RESEARCH PAPER

Neurologia i Neurochirurgia Polska
Polish Journal of Neurology and Neurosurgery
2023, Volume 57, no. 1, pages: 111–120
DOI: 10.5603/PJNNS.a2023.0010

ISSN: 0028-3843, e-ISSN: 1897-4260

LEADING TOPIC

Leading Topic Editor: Alina Kułakowska, MD, PhD, Department of Neurology, Medical University of Bialystok, Bialystok, Poland

Sex-related patient-reported brain fog symptoms in non-hospitalised COVID-19 patients

Żaneta Chatys-Bogacka[1, 2], Iwona Mazurkiewicz[1, 2], Joanna Słowik[3], Klaudia Nowak[1, 2], Wojciech Sydor[4, 5], Barbara Wizner[6, 7], Agnieszka Słowik[1, 2], Marcin Wnuk[1, 2], Leszek Drabik[8, 9]

[1]Department of Neurology, Jagiellonian University Medical College, Krakow, Poland
[2]Department of Neurology, University Hospital in Krakow, Poland
[3]Department of Periodontology, Preventive Dentistry and Oral Medicine, Institute of Dentistry, Faculty of Medicine, Jagiellonian University Medical College, Krakow, Poland
[4]Centre for Innovative Therapies, Clinical Research Coordination Centre, University Hospital in Krakow, Poland
[5]Department of Rheumatology and Immunology, Jagiellonian University Medical College, Krakow, Poland
[6]Department of Internal Medicine and Gerontology, Jagiellonian University Medical College, Krakow, Poland
[7]Department of Internal Medicine and Geriatrics, University Hospital in Krakow, Poland
[8]Department of Pharmacology, Jagiellonian University Medical College, Krakow, Poland
[9]John Paul II Hospital, Krakow, Poland

ABSTRACT

Introduction. Previous studies on the prognostic role of sex in post-COVID-associated brain fog have yielded divergent results. Moreover, limited evidence exists regarding the evolution of brain fog symptoms over time, especially in ambulatory patients and separately for women and men. Therefore, the aim of the current study was to assess brain fog symptoms in non-hospitalised patients with COVID-19, according to their sex.

Material and methods. We created a neuropsychological questionnaire including eight questions on the presence of brain fog symptoms in the following four time periods: before COVID-19, and 0–4, 4–12, and > 12 weeks post-infection. The validity and reliability of the questionnaire were assessed. In this cross-sectional study, questionnaires were filled out anonymously and retrospectively once only by patients or through a survey link posted online. Included were patients ≥ 18 years, with > 3 months since the SARS-CoV-2 infection onset confirmed by RT-PCR from a nasopharyngeal swab.

Results. The study included 303 patients (79.53% women, 47.52% medical personnel). Median time between COVID-19 onset and questionnaire completion was 208 (IQR 161–248) days. Women, compared to men, reported a higher prevalence of problems with writing, reading, and counting (< 4 weeks, OR 3.05, 95% CI: 1.38–6.72; 4–12 weeks, OR 2.51, 95% CI: 1.02–6.14; > 12 weeks, OR 3.74, 95% CI: 1.12–12.56) and thoughts communication (< 4 weeks, OR 2.53, 95% CI: 1.41–4.54; 4–12 weeks, OR 3.74, 95% CI: 1.93–7.24; > 12 weeks, OR 2.00, 95% CI: 1.01–3.99). The difference between the two sexes in answering questions in an understandable/unambiguous manner was statistically significant between four and 12 weeks after infection (OR 2.63, 95% CI: 1.36–5.10), while a sex difference in recalling new information was found below 12 weeks (OR 2.54, 95% CI: 1.44–4.48 and OR 2.43, 95% CI: 1.37–4.31 for < 4 and 4–12 weeks, respectively). No sex differences in reporting problems with multitasking, remembering information from the past, determining the current date, or field orientation were noted.

Conclusions. Non-hospitalised women and men retrospectively report a different course of COVID-19-associated brain fog.

Key words: COVID-19, brain fog, sex, course of COVID-19, long COVID

(*Neurol Neurochir Pol 2023; 57 (1): 111–120)*

Address for correspondence: Marcin Wnuk, Department of Neurology, Jagiellonian University Medical College, 2 Jakubowskiego St., 30-688 Krakow, Poland; e-mail: marcin.wnuk@uj.edu.pl

Received: 23.01.2023; Accepted: 30.01.2023; Early publication date: 16.02.2023

Introduction

The Coronavirus Disease 2019 (COVID-19) pandemic spread worldwide, resulting in 6.7 million deaths as of 21 January, 2023 [1]. A substantial number of patients experienced persistent complications after the Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2) infection, affecting not only their respiratory system but also other organs [2–4]. Neurological manifestations have been observed not only throughout the acute phase of illness [5–9] but also during the post-infection period [10, 11]. Among these persistent symptoms, cognitive, memory and concentration disturbances have been reported by approximately one in four patients with a previous SARS-CoV-2 infection [12], and their presence interfered with daily activities and delayed the chance of complete recovery [13, 14]. In the literature, the term 'brain fog' was coined in order to gather these symptoms and was intended to convey the notion of cognitive impairment including difficulties with concentration and intellectual clarity, mental fatigue, and anxiety [10, 11, 15]. The prevalence of post-COVID sequelae appears to be six-fold higher than after other viral infections [16].

So far, most studies have concentrated on the prevalence of brain fog in individuals previously hospitalised due to COVID-19 [17–19], and its association with other factors such as age and comorbidities [20]. However, studies concerning the prognostic role of sex have yielded divergent results [21–23].

