on neurocognitive tests compared to patients who did not have depression in two different investigations that evaluated the connection between depression and neurocognitive performance in post-COVID-19 syndrome[35]. As a prevalent component of the post-COVID-19 syndrome, people often reported experiencing depressive symptoms and depression of a clinically relevant level. Sex, a prior psychiatric history and psychopathology at the one-month follow-up were some factors related to the development and frequency of depression[36]. Common risk factors for depression in the general population include female sex, a history of depression in the family and other mental diseases. In particular, female sex is a risk factor for depression. However, the results of the studies on the role of age as a moderator were mixed[37].

Platelet count, neutrophil count and lymphocyte count (SII) at baseline and their variation over time were shown to predict depression symptoms at 3 months post-discharge. The research reveals that the inflammation level in individuals with COVID-19 is related to the severity of symptoms during the acute phase. Acute COVID-19 severity (i.e., severity of symptoms and amount of care needed) was not linked with a greater incidence of depressed symptoms in post-COVID-19 syndrome in this study[38]. Similarly,

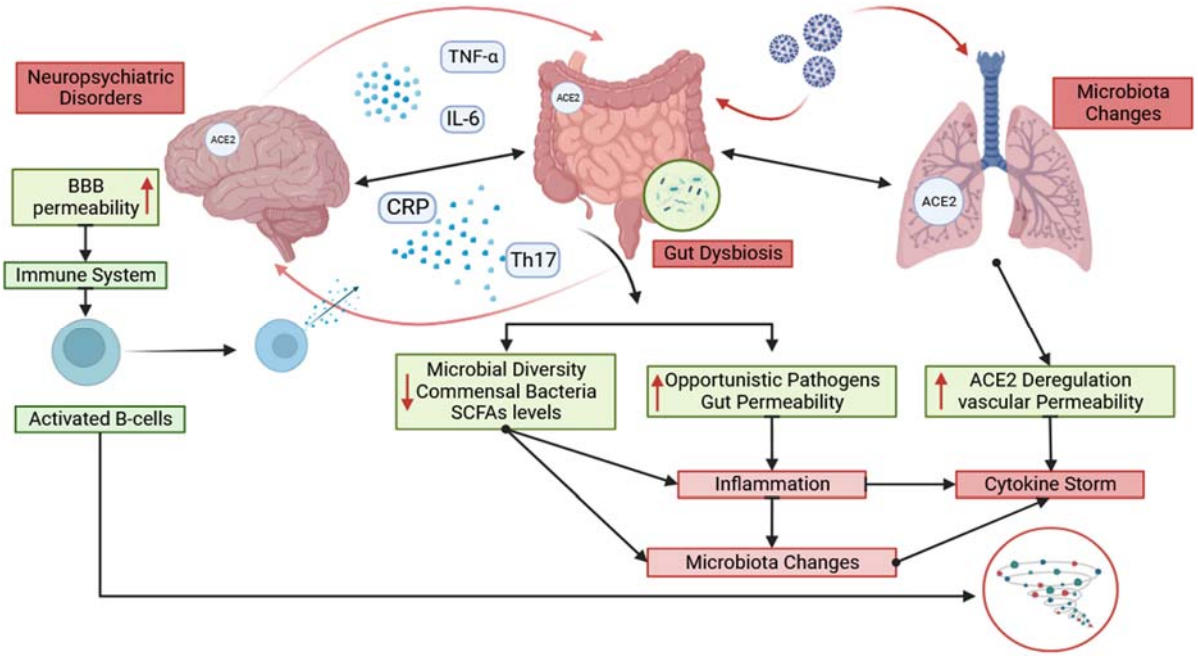


Fig. 2: Mechanisms involving microbiome shifts and neuropsychiatric disorders in COVID-19, ACE2: Angiotensin-converting enzyme 2, Interleukin-6 (IL-6), Tumor Necrosis Factor-Alpha (TNF-α), SCFA: Short-chain fatty acid, C-Reactive Protein (CRP) and Blood-brain-barrier (BBB)[52,53]

