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Sex and gender differences in the neurological and neuropsychiatric symptoms of long COVID: a narrative review

Adelaide Jensen[1,2], Alex W Castro[1], Maria Teresa Ferretti[2], Julie Martinkova[2,3], Anna Vasilevskaya[4,5,6], Antonella Santuccione Chadha[2], Maria Carmela Tartaglia[2,5,6]

[1]School of Psychology, University of Ottawa, Canada; [2]Women's Brain Project, Switzerland; [3]Cognitive Center, Department of Neurology, Second Faculty of Medicine, Charles University and Motol University Hospital, Prague, Czech Republic; [4]Institute of Medical Science, University of Toronto, Canada; [5]Tanz Centre for Research in Neurodegenerative Diseases, University of Toronto, Canada; [6]Krembil Brain Institute, University Health Network, USA

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Summary. COVID-19 was deemed a global pandemic in March 2020 and, since then, millions of people have been affected worldwide. Now, nearly two years later, the long-term sequelae of the virus are becoming increasingly apparent. This novel form of the disease, commonly referred to as "long COVID", appears to be more common in females than in males. In this narrative review, we consulted published studies on long COVID reporting sex-disaggregated findings and discuss the possible mechanisms underlying potential sex differences. We found that females are more likely to experience milder acute COVID-19 disease, lower mortality, and a higher number of persistent physical, cognitive, neurological, and neuropsychiatric symptoms compared to males. Stronger innate and adaptive immune responses in females may be one of the mechanisms underlying this sex difference. The arrival of COVID-19 presents a unique occasion to study sex differences in the prevalence, symptomatology, risk factors, and disease progression shortly after disease emergence. We argue that advantage must be taken of this opportunity to provide researchers with the proper tools to address sex differences in COVID-19 and effectively tailor assessments and treatments toward individual needs.

Key words. COVID-19, long COVID, post-COVID syndrome, sex differences, immune system, neurological, neuropsychiatric.

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) – the virus that causes the coronavirus disease 2019 (COVID-19) – has infected over 318 million people worldwide since its outbreak in late 2019 and has resulted in more than 5.5 million deaths (as of January 16th, 2022).[1] Deemed a global pandemic by the World Health Organization (WHO) on March 11th, 2020, this virus has caused unprecedented morbidity, mortality, and disruption across the globe.[2] Countless studies and scientific reviews on the topic of COVID-19 have been published to date, and it has become increasingly evident that different subgroups of individuals experience COVID-19 infection differently. These distinctions range from disease onset to symptom type and severity, to duration of infection, to risk of death, and may also depend on SARS-CoV-2 variant. For instance, older adults are more at risk of severe COVID-19 infection, whereas younger individuals (under the age of 30) are more likely to have mild disease or be asymptomatic. Although unprecedented efforts from the scientific and medical communities have been devoted to the characterization, diagnosis, and prevention of the disease, it has also become clear that males and females experience COVID-19 infection differently. Several studies have reported that males tend to experience greater severity and mortality due to COVID-19.[3,4] Globally, approximately 60% of reported COVID-19 deaths are male.[5] In contrast, infected females are more likely to suffer from prolonged symptoms.[6]

Nearly two years after COVID-19 was declared a pandemic, the long-term sequelae of the virus are becoming increasingly apparent. This novel form of the disease – which has indeterminately been coined "long COVID", "post-COVID syndrome", or "post-COVID condition"– appears to be more common among females, particularly in its neurological and psychiatric forms.[7-9] Our main goal in writing this review is to present the emerging evidence on the long-term neuropsychiatric, neurological, cognitive, and physical manifestations of COVID-19 disease and highlight the observed sex differences in these symptoms and complaints. We conclude by proposing some important considerations for scientists to adequately address sex differences in their research and, by extension, help advance individualized medicine.

