



OPEN ACCESS

EDITED AND REVIEWED BY
Leonhard Schilbach,
Ludwig Maximilian University of
Munich, Germany

*CORRESPONDENCE
César Fernández-de-las-Peñas
✉ cesar.fernandez@urjc.es

RECEIVED 02 September 2024
ACCEPTED 09 September 2024
PUBLISHED 19 September 2024

CITATION
Fernández-de-las-Peñas C and
Arendt-Nielsen L (2024) Editorial: Updating
long COVID: mechanisms, risk factors, and
treatment. *Front. Hum. Neurosci.* 18:1490242.
doi: 10.3389/fnhum.2024.1490242

COPYRIGHT
© 2024 Fernández-de-las-Peñas and
Arendt-Nielsen. This is an open-access article
distributed under the terms of the [Creative
Commons Attribution License \(CC BY\)](#). The
use, distribution or reproduction in other
forums is permitted, provided the original
author(s) and the copyright owner(s) are
credited and that the original publication in
this journal is cited, in accordance with
accepted academic practice. No use,
distribution or reproduction is permitted
which does not comply with these terms.

Editorial: Updating long COVID: mechanisms, risk factors, and treatment

César Fernández-de-las-Peñas^{1,2*} and Lars Arendt-Nielsen^{2,3,4}

¹Department of Physical Therapy, Occupational Therapy, Physical Medicine and Rehabilitation, Universidad Rey Juan Carlos, Madrid, Spain, ²Department of Health Science and Technology, Center for Neuroplasticity and Pain, School of Medicine, Aalborg University, Aalborg, Denmark, ³Department of Gastroenterology and Hepatology, Mech-Sense, Clinical Institute, Aalborg University Hospital, Aalborg, Denmark, ⁴Steno Diabetes Center North Denmark, Clinical Institute, Aalborg University Hospital, Aalborg, Denmark

KEYWORDS

COVID-19, post-COVID, long-COVID symptoms, mechanism, risk factors

Editorial on the Research Topic

Updating long COVID: mechanisms, risk factors, and treatment

Introduction

The rapid spread of the coronavirus disease, 2019 (COVID-19) has provoked the most unprecedented sanitary crisis of this century leading to up to 776 million confirmed cases and more than 7 million deaths worldwide (WHO, 2023). In fact, the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), the pathogen responsible of COVID-19, has become one of the most investigated virus due to a total explosion of research thanks to the publication of thousands and thousands of papers in a relatively small period of time.

Extensive research aiming to decrease the severity and mortality of COVID-19 has been published. For instance, administration of antivirals at an early stage of the acute COVID-19 phase has shown to decrease mortality rate, hospitalization stay, and COVID-19 severity (Zur et al., 2024). Similarly, the development of COVID-19 vaccines has been one of the most important advances in the fight against SARS-CoV-2. Thus, vaccines have demonstrated to be effective for reducing the risk of severe COVID-19 and also associated mortality (Dinagde et al., 2024); however, vaccines have not been effective for preventing SARS-CoV-2 contagion (Wang et al., 2022). In fact, SARS-CoV-2 tropism has resulted in the appearance of several variants in a short period of time (Jagst et al., 2024). The worldwide spread of new variants of concern has led to reinfections (Sciscent et al., 2021).

Albeit all the progress and efforts done for fighting against SARS-CoV-2, another growing healthcare problem derived from COVID-19 is the presence of long-lasting or persistent symptoms once the acute infection has passed. The presence of persistent long-lasting symptoms after the acute infection has received several and heterogenous names from the beginning of the pandemic (Yang et al., 2024), being long-COVID (Fernández-de-las-Peñas, 2022) or post-COVID-19 condition (Soriano et al., 2022) the terms most accepted. Some meta-analyses have reported that up to 25–30% of COVID-19 survivors exhibit post-COVID symptomatology one (Chen et al., 2022; Han et al., 2022) and two (Fernández-de-las-Peñas et al., 2024; Rahmati et al., 2023) years after an acute SARS-CoV-2 infection. Further, a recent meta-analysis estimated a pooled worldwide prevalence of long-COVID of 41.8% (95% CI 39.7–43.9%) (Sk Abd Razak et al., 2024), although this rate is based on studies including COVID-19 survivors infected during the first year of the pandemic, mostly with the historical strain and Delta variable. In fact, it has been found

that the average direct medical costs of a patient with post-COVID symptoms ranges from US \$1,264 to 79,315 (Faramarzi et al., 2024).