there was no long-term increase in the prevalence of depressed symptoms after hospitalization for COVID-19 associated with neurological problems compared to hospitalization without such complications. Regarding the severity of COVID-19 symptoms, it is yet unknown whether there is a correlation between preexisting systemic inflammation and depressed symptomatology in post-COVID-19 syndrome[39]. If depression is a symptom of the post-COVID-19 syndrome, then the systemic inflammation that develops after an acute infection only partially explains. It has been suggested that COVID-19 may cause chronic low-grade inflammation because it produces a hyperinflammatory state. More precisely, IL-6 was shown to be the most often reported cytokine raised in COVID-19 patients, along with TNF-, IFN-, IL-2, IL-4, IL-6, IL-10 and CRP. As a bonus, the correlation between depression and inflammation has been extensively studied[40]. Studies have shown that people with mood symptoms and disorders have higher than average levels of pro-inflammatory cytokines such as interleukin-6 (IL-6) (Fig. 2).

It is crucial to do longitudinal research with COVID-19 patients and a control group that is not infected with the virus in order to compare the prevalence of depression in the general population to that in post-COVID-19 syndrome. Sadly, a non-infected control group was only included in one of the experiments. Importantly, evaluation dates did not always line up with the classification of post-COVID-19 syndrome, even though the results showed that COVID-19 patients had a greater prevalence of depression. Evaluation times averaged 126 days after diagnosis and varied from 12 to 215 days. Therefore, it is recommended to use care when drawing conclusions from this study[41].

The 6 months after a COVID-19 diagnosis, the rate of mood disorders was higher than the rate of mood disorders after influenza or other respiratory tract illnesses. As this retrospective chart review did not give data on depression per se, its findings still lend credence to the idea that SARS-CoV-2 infection raises the risk for depression over the long term, notwithstanding our decision to exclude them from our results. In conclusion, post-COVID-19 syndrome patients may be more vulnerable to the impact of social,

economic and geographical variables on the emergence and maintenance of depressive symptoms. The epidemic has caused several problems, including isolation, loss of income and housing stability and the shutdown of schools[42].

**Microbiota dysbiosis in COVID-19:** A shotgun metagenomic analysis of faecal samples from 15 COVID-19 patients, spanning from admission to discharge, revealed an enrichment of harmful opportunistic bacteria and a decrease in beneficial symbiotic bacteria[43]. The severity of COVID-19 was primarily associated with the Firmicutes phylum, wherein *Coprobacillus*, *Clostridium ramosum* and *Clostridium hathewayi* showed positive correlations, while *Faecalibacterium prausnitzii, Faecalibacterium* and *Alistipes onderdonkii* of the Bacteroides phylum displayed negative correlations[44].

Another study indicated that moderate to severe COVID-19 patients exhibited a lower Firmicutes/Bacteroidetes ratio, increased Proteobacteria and reduced Lachnospiraceae and Actinobacteria compared to mild patients[45]. Furthermore, the research highlighted the higher abundance of *Collinsella aerofaciens, Collinsella tanakaei* and *Streptococcus infantis* in faecal samples from highly infectious SARS-CoV-2 individuals, while *Parabacteroides merdae, Alistipes onderdonkii, Bacteroides stercoris* and *Lachnospiraceae bacterium 1_1_57FAA* were more prevalent in cases with low to no infection[46].

A recent investigation found that COVID-19 patients exhibited increased levels of *Ruminococcus gnavus, Eggerthella, Coprobacillus, Lachnospiraceae bacterium 2_1_58 FAA* and *Clostridium ramosum,* but decreased levels of *Alistipes_sp_AP11*, *Roseburia intestinalis*, *Eubacterium hallii*, *Alistipes indistinctus*, *Coprobacter fastidiosus* and *Alistipes shahii*. In mice, SARS-CoV-2 was observed to reduce microbial diversity[47].

Additionally, 16S rRNA gene sequencing in SARS-CoV-2-positive patients revealed a low abundance of *Bifidobacterium*, *Collinsella* and *Streptococcus* alongside high levels of *Bacteroidetes* and *Enterobacteriaceae*. Critical patients also displayed deficiencies in *Faecalibacterium* and *Roseburia*. These findings suggest that COVID-19 patients experience lower microbial diversity, a decrease in commensal bacteria and an increase in opportunistic pathogens compared to healthy individuals[48]. This dysbiosis in the microbiota may persist even after SARS-CoV-2 respiratory clearance. Some studies indicated higher levels of Proteobacteria and lower levels of Actinobacteria in COVID-19 patients, while *Bifidobacterium, Collinsella* and *Streptococcus* was less abundant[49]. Conversely, other research reported an increased abundance of Actinobacteria and higher productivity of *Bifidobacterium*, *Streptococcus* and *Lactobacillus*. The interplay of factors such as ethnicity, diet, COVID-19 severity and treatment may contribute to these variations[50].