Overview of acute and long COVID

Acute COVID-19. COVID-19 is a highly contagious respiratory disease caused by the SARS-CoV-2 virus, whose primary entry point is via angiotensin-converting enzyme-2 (ACE2) receptors. ACE2 receptors are expressed in differing degrees within the lungs, myocardium, gastro-intestinal system, kidneys, and reproductive organs.[10,11] When SARS-CoV-2 binds to ACE2 receptors on cells of the respiratory system, this causes an immunological cascade of cytokine responses further resulting in inflammation (as seen in COVID-19) and other physiological sequelae.[6,12]

The median duration for symptom onset is 5 days after viral exposure and an estimated 97.5% of cases show COVID-19 symptoms within 11.5 days.[13] According to the COVID-19 report published by WHO on 55,924 laboratory confirmed cases, the most common acute symptoms include fever and dry cough (both above 67% prevalence). Other acute symptoms include fatigue, phlegm production, shortness of breath, sore throat, headache, myalgia or arthralgia, and chills, with the prevalence of each symptom ranging from 11.4-38.1%.[14] However, infected individuals vary greatly in terms of severity and clinical presentation. Population studies reported that 80-81% of individuals with COVID-19 experience mild to moderate disease (i.e., non-pneumonia and mild pneumonia), 14% have severe disease, and 5-6% develop critical illness (i.e., respiratory failure, septic shock, and/or organ failure).[15] On the other hand, infants, children, and adolescents appear to be less susceptible to COVID-19 infection and comprise only 1-3% of all reported COVID-19 cases, with less than 3% of those developing severe or critical disease. Individuals younger than 20 years are likely to be asymptomatic, although fever and cough are the most common symptoms among young symptomatic patients.[16] Older adults, on the other hand, are more likely to suffer from severe COVID-19 illness compared to their younger counterparts.[17] Common risk factors for severe acute COVID-19 include old age, frailty, and the presence of certain comorbidities (e.g., diabetes, cardiovascular disease, lung disease, obesity), among others.[17-19]

Although global COVID-19 infection rates are similar between males and females,[20,21] males are at a higher risk of severe illness and death due to COVID-19.[3,22,23] Several studies have supported these findings, as demonstrated in patient cohorts studied in China, South Korea, the United States, and Italy.[24-26] Accordingly, females are seemingly less likely to be hospitalized with acute COVID-19 than males.[27] These trends are in line with those from previous pandemics such as SARS and Middle East respiratory syndrome (MERS), which saw a higher incidence of severe cases and mortality among infected males compared to females.[28,29]

Long COVID. Although mild COVID-19 symptoms are expected to subside within two weeks, a large proportion of COVID-19 cases do not resolve within this timeframe. A recent study has shown that 87% of recovered, previously hospitalized COVID-19 patients experienced one or more symptoms persisting 2 months after initial onset of symptoms.[30] Moreover, up to two thirds of COVID-19 patients do not return to their baseline health status within 6 months after experiencing acute infection.[31-33] On October 6th, 2021, the WHO released a clinical case definition of "post COVID-19 condition" (also known as long COVID). According to this new definition, long COVID cases are identified by probable or confirmed SARS-CoV-2 infection, as patients do not consistently show positive polymerase chain reaction (PCR) or antibody tests in the months following initial COVID-19 diagnosis.[31,34]

According to the WHO, long COVID symptoms persist for at least 2 months and span a wide spectrum.[34] The most common long COVID symptoms among infected adults include fatigue, shortness of breath, and cognitive dysfunction/brain fog, though a range of other symptoms have also been reported, such as headache, joint pain, cough, chest pain, altered smell/taste, dizziness, memory issues, sleep disorders, and many more (see WHO definition for post COVID-19 condition).[34] However, long COVID does not only affect adults. Recent studies have reported that many children with symptomatic and asymptomatic acute COVID-19 also suffer from long-term effects comparable to those symptoms listed above.[35]

While findings from several studies suggest that the risk of developing long COVID is not correlated with the severity of acute illness,[36] individuals reporting certain factors during the acute stage – such as the need for prolonged ventilation, intensive care unit (ICU) admission, and higher number and severity of acute COVID-19 symptoms – appear be more likely to develop long COVID.[37,38] It should, however, be noted that such severe, hospitalized COVID-19 cases may be difficult to distinguish from patients suffering from post-intensive care syndrome, which has diverse etiological underpinnings.