Nevertheless, several gaps in different aspects of post-COVID-19 condition exist. The aim of the Research Topic “Updating long COVID: mechanisms, risk factors, and treatment” published in Frontiers has focused on several aspects of post-COVID-19 condition, a topic of emerging relevance due to the presence of millions of “long-haulers” worldwide. In this Editorial, we discuss the following topics: 1, mechanisms underlying post-COVID-19 condition; 2, clustering of post-COVID symptoms; and 3, risk factors of post-COVID-19 condition.

Mechanisms underlying post-COVID-19 condition

Several hypotheses such as viral persistence, long-lasting inflammation, endothelial dysfunction, alteration in microbiota, immune dysregulation/autoimmunity or autonomic dysfunction have been proposed for explaining the presence of post-COVID symptoms (Fernández-de-las-Peñas et al., 2023). However, the heterogeneity of post-COVID symptoms suggests an association with different predominant pathophysiological mechanism operating on each symptom. In this Research Topic, papers investigated different mechanisms potentially associated with post-COVID fatigue and neurocognitive symptoms.

da Silva et al. investigated the presence of autonomic dysfunction in individuals with post-COVID-19 condition and reported a long-lasting sympathetic predominance during the head-up tilt test. The presence of an autonomic dysfunction could explain general post-COVID symptomatology such as fatigue or even post-exertional malaise, which is experienced by almost 50% of long-haulers (Pagen et al., 2023). In a pilot study, Hofmann et al. found that the presence of post-COVID fatigue was associated with a reduction of superoxide anion (O⁻²) formation, suggesting that oxidative stress induces chronic fatigue-like symptoms in these patients. In such scenario, a long-lasting oxidative stress state may also explain the development of post-exertional malaise.

Yao et al. observed a reduced overall brain activity and a rearrangement of several brain functional networks in a small sample of individuals who had been infected with COVID-19. This study did not include subjects with post-COVID-19 condition since evaluations were conducted 28 days after the main infection, but authors proposed that the presence of brain abnormalities soon after an acute SARS-CoV-2 infection could be related to damage of the nervous system by the virus explaining the potential development of post-COVID neurocognitive symptomatology (Yao et al.). Thus, the narrative review by Zhao et al. discussed the mechanisms of neurodegenerative post-COVID diseases by examining the pathways of central nervous system infection by SARS-CoV-2. Current evidence supports that chronic inflammation and abnormal immune responses can lead to neuronal damage and long-term post-COVID neurocognitive symptomatology (Zhao et al.).

Clusters and post-COVID symptomatology

Due to the heterogeneity of post-COVID symptomatology, different attempts to identify subgroups (cluster) of patients. In fact, two different types of clusters by grouping of symptoms (e.g., neurological, cardiorespiratory or systemic/inflammatory cluster) or by prognosis (e.g., improved, non-improved, stable) have been identified (Kuodi et al., 2023). In the current Research Topic, both types of clustering were investigated.

Chen et al. identified the clinical features of three clusters based on the evolution or prognosis of symptoms based on the 3-month change in symptom number: remittent, persistent, or incident. These authors found that the incident phenotype was younger, had lower hospitalization rate but a greater number of post-COVID symptoms associated with systemic corticosteroid administration during the acute SARS-CoV-2 infection than the persistent or remittent phenotypes (Chen et al.).

Núñez et al. classified groups of patients by their different type of post-COVID symptoms and identified respiratory and neurocognitive symptoms clusters. Thus, the study by Carmona-Cervelló et al. found a heterogeneous battery of neurocognitive post-COVID symptoms associated with the presence of deficits in executive functions. This study suggests that one post-COVID symptom cluster e.g., neurocognitive, can also present different associated symptomatology (Carmona-Cervelló et al.). Finally, Fernández-de-las-Peñas et al. investigated the longitudinal evolution of three post-COVID neurocognitive symptoms (e.g., brain fog, memory loss, and concentration loss) during the first two years after the infection and, overall, they found a decreasing trend as expressed by exponential bar plots.