Fungi comprise less than 1% of the human microbiome yet regulate microbial balance and inflammation. Research found 66 fungus species in healthy faeces, with *Saccharomyces, Candida* and *Cladosporium* being the most common[5]. The COVID-19 patients had greater intestinal *Candida albicans, Candida auris* and *Aspergillus flavus* levels than controls at all times. In a study examining the fecal fungal microbiome of individuals with COVID-19, it was observed that the diversity of mycobiome escalated during hospitalization and continued to persist even after the clearance of SARS-CoV-2 in nasopharyngeal samples and the resolution of respiratory symptoms. *Candida albicans* mainly induce antifungal Th17 cells. Intestinal inflammation increases total *Candida albicans* and Th17 cells. The IBD is rife with *Candida,* which contributes to celiac disease. Following this research, COVID-19 patients' high *Candida albicans* levels during hospitalizations may indicate intestinal inflammation. Another intestinal mycobiota study in COVID-19 and H1N1 patients found that patients had an increased intestinal fungal load, fewer fungal species with crucial functions and more pathogenic opportunistic fungi than healthy controls.

*Ascomycota* and *Basidiomycota* were practically depleted. Cross-sectional research examined COVID-19 patients' intestinal mycobiota by severity. Unlike the bacterial microbiome, a single species dominated the fungal gut microbiota in most severely sick COVID-19 patients[51].

Patients with severe/critical COVID-19 disease had less gut mycobiota variety, evenness and richness but more Ascomycota. A substantial part of the human gut mycobiota is Ascomycota and Basidiomycota, indicating that the typical intestinal fungal ecosystem is destroyed. The different outcomes of this research may be due to age, sex and dietary habits. COVID-19 gut mycobiota needs further investigation. Some scientists believe intestinal mycobiota affects extraintestinal organs. The gut-lung, gut-brain and other axes may predict illness severity and prognosis via intestinal fungi and their extraintestinal targets. Cross-sectional research examined COVID-19 patients' intestinal mycobiota by seriousness. Unlike the bacterial microbiome, a single species dominated the fungal gut microbiota in most critically sick individuals. Along with the bacterial and mycobiota, the gut microbiome includes the virome. The human gut virome is highly personalized and stable. Phages make up about 90% of it, along with eukaryotic viruses. Symbiotic bacteria and bacteriophages, eukaryotic viruses and plant-derived viruses maintain the intestinal barrier and motility. A tiny amount of literature has examined COVID-19 patients' gut virome. First, mice tests checked the enterovirus group composition and variance in COVID-19 patients. The COVID-19 patients had more bacteriophages (Inoviridae and Microviridae), plant-RNA viruses, cucumber green mottle mosaic viruses and unclassified viruses and antibiotic therapy did not change enteroviruses. A metagenomic sequencing investigation examined faecal DNA and RNA viromes. Inflammation, stress and toxicity genes were more prevalent in SARS-CoV-2-infected faeces. In the study, SARS-CoV-2 infection significantly influenced enterovirus, whereas condition, sex and age had little effect. Eight DNA viruses negatively linked with COVID-19 severity and blood inflammatory indicators such as CRP, LDH and neutrophils, demonstrating that enteroviruses may modulate host immunological responses to SARS-CoV-2 infection. Compared to healthy controls, COVID-19 patients have less crass-like bacteriophages. Despite some variation, enteroviruses and bacterial communities like Tectiviridae and Microviridae, Tectiviridae and Bacteroidaceae have comparable relative abundance ranges and trends. The 3 bacteria (*Bacteroides vulgatus*, *Faecalibacterium prausnitzii* and *Ruminococcus gnavus*) and 3 microviridae bacteriophages were significant in virus-bacterial community interactions. While each virome is unique, its structure and variety match the gut flora. First, bacteria may destroy phage nucleic acid and other anti-bacteriophages and inhibit biofilm adsorption. Bacteriophages impact bacterial behaviour by transferring genes in the host inflammatory state. In the gut, bacteriophages and bacteria co-evolve[53]. Bacteria lysate OM-85 inhibits intestinal epithelial cells and down-regulates SARS-CoV-2 receptors in COVID-19 patients.