For example, a systematic review of 66 studies showed that female sex was a risk factor for neuropsychiatric sequelae of SARS-CoV-2 infection, apart from disease severity and duration of symptoms [24]. On the other hand, a recent meta-analysis of 51 studies revealed that the prevalence of persistent psychiatric and neurological symptoms after COVID-19 was only weakly correlated with other factors, including hospitalisation, severity of infection, and length of follow-up [25]. Another study evaluating 23 symptoms of COVID-19, including confusion, in 451 Norwegian non-hospitalised patients, showed that six months after infection the persistence of symptoms was associated with their number, and with the number of comorbidities, but not with sex [21]. There is also limited evidence as to how disturbances perceived as brain fog evolve over time, especially in ambulatory patients and separately for women and men.

Therefore, the aim of the current study was to assess the symptoms of brain fog in previously non-hospitalised patients with COVID-19, according to their sex.

Material and methods

Development of neuropsychological questionnaire

In a three-step approach, we prepared a short, precise questionnaire containing questions allowing the clear description of the most common neuropsychiatric problems after COVID-19 divided into three domains, including brain fog, chronic fatigue, and emotional disturbances. The impact of these symptoms on daily living and occupational activities was also investigated. In the current study, we have presented only the results related to the first part of the questionnaire involving patient-reported brain fog symptoms.

The creation of the Post-COVID Brain Fog (BF-COVID) questionnaire was described previously [26]. In brief, as a first step, we searched the PubMed database for the spectrum of post-COVID symptoms and possible tools to assess for their presence [26]. Then, we interviewed 12 neurologists who had experienced COVID-19 and asked them open-ended questions regarding their personal and professional experience of problems with concentration, memory, sleep and speech before and after their infection [26]. All interviews were recorded and lasted up to 15 minutes. The interviews were then analysed by two researchers (Żaneta Chatys-Bogacka and Iwona Mazurkiewicz) in order to bring out a specific profile and evaluation of the complaints. Based on this information, an anonymous BF-COVID questionnaire was created and included questions about the symptoms, their severity and impact on everyday life and work. In accordance with the guidelines of the National Institute for Health and Care Excellence (NICE) [10], the BF-COVID questionnaire applied retrospectively to the following time periods: before COVID-19, the acute phase of infection (i.e. 0–4 weeks since the onset of COVID-19), the post-acute phase (i.e. 4–12 weeks post-infection), and the chronic phase (i.e. more than 12 weeks post-infection). Patients were asked to complete the questionnaire retrospectively only once, and to respond if the symptoms occurred during the above-mentioned time periods. The BF-COVID questionnaire was administered in Polish, and was translated into English for the purposes of this paper. In addition, through the BF-COVID questionnaire, we collected basic epidemiological data, including age, sex, date of the confirmed COVID-19 diagnosis, date of the questionnaire completion, and date of hospitalisation due to SARS-CoV-2 infection.

Content and face validity

As a second step, the BF-COVID questionnaire was validated in a group of 70 people comprising neurologists, independent physicians, neuropsychologists, physiotherapists and speech therapists, who were asked to complete the drafted version. Based on their opinions and expert consensus, the design of the questionnaire was optimised. Eight items were corrected, i.e. questions regarding the presence of persistent fatigue, sore throat, sensation of lymph node enlargement, myalgia, arthralgia, headache, non-restorative sleep, and prolonged post-exercise fatigue were excluded from the brain fog evaluation questionnaire.

Thus, the final version of the questionnaire was created, consisting of eight detailed questions, assessed retrospectively by patients in four different time periods (Tab. 1).

Table 1. Elements of brain fog self-assessed by patients in Post-COVID Brain Fog questionnaire. Patients responded either 'yes' or 'no' to each question in four time periods assessed retrospectively

Did you experience problems with:	Before COVID-19	0–4 weeks since COVID-19 onset	4–12 weeks post-infection	More than 12 weeks post-infection
1. Writing, reading, and counting?	Yes/No	Yes/No	Yes/No	Yes/No
2. Answering questions in an understandable or unambiguous manner?	Yes/No	Yes/No	Yes/No	Yes/No
3. Thoughts communicating during a conversation in a way that others can understand?	Yes/No	Yes/No	Yes/No	Yes/No
4. Performing several independent tasks simultaneously?	Yes/No	Yes/No	Yes/No	Yes/No
5. Recalling new information?	Yes/No	Yes/No	Yes/No	Yes/No
6. Remembering information from past, for example, recognising people or remembering events?	Yes/No	Yes/No	Yes/No	Yes/No
7. Determining current date and naming days of week?	Yes/No	Yes/No	Yes/No	Yes/No
8. Finding right way in a familiar place?	Yes/No	Yes/No	Yes/No	Yes/No

As a third step, individuals attending the ambulatory for post-COVID patients in the University Hospital in Krakow were encouraged to complete the final paper version of the BF-COVID questionnaire. An invitation to complete the online version with a link was also sent to employees of the University Hospital in Krakow via mass e-mail correspondence. A link to the survey with an invitation to participate was also posted on Facebook [27].

Psychometric analysis

The validity and reliability of the BF-COVID questionnaire were assessed as described previously [26].

Study participants

Inclusion criteria for the study participation were as follows: age ≥ 18 years, > 3 months since the onset of COVID-19, confirmation of diagnosis by detection of viral RNA by reverse transcription polymerase chain reaction (RT-PCR) from a nasopharyngeal swab, and the ability to write and read.

Data collection began on 22 April, 2021 and finished on 9 August, 2021. We received 660 BF-COVID questionnaires. After exclusion of individuals previously hospitalised due to COVID-19 and incomplete questionnaires, 303 ambulatory patients with a history of SARS-CoV-2 infection were included in the final analysis.