Risk factors

Different meta-analyses identifying potential risk factor associated with post-COVID symptoms have been published (Tsampasian et al., 2023; Luo et al., 2024). These meta-analyses found that female sex, older age, severe COVID-19, previous medical comorbidities, longer hospitalization stay, and high body mass index were associated with a higher risk of post-COVID-19 condition (Tsampasian et al., 2023; Luo et al., 2024).

In the current Research Topic, a Colombian study reported that female sex, severe COVID-19 (requirement of mechanical ventilation), some medical co-morbidities e.g., such as Chronic Obstructive Pulmonary Disease (COPD) or rheumatic disease and longer hospitalization stay, but not older age, were associated with a higher risk of developing long-COVID (Martínez-Ayala et al.). A study conducted in Brazil also found that female sex and medical co-morbidities such as hypertension were also a risk factor associated with the presence of long-COVID (Eduvirgem et al.). This Brazilian study identified that suffering from a higher number of COVID-10 associated-onset symptoms and being infected with the historical strain during the first wave of

the pandemic were factors associated with a higher risk of long-COVID (Eduvirgem et al.). It seems that female sex is the risk factor most associated with the development of post-COVID-19 condition, whereas other factors, e.g., older age, severe COVID-19, or longer stay at hospital, depend on the study design. Finally, two papers published in the current Research Topic observed not only female sex as a risk factor for post-COVID symptoms but also that clinical post-COVID symptoms are experienced differently between females and males (Marcilla-Toribio et al.) and that women showed different serological biomarkers, e.g., lower ferritin and procalcitonin levels but higher TNF levels at the acute COVID-19 phase than males (Delfino et al.). Current and previous findings will support that healthcare systems should consider long-COVID from a sex perspective at all.

In conclusion, this Research Topic has permitted to advance in current knowledge of long-COVID by providing further evidence on some underlying mechanisms (such as autonomic dysfunction, hyper-oxidative stress, chronic brain inflammation, and abnormal immune responses), confirming the presence of different post-COVID clusters and also confirming that female sex is probably the risk factor most predominantly associated with the development of this condition.

As Guest Editors of this Research Topic, we would like to thank to the reviewers for their comments, to all contributors for their valuable papers, and to Frontiers Research Topic staff for their collective support and assistance during this process.