Other frequently reported risk factors to the development of long COVID include higher body mass index (BMI), the presence of one or more comorbidities, and, notably, female sex.[7-9,35,39-41] According to recent data, the risk of developing long COVID is up to two times higher in females than in males.[41-43] As significant sex differences may exist in both acute and long COVID-19 disease, we sought to review recently published scientific articles on long COVID. In the following sections, we discuss the findings from these studies that relate to sex and gender.

Literature review

Search method. A literature search was conducted on long COVID original research articles published until July 31st, 2021. A PubMed search was conducted using the terms ((COVID) OR (COVID-19) OR (SARS-CoV-2) OR (SARS-COV2)) AND ((long) OR (post) OR (post-acute)) AND ((neuro*) OR (psych*) OR (cog*)). All articles were read, summarized, and scanned for sex-disaggregated data. Information from articles reporting sex-stratified data was included in the current review.

Data collected. Our search yielded 119 articles, of which 32 stratified their data by sex and were subsequently included in our narrative review. Out of these 32 articles, 26 reported significant sex differences in long COVID symptoms. Those articles reporting sex-disaggregated data differed in terms of study design, type of data collected (self-report vs objective), sample demographics (e.g., % females vs % males), proportion of participants experiencing long COVID symptoms, primary outcomes and variables of interest, intervals between acute COVID-19 and development of long COVID, criteria for COVID-19 diagnosis, and patient characteristics (e.g., pre-existing comorbidities). Such factors are important to consider when comparing findings between studies. For instance, many of the participant samples of the prospective studies we report consist of COVID-19 patients who were recontacted following hospital discharge. Of those participants, only a subset developed long COVID, which may explain the lower percentage of female long COVID patients in these samples. In Table 1S (available online at www.gendermedjournal.it as Supplementary material) we summarize the sex- and gender-related findings, participant characteristics (i.e., sample size, age, severity of acute COVID-19 illness, percentage of sample with long COVID symptoms, and pre-existing comorbidities), and methodology (i.e., interval between acute illness and time at assessment, study design, and criteria for COVID-19 diagnosis) of each study we reviewed.

Sex differences in long COVID

Although relatively few studies have included biological sex as a variable of interest in their analyses, many of those reporting sex-disaggregated data have shown that female sex may be predictive of post-covid sequelae,[7-9,39,40] but only among younger age groups (<60-70 years old).[42] Accordingly, some reports have described their long COVID patient cohorts as having large female-to-male ratios (as great as 2:1).[31,44] Additionally, females have been shown to be less likely to have recovered 6-8 months following acute illness compared to males.[38] For instance, Goertz et al. (2021) remarked that 85% of individuals in their sample who reported experiencing long COVID symptoms were female.[27] Furthermore, females were more likely to report a higher number of persistent symptoms following acute COVID-19 compared to males, irrespective of acute illness severity and hospitalization status.[9,37,38,45,46] For instance, in a sample of home-isolated participants (i.e., mild cases), females consisted of 72% of those reporting symptoms after 12 months,[45] while in a sample of hospitalized COVID-19 patients (i.e., moderate to severe cases), 81% of females (vs 73% of males) had persistent symptoms 6 months after symptom onset.[8]

Aside from differences in the frequency of long COVID symptoms, sex differences in symptom type and expression have also been identified. Almost all long COVID symptoms, including neuropsychiatric, cognitive, neurological, and physical symptoms, appear to be more common in females than in males. Below we outline the sex differences in long COVID symptoms identified in research articles reporting sex-disaggregated findings (summarized in Table 1S).