Statistics

Continuous variables were presented as medians (interquartile ranges) and compared by the Mann-Whitney U or Kruskal-Wallis test since all distributions were non-normal according to the Shapiro-Wilk test. For clarity, the number of multiple symptoms of brain fog was presented as mean ± standard deviation. Categorical variables were demonstrated as counts and percentages and analysed using the Chi-square test, Fisher's exact, or McNemar's test, as appropriate. These results were expressed as odds ratio (OR) and 95% confidence interval (CI). Bonferroni correction was applied for pairwise comparisons, and the p-value was set at < 0.008. For other comparisons, the significance level was set at $p < 0.05$. Data was analysed using STATISTICA v13.0 software (Statsoft Inc., Tulsa, OK, USA).

Ethics approval and consent to participate

This study was performed as part of the CRACoV-HHS project (CRAcow in CoVid pandemics — Home, Hospital and Staff) for which Jagiellonian University Bioethics Committee approval was received. Due to the fact that the BF-COVID survey was anonymous, after consulting a legal opinion it was established that data collection in this study did not require additional approval from the Bioethics Committee. The study was performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants recruited in the ambulatory for post-COVID patients in the University Hospital in Krakow before they filled out a paper version of the BF-COVID questionnaire. According to Polish law, when online questionnaires are completed anonymously, no written consent to obtain is needed from these subjects, although the aim of such a survey must be provided. Therefore, data collection with the use of an online anonymous link in this study was performed according to the above-mentioned legal guidelines.

Availability of data and material

The dataset analysed during the current study is not publicly available due to privacy restrictions, but is available from the corresponding author upon reasonable request.

Results

Psychometric properties

The results of the psychometric analysis of the BF-COVID questionnaire can be found in our previous paper [26].

Patient characteristics

A total of 303 patients, females n = 241 (79.53%), medical personnel n = 144 (47.52%), were included in this

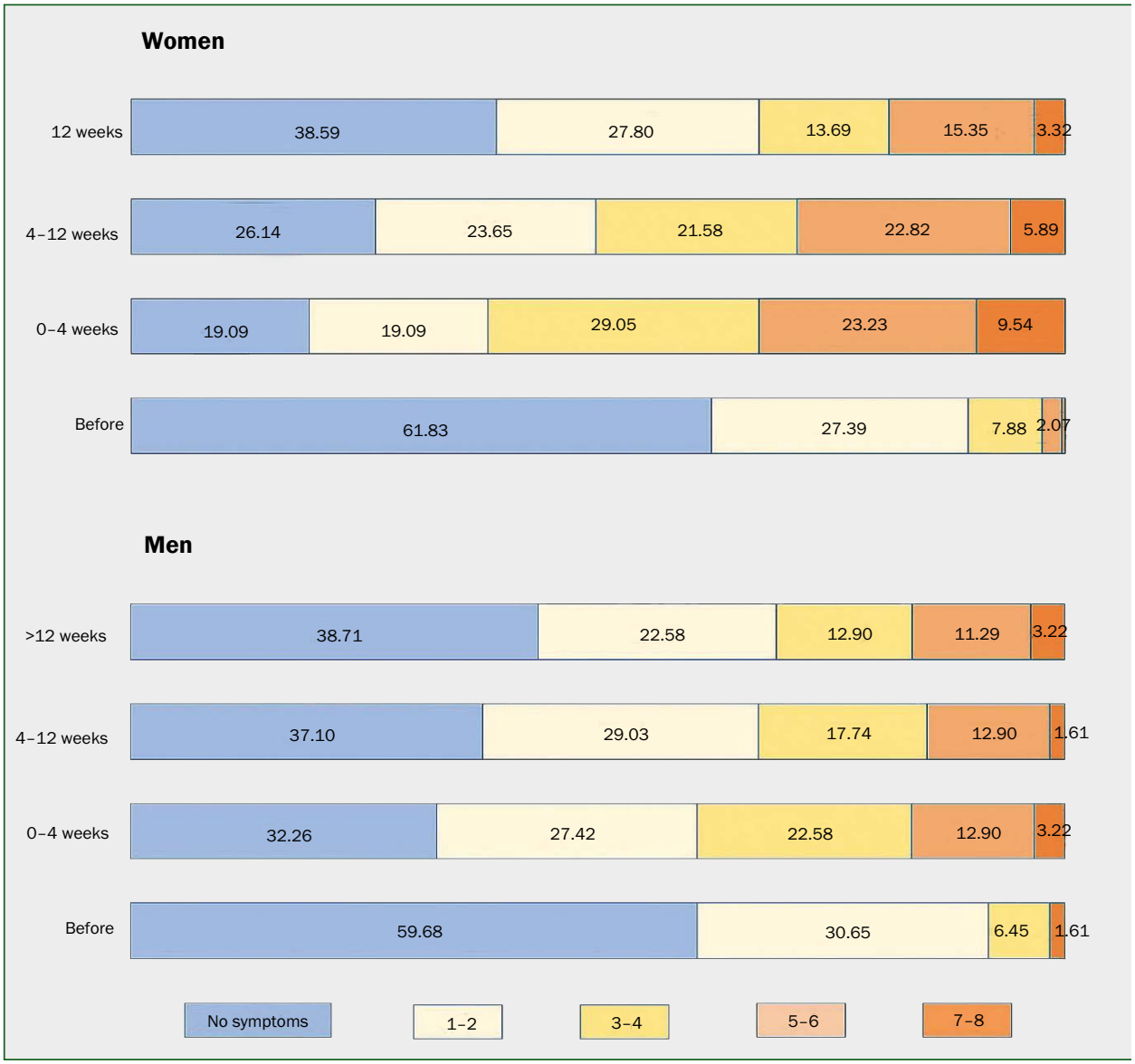

Figure 1. Prevalence of multiple brain fog symptoms in four time periods reported retrospectively by women and men. Data is presented as a percentage of positive responses to Questions 1–8

cross-sectional study. Median time between COVID-19 onset and completion of the BF-COVID questionnaire was 208 days (interquartile range 161–248). There were no differences in age between females and males [39 (30–49) *vs.* 35 (31–40) years, p = 0.149].