## CONCLUSION

The research concludes by exploring the complex link between mental health and digestive function in the setting of post-acute COVID-19 syndrome. The results show that many people have neurological and neuropsychiatric symptoms even after the acute phase of the illness has passed. Significantly, post-COVID-19 syndrome symptoms such as exhaustion, cognitive impairment and sleep irregularities persisted and even worsened over time. The studies also show how these symptoms are complicated, with varying rates of occurrence and duration across various neurological and psychiatric aspects. The results of this research provide important new information on the incidence and causes of depression after COVID-19, highlighting the roles played by characteristics such as gender, previous mental history and inflammation. There is mounting evidence that systemic inflammation plays a role in the development of post-acute COVID-19 syndrome; nevertheless, the link between inflammation and depressive symptomatology is complex and far from understood. Completely assessing the frequency and long-term impact of depression in post-COVID-19 syndrome requires longitudinal research comparing infected individuals with non-infected control groups. Beyond its immediate health effects, the study highlights

the larger ramifications of the COVID-19 pandemic. Patients with post-COVID-19 syndrome are susceptible to developing and persisting depression symptoms for a variety of socioeconomic and geographical reasons. Individuals recuperating from COVID-19 are more susceptible to psychological distress because of issues including isolation, loss of money, housing instability and interruptions in schooling. Ultimately, the findings of this research highlight the critical need for a multifaceted strategy for treating post-acute COVID-19 syndrome, including medical, psychological and social therapies. Healthcare practitioners and politicians may improve gastrointestinal health via the development of focused therapies and support systems if they have a thorough grasp of the complex interaction between psychological and social variables. Not only do people infected with COVID-19 need access to medical care, but they also need access to mental health services, financial aid and opportunities to reintegrate into society.

## SIGNIFICANCE STATEMENT

The relationship between mental health and GI function in long-term COVID patients is the focus of this study. Findings show that symptoms of neurological and psychotic disorders continue and even increase after acute COVID-19 has passed. Increased psychological distress owing to isolation, financial instability and school interruption was highlighted among survivors and the research reveals risk variables for depression, such as age, gender and inflammatory condition. Furthermore, the study highlights the gut-brain relationship and explores systemic inflammation as well as microbial dysbiosis. The results highlight the intricate relationship between psychological, social and gastrointestinal factors in chronic COVID, providing important information for all-encompassing treatments to tackle its enduring impacts.