Neuropsychiatric sequelae. Many studies that have examined neuropsychiatric and psychological outcomes related to long COVID have reported that females more frequently experience symptoms of depression and anxiety within the months following acute COVID-19 illness.[8,47-49] Gebhard and colleagues (2021) conducted long-term follow-up (6.5 months) interviews of individuals who tested positive for COVID-19 and found that 43% of females and 31.5% of males of their sample reported at least one persistent neuropsychiatric symptom. Only 16.5% of these individuals were outpatients while the rest were hospitalized for acute COVID-19.[37]

Post-traumatic stress. Beck et al. (2021) investigated persistent psychological distress in patients who tested positive for COVID-19 via telephone interviews and found that female sex was positively associated with experiencing psychological distress one month following hospital discharge. In the same sample, 90% of those experiencing long-term post-traumatic stress disorder (PTSD) symptoms were female.[50] Furthermore, a higher prevalence of PTSD symptoms in females compared to males was identified among COVID-19 patients admitted to ICU.[39] Among ward patients, however, the proportion of PTSD symptoms was similar between the sexes.[39] Similarly, female COVID-19 inpatients demonstrated significantly higher scores on a PTSD checklist compared to males 3 weeks following hospital discharge.[51]

Depressive symptoms. Mazza and colleagues (2021) followed acute COVID-19 patients for 3 months after hospital discharge and found greater persistence of depressive symptoms and a higher number of psychopathological symptoms (i.e., depression, anxiety, PTSD, and obsessive-compulsive disorder) among females compared to males in their study sample.[52] In the same study, females also displayed better systemic immune-inflammatory scores (i.e., index scores based on platelet, peripheral lymphocyte, and neutrophil counts) compared to males, a factor proposed to be associated with the severity of depressive symptoms in this group.[52] In a sample of participants who experienced mostly mild to moderate COVID-19 illness, a higher percentage of females reported symptoms of stress and depression 6 to 8 months following acute illness.[38] Finally, Sykes and

colleagues (2021) followed-up with severe COVID-19 patients hospitalized for COVID-19 pneumonia nearly 4 months after hospital discharge and found that females reported more anxiety and lower mood compared to males, among other neurological and cognitive impairments (discussed in more detail below).[53] It may be relevant to note here that 14.2% of these participants had 3 or more pre-existing comorbidities, the most common being smoking history (44%), alcohol use (42.5%) and hypertension (41%); however, psychopathological history of participants was not assessed in this sample.[53]

This discrepancy between the sexes may in part be explained by the higher female prevalence of depression, anxiety, and PTSD in the general population. On the other hand, the experience of COVID-19 and its long-term sequelae may also have worsened pre-existing psychopathology or triggered the onset of depression or anxiety symptoms in these cohorts.[52] Indeed, Graham and colleagues (2021) found a higher prevalence (compared to rates in the general population) of premorbid depression and anxiety symptoms among patients with long COVID, suggesting a possible underlying neuropsychiatric vulnerability toward the development of long COVID.[44] Some studies reviewed in this section found that pre-existing psychopathology predicted neuropsychological symptoms post-COVID.[37,52] However, other studies found sex differences in post-COVID neuropsychiatric symptoms in their samples even after controlling for pre-existing neuropsychiatric comorbidities,[8] or found no associations between comorbidities and neuropsychiatric symptoms.[47] Altogether, these findings point towards there being possible sex differences in the neuropsychiatric sequelae of COVID-19.