Complex symptomatology of brain fog

The mean number of brain fog symptoms was 0.79 ± 1.32, 3.01 ± 2.35, 2.57 ± 2.31 and 1.91 ± 2.17 for the pre-COVID, < 4 weeks, 4–12 weeks, and > 12 weeks intervals, respectively (p < 0.001).

Regarding the pre-COVID-19 period, 38.61% of patients responded positively to at least one questionnaire question, including 28.05%, 7.59%, 1.65% and 0.66% for multiple positive responses to 1–2, 3–4, 5–6, and 7–8 questions respectively. When retrospective analysis of the four weeks since a positive PCR test was made, 78.22% of patients declared at least one positive response, with a growing prevalence of multiple positive responses (20.79%, 27.72%, 21.12%, 8.25% for 1–2, 3–4, 5–6 and 7–8 symptoms, respectively). When reporting symptoms after 12 weeks, 61.39% of patients declared at least one symptom, and the prevalence of multiple positive responses remained high at 26.73%, 13.53%, 14.52%, and 3.30%, respectively.

Women, compared to men, had a higher prevalence of any, and of multiple, reported brain fog symptoms within four and 12 weeks since the onset of COVID-19 (3.20 ± 2.39 *vs.* 2.28 ± 2.03, p = 0.007 and 2.76 ± 2.35 *vs.* 1.85 ± 2.00, p = 0.008, respectively). There was no difference in the number of self-declared brain fog symptoms between the groups before COVID-19 (p = 0.728) and after more than 12 weeks post-infection (p = 0.259) (Fig. 1).

Burden of elements of brain fog in four time periods reported retrospectively by patients

Women

The prevalence of all symptoms increased during the first four weeks of infection (Questions 1–8, Suppl. Fig. 1, Tab. 2). After more than 12 weeks since the COVID-19 onset, self-reported problems with writing, reading and counting, answering questions in an understandable/unambiguous manner, communication of thoughts, multitasking and memory (Questions 1–6) partially, but not completely, diminished. A normalisation was observed for determining the current date and field orientation (Questions 7–8, Suppl. Fig. 1, Tab. 2).

Men

Within the first four weeks of infection, an increase in problems with writing, reading and counting, answering questions in an understandable/unambiguous manner, thoughts communication, multitasking, and fresh memory impairment was reported (Questions 1–5, Suppl. Fig. 1, Tab. 2). There was an increase in the number of patients with a self-declared long-term memory impairment, problems determining the date, and field orientation (Questions 6–8), which was statistically insignificant.

Regarding symptoms resolution, the frequency of perceived writing, reading and counting problems normalised within 4–12 weeks; multitasking problems did so in more than 12 weeks. The remaining symptoms (i.e. precise response, communication of thoughts, and partial impairment of fresh memory, covered in Questions 2, 3 and 5) decreased after more than 12 weeks since the COVID-19 onset (Suppl. Fig.1, Tab. 2).

Differences in brain fog symptoms between women and men

Women, compared to men, reported a higher prevalence of problems with writing, reading, and counting [Question 1; for < 4 weeks, odds ratio (OR) 3.05, 95% confidence interval (CI): 1.38–6.72; for 4–12 weeks, OR 2.51, 95% CI: 1.02–6.14; for >12 weeks, OR 3.74, 95% CI: 1.12–12.56) and communication of thoughts (Question 3; for < 4 weeks, OR; 2.53, 95% CI: 1.41–4.54; for 4–12 weeks, OR; 3.74, 95% CI: 1.93–7.24; for > 12 weeks OR 2.00, 95% CI: 1.01–3.99) (Fig. 2, Suppl. Fig. 1). A difference in the self-declared 'answering questions in an understandable/unambiguous manner' (Question 2) was statistically significant between 4–12 weeks post-infection (OR 2.63, 95% CI: 1.36–5.10), while impairment of recalling new information (Question 5) was observed below 12 weeks (OR 2.54, 95% CI: 1.44-4.48 and OR 2.43, 95% CI: 1.37–4.31 for < 4 weeks and 4–12 weeks, respectively) (Fig. 2). There was a trend towards persistence of both symptoms for 12 weeks (Question 2, p = 0.065 and Question 5, p = 0.073). We observed no sex differences in reporting problems with multitasking (Question 4), remembering information from the past (Question 6), determining the current date (Question 7), or field orientation (Question 8).

Table 2. Elements of brain fog in four time periods reported retrospectively by women and men after COVID-19