## REFERENCE

1. Logue, J.K., N.M. Franko, D.J. McCulloch, D. McDonald, A. Magedson, C.R. Wolf and H.Y. Chu, 2021. Sequelae in adults at 6 months after COVID-19 infection. JAMA Network Open, Vol. 4. 10.1001/jamanetworkopen.2021.0830.
2. Venkatesan, P., 2021. NICE guideline on long COVID. Lancet Respir. Med., Vol. 9. 10.1016/S2213-2600(21)00031-X.
3. Gupta, A., M.V. Madhavan, K. Sehgal, N. Nair and S. Mahajan *et al*., 2020. Extrapulmonary manifestations of COVID-19. Nat. Med., 26: 1017-1032.
4. Singh, K.K., G. Chaubey, J.Y. Chen and P. Suravajhala, 2020. Decoding SARS-CoV-2 hijacking of host mitochondria in COVID-19 pathogenesis. Am. J. Physiol. Cell Physiol., 319: C258-C267.
5. Dixon, L., C. McNamara, P. Gaur, D. Mallon and C. Coughlan *et al*., 2020. Cerebral microhaemorrhage in COVID-19: A critical illness related phenomenon? Stroke Vasc. Neurol., Vol. 5. 10.1136/svn-2020-000652.
6. Buzhdygan, T.P., B.J. DeOre, A. Baldwin-Leclair, T.A. Bullock and H.M. McGary *et al*., 2020. The SARS-CoV-2 spike protein alters barrier function in 2D static and 3D microfluidic *in-vitro* models of the human blood-brain barrier. Neurobiol. Dis., Vol. 146. 10.1016/j.nbd.2020.105131.
7. Crook, H., S. Raza, J. Nowell, M. Young and P. Edison, 2021. Long COVID-mechanisms, risk factors, and management. BMJ, Vol. 374. 10.1136/bmj.n1648.
8. Taquet, M., J.R. Geddes, M. Husain, S. Luciano and P.J. Harrison, 2021. 6-month neurological and psychiatric outcomes in 236 379 survivors of COVID-19: A retrospective cohort study using electronic health records. Lancet Psychiatry, 8: 416-427.
9. Nguyen, N.N., van Thuan Hoang, J.C. Lagier, D. Raoult and P. Gautret, 2021. Long-term persistence of olfactory and gustatory disorders in COVID-19 patients. Clin. Microbiol. Infect., 27: 931-932.
10. Estiri, H., Z.H. Strasser, G.A. Brat and Y.R. Semenov, 2021. Evolving phenotypes of non-hospitalized patients that indicate long COVID. BMC Med., Vol. 19. 10.1186/s12916-021-02115-0.
11. Najjar, S., A. Najjar, D.J. Chong, B.K. Pramanik and C. Kirsch *et al*., 2020. Central nervous system complications associated with SARS-CoV-2 infection: Integrative concepts of pathophysiology and case reports. J. Neuroinflammation, Vol. 17. 10.1186/s12974-020-01896-0.

12. Wu, K.E., F.M. Fazal, K.R. Parker, J. Zou and H.Y. Chang, 2020. RNA-GPS predicts SARS-CoV-2 RNA residency to host mitochondria and nucleolus. Cell Syst., 11: 102-108.E3.
13. Theoharides, T.C., C. Cholevas, K. Polyzoidis and A. Politis, 2021. Long-COVID syndrome associated brain fog and chemofog: Luteolin to the rescue. BioFactors, 47: 232-241.
14. Morin, C.M., B. Bjorvatn, F. Chung, B. Holzinger and M. Partinen *et al*., 2021. Insomnia, anxiety, and depression during the COVID-19 pandemic: An international collaborative study. Sleep Med., 87: 38-45.
15. Mikkelsen, M.E., J.D. Christie, P.N. Lanken, R.C. Biester and B.T. Thompson *et al*., 2012. The adult respiratory distress syndrome cognitive outcomes study: Long-term neuropsychological function in survivors of acute lung injury. Am. J. Respir. Crit. Care Med., 185: 1307-1315.