Fatigue. Fatigue is a non-specific symptom of disease and can refer to feelings of weakness, tiredness, or general lack of energy.[54] It is one of the most prevalent long COVID symptoms and is reported significantly more often by female compared to male long COVID patients.[8,38,46,49,53,55] Blomberg et al. (2021) found that female sex was associated with fatigue 6 months following acute COVID-19 illness in home-isolated patients 16 years and older.[56] This sex difference is consistent with the female-to-male ratio (3:1 to 4:1) commonly observed in myalgic encephalomyelitis (ME), also known as chronic fatigue syndrome (CFS).[57,58] Long COVID and post-infectious ME/CFS share many similarities. In their systematic review on long COVID symptomatology, Wong & Weitzer (2021) found that most of the published studies on long COVID reported several overlapping ME/CFS symptoms, including the main criteria for ME/CFS: fatigue (including post-exertion fatigue) and reduced daily activity.[58]

Cognitive symptoms. Like acute COVID-19, long COVID cases have been characterized in part by a high incidence of cognitive impairment, including mild cognitive symptoms referred to as "brain fog". Although sex differences in such outcomes have not been thoroughly studied, some reports have suggested that cognitive impairment characterized by decline in memory is more prevalent among female long COVID patients.[52,53] In their attempt to identify the relationship between systemic inflammation during acute COVID-19 and subsequent psychopathology in the post-acute phase, Mazza and colleagues (2021) found that females showed more severe psychopathological symptoms along with lower working memory scores compared to males.[52]

Other neurological symptoms. Several studies have identified headache as a frequently reported long COVID symptom among females, next to fatigue and neuropsychiatric symptoms, as previously described.[31,46,49] Other prolonged neurological manifestations of COVID-19 more frequently reported in females include myalgia (i.e., muscle/body pain) and joint pain,[31,46] both of which are common symptoms of long COVID. Sleep disturbance has also been identified as a recurrent long COVID symptom across several studies.[8,53,59,60] Similar to rates in the general population, sleep problems have been more commonly reported among female compared to male long COVID patients.[53,59] Overall, despite methodological differences between studies, neurological symptoms such as headache, myalgia, and sleep disturbances were consistently reported to be worse in females with long COVID.

Physical and general well-being. Although our focus is mainly on the neurological and neuropsychiatric sequelae of long COVID, we also report briefly on the physical symptoms reported in the articles we reviewed. Bierle and colleagues (2021) identified a higher incidence of anorexia (a seemingly rare symptom in long COVID) in females, along with headache and joint pain, while chest pain and paresthesia were more often reported in males.[31] Shortness of breath, a common symptom of both acute COVID-19 and long COVID, has also been more frequently reported by females, along with older and hospitalized patients.[38] Generally females have been shown to suffer from more long-term healthcare problems than males following COVID-19 illness and experience more severe functional limitations that impact their personal care and ability to perform daily activities.[59,61] Halpin et al. (2021) noted a higher female prevalence of quality-of-life problems such as difficulties with mobility, self-care, and daily activities in their sample of long COVID patients.[39] It has been proposed that sex differences in physical and general well-being in the months following acute COVID-19 illness may be due in part to pre-existing comorbidities, number and severity of symptoms experienced during the acute phase, as

well as several biopsychosocial factors (including lower self-rated health before the pandemic).[9,46,53,62,63] In contrast, one study found no association between sex and persistence of functional impairment in a sample of hospitalized and non-hospitalized COVID-19 patients.[64]

Summary of sex differences in long COVID

Our literature search revealed sex differences in long-term neurological, cognitive, neuropsychiatric, and physical symptoms associated with COVID-19, such that females appear to be more likely to report and experience such symptoms compared to males. Furthermore, the magnitude of these effects may be influenced by hospitalization status, age, and pre-existing comorbidities, among other factors related to study design and methodology. Indeed, several studies reporting sex differences included participants with two or more underlying comorbidities (i.e., multimorbidity), which may have contributed to the incidence of long COVID and differences in symptoms between the sexes in these samples. Additionally, some studies reporting sex-disaggregated data did not find sex to be associated with long COVID or related symptoms.[22,32,64-69] As we are only beginning to study the long-term outcomes of COVID-19, it is currently not feasible to draw definitive conclusions about sex differences in this disease. More studies are needed to assess the extent to which COVID-19 differentially impacts the sexes in both the acute and post-acute phases.