Problems with:	Prior to COVID-19			0–4 weeks			4–12 weeks			> 12 weeks		
	Women	Men	p-value	Women	Men	p-value	Women	Men	p-value	Women	Men	p-value
1. Writing, reading, and counting, n (%)	7 (2.92)	1 (1.61)	1.000	75 (31.12)	8 (12.90)	0.004	51 (21.16)	6 (9.68)	0.039	40 (16.95)	3 (5.17)	0.022
2. Answering the questions in an understandable or unambiguous manner, n (%)	14 (5.81)	3 (4.84)	1.000	104 (43.15)	21 (33.87)	0.186	99 (41.08)	13 (20.97)	0.003	69 (29.24)	10 (17.24)	0.065
3. Thoughts communicating during a conversation in a way that others can understand, n (%)	36 (14.94)	4 (6.45)	0.929	136 (56.43)	21 (33.87)	0.002	120 (49.79)	13 (20.97)	< 0.001	81 (34.32)	12 (20.69)	0.046
4. Performing several independent tasks simultaneously, n (%)	33 (13.69)	13 (20.97)	0.154	137 (56.85)	32 (51.61)	0.459	127 (52.70)	25 (40.32)	0.082	88 (37.29)	19 (32.76)	0.521
5. Recalling new information, n (%)	54 (22.41)	8 (12.90)	0.099	163 (67.63)	28 (45.16)	< 0.001	146 (60.58)	24 (38.71)	0.002	108 (45.76)	19 (32.76)	0.073
6. Remembering information from the past, for example, recognizing people or remembering events, n (%)	27 (10.79)	11 (17.74)	0.136	68 (28.22)	20 (32.26)	0.531	52 (21.58)	20 (32.26)	0.078	41 (17.37)	14 (24.14)	0.237
7. Determining the current date and naming the days of the week, n (%)	15 (6.22)	6 (9.68)	0.340	54 (22.41)	7 (11.29)	0.512	44 (18.26)	7 (11.29)	0.191	30 (12.71)	7 (12.07)	0.895
8. Finding the right way in a familiar place, n (%)	6 (2.49)	2 (3.23)	0.668	34 (14.11)	4 (6.45)	0.132	25 (10.37)	7 (11.29)	0.843	17 (7.20)	4 (6.90)	1.000

Data is presented as numbers and percentages of patients who responded 'yes' to each question in each of four time periods assessed retrospectively

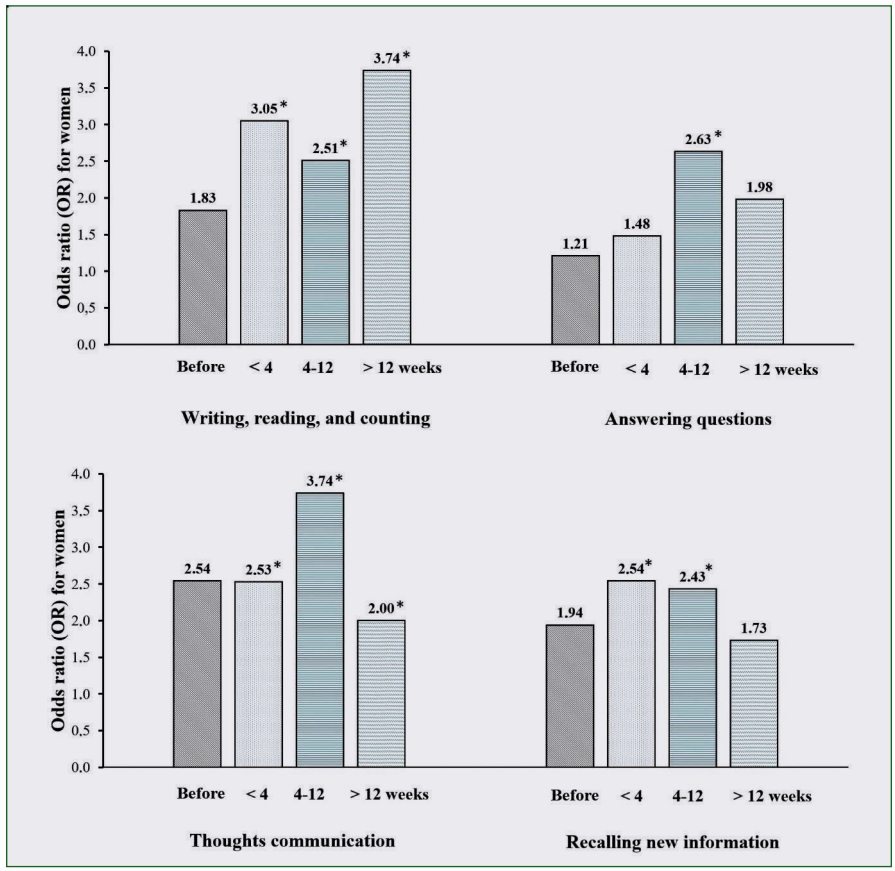

Figure 2. Sex-related risk of brain fog symptoms during four time periods assessed retrospectively by patients. OR — odds ratio

Discussion

To the best of our knowledge, this is one of the first studies to reveal that the retrospectively self-reported course of brain fog after COVID-19 in women compared to men differs in relation both to the quality and the quantity of symptoms. Women more often reported problems with writing, reading, counting and communication of thoughts. They also more often declared difficulties with answering questions in an understandable/unambiguous manner between four and 12 weeks after the onset of COVID-19, and in recalling new information up to 12 weeks after infection. To date, one retrospective study has investigated the quality of brain fog symptoms in 50 individuals from the UK, the majority of whom were not hospitalised due to COVID-19 [28]. In this group, mostly females (n = 42) contacted by e-mail 4–6 months after illness, it was shown that difficulties in memory, language, attention and executive function reported by patients lasted from weeks to months after the acute phase of the SARS-CoV-2 infection, and then gradually improved over months [28]. Due to the small sample size, the authors, however, were unable to search for sex differences.

In a large study comprising nearly 1,600 patients from five hospitals in Spain, and followed during two visits — at mean 8.5 and 13.2 months after hospital discharge — it was shown that the prevalence of brain fog, concentration and memory loss decreased between the first and the second follow-up visit, although between 2.4% and 6.3% of patients developed these symptoms only during the second visit [29]. No sex differences were noted between patients who reported new-onset cognitive symptoms during the first and the second follow-up visit; however, this studied group was older (mean age 61.5 years) than the patients participating in our research [29]. A previous study of 303 non-hospitalised patients from the USA who completed an online survey showed that the prevalence of brain fog at 30 and at more than 60 days after SARS-CoV-2 infection onset was similar, being 30.8% and 33.1% respectively [30]. The number of persistent COVID-19 symptoms did not change during the follow-up period; no significant sex differences were found, although women more often suffered from post-COVID sequelae, including brain fog, fatigue, and stress or anxiety [30]. A recent Iranian study on a large sample of nearly 2,700 hospitalised patients based on telephone interviews showed that female sex was a risk factor for reporting brain fog three months after SARS-CoV-2 infection, although only one question concerning the ability to concentrate compared to their pre-COVID ability was asked [31]. A large meta-analysis of 20 studies on more than 13,000 hospitalised patients showed that female sex increased the risk of any new or persistent mental health symptom 1.67-fold after COVID-19 [23].