16. Rawal, G., S. Yadav and R. Kumar, 2017. Post-intensive care syndrome: An overview. J. Transl. Intern. Med., 5: 90-92.
17. Poloni, T.E., V. Medici, M. Moretti, S.D. Visonà and A. Cirrincione *et al*., 2021. COVID-19-related neuropathology and microglial activation in elderly with and without dementia. Brain Pathol., Vol. 31. 10.1111/bpa.12997.
18. Solomon, I.H., E. Normandin, S. Bhattacharyya, S.S. Mukerji and K. Keller *et al*., 2020. Neuropathological features of Covid-19. N. Engl. J. Med., 383: 989-992.
19. Huth, S.F., S.M. Cho, C. Robba, D. Highton and D. Battaglini *et al*., 2021. Neurological manifestations of coronavirus disease 2019: A comprehensive review and meta-analysis of the first 6 months of pandemic reporting. Front. Neurol., Vol. 12. 10.3389/fneur.2021.664599.
20. Generoso, J.S., J.L.B. de Quevedo, M. Cattani, B.F. Lodetti and L. Sousa *et al*., 2021. Neurobiology of COVID-19: How can the virus affect the brain? Braz. J. Psychiatry, 43: 650-664.
21. Augustin, M., P. Schommers, M. Stecher, F. Dewald and L. Gieselmann *et al*., 2021. Post-COVID syndrome in non-hospitalised patients with COVID-19: A longitudinal prospective cohort study. Lancet Reg. Health-Europe, Vol. 6. 10.1016/j.lanepe.2021.100122.
22. Bellan, M., D. Soddu, P.E. Balbo, A. Baricich and P. Zeppegno *et al*., 2021. Respiratory and psychophysical sequelae among patients with COVID-19 four months after hospital discharge. JAMA Network Open, Vol. 4. 10.1001/jamanetworkopen.2020.36142.
23. Garrigues, E., P. Janvier, Y. Kherabi, A.L. Bot and A. Hamon *et al*., 2020. Post-discharge persistent symptoms and health-related quality of life after hospitalization for COVID-19. J. Infect., 81: E4-E6.
24. Morin, L., L. Savale, T. Pham, R. Colle and S. Figueiredo *et al*., 2021. Four-month clinical status of a cohort of patients after hospitalization for COVID-19. JAMA, 325: 1525-1534.
25. Huang, C., L. Huang, Y. Wang, X. Li and L. Ren *et al*., 2021. Retracted: 6-month consequences of COVID-19 in patients discharged from hospital: A cohort study. Lancet, 397: 220-232.
26. Lu, Y., X. Li, D. Geng, N. Mei and P.Y. Wu *et al*., 2020. Cerebral micro-structural changes in COVID-19 patients-An MRI-based 3-month follow-up study. eClinicalMedicine, Vol. 25. 10.1016/j.eclinm.2020.100484.
27. Barani, K. and R. Padmavathi, 2013. Two rare cases of malignant mixed mullerian tumor. Internet J. Pathol., Vol. 15.
28. Orrù, G., D. Bertelloni, F. Diolaiuti, F. Mucci and M.D. Giuseppe *et al*., 2021. Long-COVID syndrome? A study on the persistence of neurological, psychological and physiological symptoms. Healthcare, Vol. 9. 10.3390/healthcare9050575.
29. Taylor, R.R., B. Trivedi, N. Patel, R. Singh and W.M. Ricketts *et al*., 2021. Post-COVID symptoms reported at asynchronous virtual review and stratified follow-up after COVID-19 pneumonia. Clin. Med., 21: e384-e391.
30. Ugurlu, B.N., O. Akdogan, Y.A. Yilmaz, D. Yapar, G.A. Ugurlu, H.S. Yerlikaya and S.A. Felek, 2021. Quantitative evaluation and progress of olfactory dysfunction in COVID-19. Eur. Arch. Oto-Rhino-Laryngology, 278: 2363-2369.