Proposed risk factors and mechanisms underlying the observed sex differences in long COVID

Although published investigations on long COVID are only now beginning to emerge, researchers have attempted to explain the potential biological mechanisms underlying the observed sex differences. Several factors appear to be at play, including sex differences in immunological responses and ACE2 expression and activity, both of which are strongly related to genetics and reproductive hormones,[6,70-72] as well as differences in rates of comorbidities between males and females.

Immune mechanisms. Epidemiological studies report that adult females generally mount stronger, more rapid innate and adaptive immune responses to pathogens compared to males.[73] These mechanisms lead to a faster clearance of pathogens and greater vaccine efficacy, rendering females more prone to developing autoimmune and inflammatory diseases.[74] In contrast, males have a more attenuated viral response, thus increasing their susceptibility to severe disease.[72] Higher severity of COVID-19 illness in males is correlated with increased plasma cytokine levels of the innate immune system, including interleukin-8 (IL-8) and IL-18. In contrast, reduced severity in females corresponds with higher T-cell activation.[4]

According to a recent study, individuals with COVID-19 exhibit higher autoantibody reactivities compared to non-infected individuals.[10] In addition to recent studies demonstrating a higher female prevalence of long COVID symptoms, these findings raise the question of whether long COVID is of autoimmune etiology.[71] This observation is not surprising, as sex differences exist in almost every known disease – they just have not all been thoroughly studied. Many researchers have postulated that the heightened immune response in females may help explain in part why COVID-19 presents more severely in males, and why a higher proportion of females show post-infectious autoimmune-like and inflammatory sequelae.[6,71,75,76] Consistent with this notion, most autoimmune diseases, including ME/CFS, multiple sclerosis, rheumatoid arthritis, autoimmune encephalitis syndromes, systemic lupus erythematosus, and many others, are more common in the female sex.[71,77]. Moreover, sex differences in several neurological and neuropsychiatric disorders, some of which can arise following viral infections, also have a higher prevalence rate and present differently in each sex. For example, ME/CFS, a rare, immune-mediated illness characterized mainly by prolonged periods of dysfunction, affects primarily females, with the female-to-male ratio reaching up to 4:1 in the general population.[78,79] Many cases resembling ME/CFS have been reported during the 2002-2004 SARS outbreak, with 40% of survivors experiencing symptoms up to 4 years following initial infection.[80] Long-term symptoms similar to those expressed by individuals with ME/CFS (e.g., fatigue) are now being observed among survivors of mild COVID-19, the majority of whom are female.[58]

Angiotensin-converting enzyme-2 (ACE2) expression. A sex dimorphism in ACE2 expression may also play a role in the sex differences observed in acute COVID-19 and long COVID. ACE2 receptors are located mainly in epithelial cells and are expressed in differing degrees within the lungs, myocardium, gastro-intestinal system, kidneys, and reproductive organs. Consequently, many of these organs show radiological abnormalities following SARS-CoV-2 infection (i.e., tissue scarring, inflammation, and multiorgan impairment).[10,11] Importantly, ACE2 receptors are the primary entry point of SARS-CoV-2. When SARS-CoV-2 binds to ACE2 receptors on cells of the respiratory system, this causes an immunological cascade of cytokine responses further resulting in inflammation (as seen in COVID-19), as well as other physiological effects.[6,12]

Sex differences in the expression and regulation of ACE2 have been shown to exist and may involve both genetic and hormonal mechanisms. Males have higher plasma ACE2 levels than females,[81] which may stem from the fact that the ACE2 gene is located on the X chromosome (of which females have two).[82] ACE2 receptors are found in different densities within the male and female reproductive organs such that higher concentrations of ACE2 receptors exist in the testes compared to the ovaries.[83] ACE2 expression is also known to be modulated by sex steroid hormones (including estrogen, progesterone, and testosterone). In particular, estradiol (the main form of estrogen in premenopausal women) has been shown to positively regulate ACE2 expression.[84,85] Although the exact mechanisms are not yet fully understood, the apparent sex- and hormonal-mediated differences in the immune system and ACE2 expression may be important contributors to the sex differences seen in response to SARS-CoV-2 and may help explain why females are more protected against severe COVID-19 illness than males.