A higher prevalence of neurological long COVID symptoms in women was also confirmed in a recent retrospective study of 213 subjects attending outpatient service [32]. In a mixed cohort of 217 hospitalised and non-hospitalised patients from Spain, it was shown that during follow-up visits two and six months after the onset of COVID-19, symptoms such as fatigue, emotional affectation, and cognitive deficits were more prominent in women than in men [33]. The exception here was depression, more often found in men two months, but not six months, after SARS-CoV-2 infection [33]. Another study of Italian patients with COVID-19, half of whom were hospitalised, revealed that female sex increased the risk of psychological distress more than 5-fold [34]. A large multicentre UK study of 1,077 patients showed that female sex, apart from middle age (between 40 and 59 years), a higher number of comorbidities (two or more), and a greater severity of the acute phase of illness, increased the risk of the lack of recovery six months after hospital discharge due to COVID-19 [35]. However, cognitive impairment remained independent from the recovery cluster [35]. Finally, a retrospective analysis of electronic records of more than 270,000 COVID-19 survivors showed that the risk of long COVID was slightly higher in females [36]. Recent studies have revealed that post-COVID sequelae are more common in middle-aged women [37] and in those aged 20 or older [38], suggesting the potential role of an interaction between age and sex.

Therefore, the results of our research are consistent with previous studies showing that female sex increases the risk of post-COVID brain fog symptoms. Our study additionally has revealed that self-declared neurocognitive symptoms of brain fog, affecting memory, language, and attention, are especially more common in women after the SARS-CoV-2 infection.

Our study, although of a retrospective design, is among the first to have shed more light on the course of brain fog symptoms during and after COVID-19. In a previous Brazilian study of 236 patients, of whom 86.3% were non-hospitalised, and who were at a similar median age as our group, the authors compared symptoms during the acute phase of COVID-19 and long COVID, i.e. 5-8 months after the infection [39]. They found that fatigue was present in 33.9% of patients in the acute phase and persisted in 21.2% of individuals [39]. Memory problems were reported by 39.8% of patients only during long COVID, and were then associated with sleep complaints and depressive mood [39].

In our study on the contrary, memory problems were most commonly reported retrospectively by patients during the first four weeks of disease. Sarabadani et al. [40] studied the change of COVID-19 symptoms over time in social media, based on nearly 23,000 Reddit posts, with the use of machine learning tools. The authors were able to show that symptoms perceived as brain fog, such as mental discomfort, distress, and confusion, were prominent after recovery from the acute phase of illness and remained longer, even for as long as 38 to 50 days, compared to other symptoms [40]. However, the number of COVID-19 symptoms was smaller after the acute phase of the disease [40]. On the other hand, in an Italian study of 465 patients, it was shown than any of the COVID-19 symptoms, including fatigue, had decreased at 9-month follow-up compared to the onset of infection [34]. Similar conclusions came from a study of Ecuadorian patients with mild COVID-19, in whom improvement in cognitive performance measured by Montreal Cognitive Assessment (MoCA) score was noted within 18 months after infection [41].

Thus, it seems that brain fog symptoms tend to decrease over the next few months after the onset of the SARS-CoV-2 infection.

With the increasing prevalence of post-COVID brain fog symptoms worldwide, the need for an easily obtained yet sensitive assessment tool still exists. The authors of previous studies used different ways to evaluate post-COVID symptoms, both prospectively and retrospectively. For example, one question regarding concentration ability was asked by telephone interview three months after hospital discharge [31], whereas other researchers used a list of 25 possible post-COVID symptoms that was shown to patients every three months during an online survey [30]. There have also been studies that have used more specific neuropsychological testing, such as MoCA [42], the 10-item Kessler Psychological Distress Scale questionnaire [34], or even a battery of standardised neurocognitive instruments [43]. Similarly to our study, researchers from Wuhan first interviewed 30 patients who recovered from COVID-19, and on the basis of these interviews, as well as medical expert opinion, developed a follow-up questionnaire regarding post-COVID symptoms [44].

Nevertheless, there is still no consensus regarding the type of tool preferred to assess post-COVID symptoms, although NICE guidelines underline that patients after the acute phase of infection should be specifically asked about possible symptoms such as fatigue, brain fog, concentration or memory loss, and sleep disturbances [10].

Currently, there are several hypotheses for the pathophysiology of neuropsychiatric symptoms after COVID-19, including brain fog. An Italian study of 67 patients after mild SARS-CoV-2 infection revealed that COVID-19 survivors compared to healthy controls more often experienced cognitive difficulties that were confirmed during neuropsychological testing showing impairments in attention and executive functions [45]. The presence of these deficits was associated with reduced primary motor cortex excitability and several other parameters in transcranial magnetic stimulation studies, suggesting alterations of cholinergic and GABA-ergic neurotransmission [45]. It also seems that metabolic dysfunction, with insulin resistance and obesity, together with chronic inflammation, may predispose to the post-acute sequelae of COVID-19 [46]. Persistent neuropsychiatric symptoms may develop due to neuroinflammation [47], leading to a dysfunction of microglia and mitochondria [48] and the aggregation of tau protein and subsequent neurodegeneration [49].