References

- Chen, C., Hauptert, S. R., Zimmermann, L., Shi, X., Fritsche, L. G., Mukherjee, B., et al. (2022). Global prevalence of post COVID-19 condition or long COVID: a meta-analysis and systematic review. *J. Infect. Dis.* 226, 1593–1607. doi: 10.1093/infdis/jiac136
- Dinagde, D. D., Degefa, B. D., Kitil, G. W., Feyisa, G. T., and Marami, S. N. (2024). SARS-CoV-2 infection after COVID-19 vaccinations among vaccinated individuals, prevention rate of COVID-19 vaccination: a systematic review and meta-analysis. *Heliyon* 10:e30609. doi: 10.1016/j.heliyon.2024.e30609
- Faramarzi, A., Norouzi, S., Dehdarirad, H., Aghlmand, S., Yusefzadeh, H., Javan-Noughabi, J., et al. (2024). The global economic burden of COVID-19 disease: a comprehensive systematic review and meta-analysis. *Syst. Rev.* 13:68. doi: 10.1186/s13643-024-02476-6
- Fernández-de-las-Peñas, C. (2022). Long COVID: current definition. *Infection* 50, 285–286. doi: 10.1007/s15010-021-01696-5
- Fernández-de-las-Peñas, C., Notarte, K. I., Macasaet, R., Velasco, J. V., Catahay, J. A., Therese Ver, A., et al. (2024). Persistence of post-COVID symptoms in the general population two years after SARS-CoV-2 infection: a systematic review and meta-analysis. *J. Infect.* 88, 77–88. doi: 10.1016/j.jinf.2023.12.004
- Fernández-de-las-Peñas, C., Raveendran, A. V., Giordano, R., and Arendt-Nielsen, L. (2023). Long COVID or post-COVID-19 condition: past, present and future research directions. *Microorganisms* 11:2959. doi: 10.3390/microorganisms11122959
- Han, Q., Zheng, B., Daines, L., and Sheikh, A. (2022). Long-term sequelae of COVID-19: a systematic review and meta-analysis of one-year follow-up studies on post-COVID symptoms. *Pathogens* 11:269. doi: 10.3390/pathogens111020269
- Jagst, M., Pottkämper, L., Gömer, A., Pitarokoili, K., and Steinmann, E. (2024). Neuroinvasion and neurotropism of severe acute respiratory syndrome coronavirus 2 infection. *Curr. Opin. Microbiol.* 79:102474. doi: 10.1016/j.mib.2024.102474
- Kuodi, P., Gorelik, Y., Gausi, B., Bernstine, T., and Edelstein, M. (2023). Characterization of post-COVID syndromes by symptom cluster and time period up to 12 months post-infection: a systematic review and meta-analysis. *Int. J. Infect. Dis.* 134, 1–7. doi: 10.1016/j.ijid.2023.05.003
- Luo, D., Mei, B., Wang, P., Li, X., Chen, X., Wei, G., et al. (2024). Prevalence and risk factors for persistent symptoms after COVID-19: a systematic review and meta-analysis. *Clin. Microbiol. Infect.* 30, 328–335. doi: 10.1016/j.cmi.2023.10.016
- Pagen, D. M. E., Van Herck, M., van Bilsen, C. J. A., Brinkhues, S., Konings, K., den Heijer, C. D. J., et al. (2023). High proportions of post-exertional malaise and orthostatic intolerance in people living with post-COVID-19 condition: The PRIME post-COVID study. *Front. Med.* 10:1292446. doi: 10.3389/fmed.2023.1292446
- Rahmati, M., Udeh, R., Yon, D. K., Lee, S. W., Dolja-Gore, X., McEvoy, M., et al. (2023). A systematic review and meta-analysis of long-term sequelae of COVID-19 2-year after SARS-CoV-2 infection: a call to action for neurological, physical, and psychological sciences. *J. Med. Virol.* 95:e28852. doi: 10.1002/jmv.28852
- Sciscent, B. Y., Eisele, C. D., Ho, L., King, S. D., Jain, R., Golamari, R. R., et al. (2021). COVID-19 reinfection: the role of natural immunity, vaccines, and variants. *J. Commun. Hosp. Intern. Med. Perspect.* 11, 733–739. doi: 10.1080/20009666.2021.1974665
- Sk Abd Razak, R., Ismail, A., Abdul Aziz, A. F., Suddin, L. S., Azzeri, A., and Sha'ari, N. I. (2024). Post-COVID syndrome prevalence: a systematic review and meta-analysis. *BMC Public Health* 24:1785. doi: 10.1186/s12889-024-19264-5
- Soriano, J. B., Murthy, S., Marshall, J. C., Relan, P., Diaz, J. V., and WHO Clinical Case Definition Working Group on Post-COVID-9 Condition (2022). A clinical case definition of post-COVID-19 condition by a Delphi consensus. *Lancet Infect Dis.* 22, e102–e107. doi: 10.1016/S1473-3099(21)00703-9
- Tsampasian, V., Elghazaly, H., Chattopadhyay, R., Debski, M., Naing, T. K. P., Garg, P., et al. (2023). Risk factors associated with post-COVID-19 condition: A systematic review and meta-analysis. *JAMA Int. Med.* 183, 566–580. doi: 10.1001/jamainternmed.2023.0750

Author contributions

CF-d-l-P: Conceptualization, Investigation, Validation, Visualization, Writing – original draft, Writing – review & editing. LA-N: Conceptualization, Investigation, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Wang, K., Wang, L., Li, M., Xie, B., He, L., Wang, M., et al. (2022). Real-world effectiveness of Global COVID-19 vaccines against SARS-CoV-2 variants: a systematic review and meta-analysis. *Front. Med.* 9:820544. doi: 10.3389/fmed.2022.820544

WHO (2023). WHO Coronavirus (COVID-19) Dashboard. Available at: <https://covid19.who.int/> (accessed September 1, 2024).

Yang, J., Markus, K., Andersen, K. M., Rudolph, A. E., McGrath, L. J., Nguyen, J. L., et al. (2024). Definition and measurement of post-COVID-19 conditions in real-world practice: a global systematic literature review. *BMJ Open* 14:e077886. doi: 10.1136/bmjopen-2023-077886

Zur, M., Peselev, T., Yanko, S., Rotshild, V., and Matok, I. (2024). Efficacy and safety of antiviral treatments for symptomatic COVID-19 outpatients: systematic review and network meta-analysis. *Antiviral Res.* 221:105768. doi: 10.1016/j.antiviral.2023.105768