Age. While older age appears to be a risk factor for acute COVID-19, the data on long COVID are not as well-defined. Some studies have found long COVID to be more common among older age groups (>50 years),[41] whereas other datasets suggest that individuals from younger age groups are more at risk. According to a recent analysis of long COVID prevalence by age group, individuals aged 30-49 years are seemingly most affected by long COVID (26.8%), followed by those aged 50-69 years (26.1%), and those above 70 years old (18%).[86,87] When factoring in the sex of patients, females under the age of 50 have been shown to be more likely than males to experience long COVID symptoms.[88] Given these findings, further studies and reviews are needed to assess the interactive effects of age by sex in long COVID.

Comorbidities. Another potentially contributing factor to sex differences in COVID-19 may involve the higher prevalence of somatic comorbidities in males versus females. Pre-existing comorbidities in COVID-19 patients, including cardiovascular disease, obesity, ischemic heart disease, hypertension, and diabetes, have been associated with severity of acute COVID-19 infection.[8] Given that males are more prone to comorbidities than females, this may increase their risk of severe acute illness and mortality due to SARS-CoV-2 infection, and in turn may in part help to explain the emerging sex difference in acute COVID-19 disease.[89]

Similarly, numerous studies have reported that females more frequently experience comorbidities of neuropsychiatric nature, which may lead to an increased prevalence of long-term neuropsychiatric symptoms following COVID-19 in this sex. The higher prevalence of depression and anxiety/PTSD symptoms in females with long COVID may be explained by the higher female susceptibility to these disorders in the general population.[90] It has been suggested that these premorbid symptoms could have contributed to long COVID risk,[37] either exacerbated by the illness or resulting from the negative social effects of the pandemic (e.g., social isolation). Nevertheless, these considerations do not in any way discount the severity of neuropsychiatric symptoms experienced by female COVID-19 survivors. Therefore, it is important that future studies assess how the presence of comorbidities and multimorbidity in long COVID patients contributes to observed sex differences in this disease.

Sociocultural differences. In addition to biological factors, group differences in long COVID may also in part be explained by behavioural and social differences between the genders. For instance, the prevailing tendency for men to engage in higher-risk activities (e.g., smoking, alcohol use, etc.) compared to women may render men more susceptible to severe acute COVID-19 disease (in combination with other biological and environmental factors). Additionally, other factors such as gender roles and societal expectations have been shown to differentially influence the risk of long COVID in men and women. For instance, Gebhard and colleagues (2021) found that feminine gender identity (measured by the Bem Sex-Role Inventory) was associated with higher risk of developing long COVID in women.[37] In the same study, women and men caring for family members, and men who were responsible for household chores at the time of acute illness, were at a lower risk of developing long COVID.[37] In contrast, pre-existing mental illness and cardiovascular risk factors increased the risk of long COVID in women but not in men.[37] Finally, women are generally more likely to report symptoms and seek care compared to men,[91,92] which may also contribute to the observed sex and gender differences in long COVID.

Limitations

Although it is still very early in the research lifecycle, several limitations exist in the literature which may affect the interpretation of data summarized in the present review and thus should be noted. First, studies on mild and asymptomatic COVID-19 cases are lacking, as these cases often go undocumented. Most studies have examined hospitalized COVID-19 patients suffering from disease of moderate to critical severity, which limits our understanding of the prevalence, causes, and expression of long COVID. Second, many of the studies that we discuss here analyzed self-report data. While