The higher incidence and longer duration of self-declared cognitive symptoms in women could be explained by their

stronger immune responses and chronic inflammatory cascade induced by the SARS-CoV-2 viral fragments hidden in the brain or other reservoirs [50]. The complex interplay between genetic and hormonal factors could also contribute to the sex differences in the course of COVID-19-associated brain fog [51]. Oestrogen can exert a pro-inflammatory activity, and genes of immune regulation are encoded on X chromosomes [52]. Previous studies also showed that in many neurological and psychiatric illnesses, sex-associated differences in response to stress stimuli might affect brain health, and thus cognitive symptoms and their recovery [53]. This has also been shown in depression and anxiety disorders, and their influence on the higher prevalence of brain fog symptoms in women could have been amplified during the COVID-19 pandemic [54]. Additionally, anxiety, depression, and stress may share similar proinflammatory pathophysiological pathways that in the case of COVID-19 were found to be altered by a patients's biological sex [55].

Therefore, the results of our study could be perceived as hypothesis-generating.

Our study has important limitations. Firstly, the research had a cross-sectional design and was based on symptoms reported retrospectively by patients a few months after COVID-19 onset, with questionnaires filled out only once. Moreover, as the questionnaires were filled out anonymously, it was not possible to confirm the validity of responses. Secondly, in the literature there are different definitions regarding what is perceived to be brain fog, although we used the meaning proposed by NICE and the Centers for Disease Control and Prevention [10, 15]. Thirdly, there was an uneven distribution of sex in our sample, with nearly 80% of our patients being female. However, when performing a post hoc power calculation, this is satisfactory. Fourthly, there was a potential bias in response to the online survey between sexes because females tend to participate more often in such surveys, a phenomenon observed in previous studies [56]. Fifthly, there was no data regarding education, ethnicity and comorbidities, even though an influence of the latter on the prognosis in long COVID-19 has been previously documented [57]. There was also no information on the presence of neurological and psychiatric conditions that could have influenced the act of filling out the questionnaire, as well as no data on the results of additional diagnostic tests [58]. Finally, some patients were vaccinated against COVID-19 before filling out the questionnaire, although this applied only to 19% of cases.

In conclusion, our present study suggests that brain fog symptoms in non-hospitalised patients with the SARS-CoV-2 infection differ between women and men. Our study is also among the first to present details on the timeline of brain fog symptoms during and after COVID-19. Future studies will deliver new data on this topic, and — hopefully — also treatment options in women and men [59].

Conflict of interests: *None.*

Funding: *This study was supported by a grant from the National Centre for Research and Development CRACoV-HHS project (Model of multi-specialist hospital and non-hospital care for patients with SARS-CoV-2 infection) through the initiative 'Support for specialist hospitals in fighting the spread of SARS--CoV-2 infection and in treating COVID-19' (contract number — SZPITALE-JEDNOIMIENNE/18/2020). The described research was implemented by a consortium of the University Hospital in Krakow and the Jagiellonian University Medical College.*

References

1. Xu Bo, Kraemer MUG. Open COVID-19 Data Curation Group. Open access epidemiological data from the COVID-19 outbreak. Lancet Infect Dis. 2020; 20(5): 534, doi: 10.1016/S1473-3099(20)30119-5, indexed in Pubmed: 32087115.
2. Nalbandian A, Sehgal K, Gupta A, et al. Post-acute COVID-19 syndrome. Nat Med. 2021; 27(4): 601–615, doi: 10.1038/s41591-021-01283-z, indexed in Pubmed: 33753937.
3. Wnuk M, Sawczyńska K, Kęsek T, et al. Neurological symptoms in hospitalised patients with COVID-19 and their association with in-hospital mortality. Neurol Neurochir Pol. 2021; 55(3): 314–321, doi: 10.5603/PJNNS.a2021.0039, indexed in Pubmed: 34037979.
4. Drabik L, Derbisz J, Chatys-Bogacka Z, et al. Neurological Prognostic Factors in Hospitalized Patients with COVID-19. Brain Sci. 2022; 12(2), doi: 10.3390/brainsci12020193, indexed in Pubmed: 35203956.
5. Sawczyńska K, Wnuk M, Jagiełła J, et al. 4C Mortality Score correlates with in-hospital functional outcome after COVID-19-associated ischaemic stroke. Neurol Neurochir Pol. 2021; 55(3): 295–299, doi: 10.5603/PJNNS.a2021.0037, indexed in Pubmed: 33949676.
6. Montalvan V, Lee J, Bueso T, et al. Neurological manifestations of COVID-19 and other coronavirus infections: A systematic review. Clin Neurol Neurosurg. 2020; 194: 105921, doi: 10.1016/j.clineuro.2020.105921, indexed in Pubmed: 32422545.
7. Nejad JH, Allahyari F, Hosseinzadeh R, et al. Neurological symptoms of COVID-19 infection; a cross-sectional study on hospitalized COVID-19 patients in Iran. Clin Neurol Neurosurg. 2021; 210: 106985, doi: 10.1016/j.clineuro.2021.106985, indexed in Pubmed: 34700274.
8. Sawczyńska K, Wężyk K, Bosak M, et al. Acute-onset chorea and confusional state in 77-year-old COVID-19 patient: a case report. Neurol Neurochir Pol. 2022; 56(1): 106–110, doi: 10.5603/PJNNS.a2022.0003, indexed in Pubmed: 34985113.
9. Słyk S, Domitrz I. Neurological manifestations of SARS-CoV-2 - a systematic review. Neurol Neurochir Pol. 2020; 54(5): 378–383, doi: 10.5603/PJNNS.a2020.0050, indexed in Pubmed: 32667047.
10. Shah W, Hillman T, Playford ED, et al. Managing the long term effects of covid-19: summary of NICE, SIGN, and RCGP rapid guideline. BMJ. 2021; 372: n136, doi: 10.1136/bmj.n136, indexed in Pubmed: 33483331.
11. Shimohata T. Neuro-COVID-19. Clin Exp Neuroimmunol. 2022; 13(1): 17–23, doi: 10.1111/cen3.12676, indexed in Pubmed: 34899999.
12. Rass V, Beer R, Schiefecker AJ, et al. Neurological outcomes 1 year after COVID-19 diagnosis: A prospective longitudinal cohort study.