31. Davis, H.E., G.S. Assaf, L. McCorkell, H. Wei and R.J. Low *et al*., 2021. Characterizing long COVID in an international cohort: 7 months of symptoms and their impact. eClinicalMedicine, Vol. 38. 10.1016/j.eclinm.2021.101019.
32. Romero-Duarte, Á., M. Rivera-Izquierdo, I.G.F. de Alba, M. Pérez-Contreras and N.F. Fernández-Martínez *et al*., 2021. Sequelae, persistent symptomatology and outcomes after COVID-19 hospitalization: The ANCOHVID multicentre 6-month follow-up study. BMC Med., Vol. 19. 10.1186/s12916-021-02003-7.
33. Gallegos, M., P. Martino, T. Caycho-Rodríguez, M. Calandra and A. Razumovskiy *et al*., 2022. What is post-COVID-19 syndrome? Definition and update. Gaceta Médica México, 158: 442-446.
34. Mattioli, F., C. Stampatori, F. Righetti, E. Sala, C. Tomasi and G. de Palma, 2021. Neurological and cognitive sequelae of Covid-19: A four month follow-up. J. Neurol., 268: 4422-4428.
35. Gennaro, M.M., P. Mariagrazia, de Lorenzo Rebecca, M. Cristiano and P. Sara *et al*., 2021. Persistent psychopathology and neurocognitive impairment in COVID-19 survivors: Effect of inflammatory biomarkers at three-month follow-up. Brain Behav Immun., 94: 138-147.
36. Christensen, K.S., I. Sokolowski and F. Olesen, 2011. Case-finding and risk-group screening for depression in primary care. Scand. J. Primary Health Care, 29: 80-84.
37. Zeng, F., Y. Huang, Y. Guo, M. Yin, X. Chen, L. Xiao and G. Deng, 2020. Association of inflammatory markers with the severity of COVID-19: A meta-analysis. Int. J. Infect. Dis., 96: 467-474.
38. Daher, A., C. Cornelissen, N.U. Hartmann, P. Balfanz and A. Müller *et al*., 2021. Six months follow-up of patients with invasive mechanical ventilation due to COVID-19 related ARDS. Int. J. Environ. Res. Public Health, Vol. 18. 10.3390/ijerph18115861.
39. Ragab, D., H.S. Eldin, M. Taeimah, R. Khattab and R. Salem, 2020. The COVID-19 cytokine storm; what we know so far. Front. Immunol., Vol. 11. 10.3389/fimmu.2020.01446.
40. Liu, Y., R.C.M. Ho and A. Mak, 2012. Interleukin (IL)-6, tumour necrosis factor alpha (TNF-α) and soluble interleukin-2 receptors (sIL-2R) are elevated in patients with major depressive disorder: A meta-analysis and meta-regression. J. Affective Disord., 139: 230-239.
41. Karikalan, B. and S. Chakravarthi, 2022. Target therapy and immunotherapy for gastric cancer-recent updates. Curr. Cancer Ther. Rev., 18: 202-208.
42. Szlamka, Z., M. Kiss, S. Bernáth, P. Kámán, A. Lubani, O. Karner and Z. Demetrovics, 2021. Mental health support in the time of crisis: Are we prepared? experiences with the COVID-19 counselling programme in hungary. Front. Psychiatry, Vol. 12. 10.3389/fpsyt.2021.655211.
43. Moreira-Rosário, A., C. Marques, H. Pinheiro, J.R. Araújo and P. Ribeiro *et al*., 2021. Gut microbiota diversity and C-reactive protein are predictors of disease severity in COVID-19 patients. Front. Microbiol., Vol. 12. 10.3389/fmicb.2021.705020.
44. Zuo, T., F. Zhang, G.C.Y. Lui, Y.K. Yeoh and A.Y.L. Li *et al*., 2020. Alterations in gut microbiota of patients with COVID-19 during time of hospitalization. Gastroenterology, 159: 944-955.e8.
45. Cao, J., C. Wang, Y. Zhang, G. Lei and K. Xu *et al*., 2021. Integrated gut virome and bacteriome dynamics in COVID-19 patients. Gut Microbes, Vol. 13. 10.1080/19490976.2021.1887722.
46. Tao, W., G. Zhang, X. Wang, M. Guo and W. Zeng *et al*., 2020. Analysis of the intestinal microbiota in COVID-19 patients and its correlation with the inflammatory factor IL-18. Med. Microecol., Vol. 5. 10.1016/j.medmic.2020.100023.
47. Kumamoto, C.A., 2016. The fungal mycobiota: Small numbers, large impacts. Cell Host Microbe, 19: 750-751.
48. Sokol, H., V. Leducq, H. Aschard, H.P. Pham and S. Jegou *et al*., 2017. Fungal microbiota dysbiosis in IBD. Gut, 66: 1039-1048.
49. Strati, F., M.D. Paola, I. Stefanini, D. Albanese and L. Rizzetto *et al*., 2016. Age and gender affect the composition of fungal population of the human gastrointestinal tract. Front. Microbiol., Vol. 7. 10.3389/fmicb.2016.01227.

50. Lopetuso, L.R., G. Ianiro, F. Scaldaferri, G. Cammarota and A. Gasbarrini, 2016. Gut virome and inflammatory bowel disease. Inflammatory Bowel Dis., 22: 1708-1712.
51. Simmons, E.L., K. Drescher, C.D. Nadell and V. Bucci, 2018. Phage mobility is a core determinant of phage-bacteria coexistence in biofilms. ISME J., 12: 532-543.
52. Manosso, L.M., C.O. Arent, L.A. Borba, L.B. Ceretta, J. Quevedo and G.Z. Réus, 2021. Microbiota-gut-brain communication in the SARS-CoV-2 infection. Cells, Vol. 10. 10.3390/cells10081993.
53. Ng, H.Y., W.K. Leung and K.S. Cheung, 2023. Association between gut microbiota and SARS-CoV-2 infection and vaccine immunogenicity. Microorganisms, Vol. 11. 10.3390/microorganisms11020452.