self-report data has immense value for the characterization of patient experience and of the diversity of COVID-19 symptoms, it is difficult to generalize these findings to those from studies reporting prospective data obtained from objective scales and measures, which can be more reliable and quantifiable. Finally, most of the research articles covered in this review included participants with laboratory-confirmed COVID-19 tests; however, some did not, whereas others did not specify their criteria for inclusion (Table 1S). As previously mentioned, laboratory-confirmed SARS-CoV-2 infection is not a requisite for identification of long COVID,[34] nor is it consistently encountered in studies of long COVID patients.[93] This inconsistency may be explained by several factors. First, females have been shown to maintain SARS-CoV-2 antibody positivity for a significantly shorter duration compared to males,[94] thus raising questions about the sensitivity of current serologic tests to previous SARS-CoV-2 infection, especially in female samples. Second, the lack of access to testing in many countries has resulted with many people showing symptoms and signs of COVID-19, without confirmation from laboratory tests. That said, given the nonspecific nature of many of the symptoms seen in long COVID, such as fatigue, mood, and cognitive and neurological changes (e.g., brain fog, headache), it is important to consider other causes in individuals with long COVID without positive SARS-CoV-2 tests.

Conclusion

Recent findings suggest that sex differences exist in both the acute and post-acute phases of COVID-19. Males have consistently been shown to experience more severe acute illness and higher mortality due to COVID-19, whereas females are more likely to face milder disease yet prolonged symptoms. Although several interrelated factors are likely to contribute to this apparent sex difference, one of the prevailing hypotheses for the underlying mechanisms is the higher immune response in females compared to males.

It has been almost two years since COVID-19 was declared a pandemic. The spectrum of long-term manifestations of COVID-19 is growing by the day and will keep changing with time and the emergence of new variants. Nevertheless, according to the current literature, sex differences are apparent in long COVID, and these should not be ignored. Special attention needs to be devoted to sex and gender determinants in the outcomes of this disease, as these have been largely overlooked in the early studies of many sexually dimorphic autoimmune, neurological, and neuropsychiatric diseases. These limitations have led to clinical consequences for individuals most strongly affected by such diseases (i.e., females) who did not initially benefit from therapeutic outcomes predominantly tailored toward the male sex. Moreover, the examination of sex differences can reveal more complex interactions across a variety of organ systems which may also differ in presentation between males and females. While some may incorrectly localize the COVID-19 virus solely within the lungs, research is showing that COVID-19 extends to and interacts substantially with other organ systems, particularly linking the immune system to brain health and broader cognitive function. The rather unfortunate surfacing of COVID-19 presents a unique and valuable opportunity to consider both sexes in clinical and experimental research beginning soon after disease emergence. Future studies will be required that systematically examine sex differences in long COVID as the literature grows, with the goal of preventing sex and gender biases in the diagnosis and treatment of COVID-19. We must take advantage of this opportunity to provide professionals with the adequate tools to address such discrepancies and effectively tailor assessments and treatments toward individual needs, thus advancing precision medicine.

Key messages

- Males tend to experience higher disease severity and mortality due to COVID-19.
- Long COVID is characterized by new or persistent symptoms following acute COVID-19 infection.
- The most reported long COVID symptoms include fatigue, shortness of breath, cognitive dysfunction/brain fog, and neuropsychiatric symptoms such as depression and post-traumatic stress.
- Long COVID appears to be more common in females compared to males.
- Studies have shown that females experience more prolonged neurological, neuropsychiatric, cognitive, and physical symptoms following COVID-19 infection.
- This apparent sex difference in long COVID may be due to the higher adaptive and innate immune responses in females, among other biological and sociocultural factors.

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Conflict of interest statement: Maria Teresa Ferretti is the co-founder and Chief Scientific Officer of the Women's Brain Project. She has received personal fees from Eli Lilly and Roche for projects unrelated to the present manuscript. The other Authors declare no conflicts of interest.

Correspondence to:
Adelaide Jensen
School of Psychology, University of Ottawa
136 Jean Jacques Lussier
Ottawa, ON, Canada
K1N 6N5
email: ajens098@uottawa.ca