Eur J Neurol. 2022; 29(6): 1685–1696, doi: 10.1111/ene.15307, indexed in Pubmed: 35239247.
13. Vanderlind WM, Rabinovitz BB, Miao IYi, et al. A systematic review of neuropsychological and psychiatric sequalae of COVID-19: implications for treatment. Curr Opin Psychiatry. 2021; 34(4): 420–433, doi: 10.1097/YCO.0000000000000713, indexed in Pubmed: 34016818.
14. Del Brutto OH. Cognitive sequelae of COVID-19, a post-pandemic threat. Should we be worried about the brain fog? Arq Neuropsiquiatr. 2022; 80(3): 215–216, doi: 10.1590/0004-282X-ANP-2022-E003, indexed in Pubmed: 35416840.
15. Artal FC. Síndrome post-COVID-19: epidemiología, criterios diagnósticos y mecanismos patogénicos implicados. Revista de Neurología. 2021; 72(11): 384, doi: 10.33588/rn.7211.2021230.
16. Lippi G, Sanchis-Gomar F, Henry BM. COVID-19 and its long-term sequelae: what do we know in 2023? Pol Arch Intern Med. 2023 [Epub ahead of print], doi: 10.20452/pamw.16402, indexed in Pubmed: 36626183.
17. Morin L, Savale L, Pham T, et al. Writing Committee for the COMEBAC Study Group. Four-Month Clinical Status of a Cohort of Patients After Hospitalization for COVID-19. JAMA. 2021; 325(15): 1525–1534, doi: 10.1001/jama.2021.3331, indexed in Pubmed: 33729425.
18. Cacciatore M, Raggi A, Pilotto A, et al. Neurological and Mental Health Symptoms Associated with Post-COVID-19 Disability in a Sample of Patients Discharged from a COVID-19 Ward: A Secondary Analysis. Int J Environ Res Public Health. 2022; 19(7): 4242, doi: 10.3390/ijerph19074242.
19. Comelli A, Viero G, Bettini G, et al. Patient-Reported Symptoms and Sequelae 12 Months After COVID-19 in Hospitalized Adults: A Multicenter Long-Term Follow-Up Study. Front Med (Lausanne). 2022; 9: 834354, doi: 10.3389/fmed.2022.834354, indexed in Pubmed: 35391879.
20. de Miranda DAP, Gomes SVC, Filgueiras PS, et al. Long COVID-19 syndrome: a 14-months longitudinal study during the two first epidemic peaks in Southeast Brazil. Trans R Soc Trop Med Hyg. 2022; 116(11): 1007–1014, doi: 10.1093/trstmh/trac030, indexed in Pubmed: 35514142.
21. Stavem K, Ghanima W, Olsen MK, et al. Persistent symptoms 1.5–6 months after COVID-19 in non-hospitalised subjects: a population-based cohort study. Thorax. 2021; 76(4): 405–407, doi: 10.1136/thoraxjnl-2020-216377, indexed in Pubmed: 33273028.
22. Taboada M, Moreno E, Cariñena A, et al. Quality of life, functional status, and persistent symptoms after intensive care of COVID-19 patients. Br J Anaesth. 2021; 126(3): e110–e113, doi: 10.1016/j.bja.2020.12.007, indexed in Pubmed: 33413976.
23. Maglietta G, Diodati F, Puntoni M, et al. Prognostic factors for post-covid-19 syndrome: a systematic review and meta-analysis. J Clin Med. 2022; 11(6), doi: 10.3390/jcm11061541, indexed in Pubmed: 35329867.
24. Schou TM, Joca S, Wegener G, et al. Psychiatric and neuropsychiatric sequelae of COVID-19 - a systematic review. Brain Behav Immun. 2021; 97: 328–348, doi: 10.1016/j.bbi.2021.07.018, indexed in Pubmed: 34339806.
25. Badenoch JB, Rengasamy ER, Watson C, et al. Persistent neuropsychiatric symptoms after COVID-19: a systematic review and meta-analysis. Brain Commun. 2022; 4(1): fcab297, doi: 10.1093/braincomms/fcab297, indexed in Pubmed: 35169700.
26. Chatys-Bogacka Z, Mazurkiewicz I, Slowik J, et al. Brain fog and quality of life at work in non-hospitalized patients after COVID-19. Int J Environ Res Public Health. 2022; 19(19), doi: 10.3390/ijerph191912816, indexed in Pubmed: 36232113.
27. Thornton L, Batterham PJ, Fassnacht DB, et al. Recruiting for health, medical or psychosocial research using Facebook: Systematic review. Internet Interv. 2016; 4: 72–81, doi: 10.1016/j.invent.2016.02.001, indexed in Pubmed: 30135792.
28. Callan C, Ladds E, Husain L, et al. 'I can't cope with multiple inputs': a qualitative study of the lived experience of 'brain fog' after COVID-19. BMJ Open. 2022; 12(2): e056366, doi: 10.1136/bmjopen-2021-056366, indexed in Pubmed: 35149572.
29. Fernández-de-las-Peñas C, Martín-Guerrero J, Cancela-Cilleruelo I, et al. Exploring the trajectory recovery curve of the number of post-COVID Symptoms: The LONG-COVID-EXP-CM Multicenter Study. International Journal of Infectious Diseases. 2022; 117: 201–203, doi: 10.1016/j.ijid.2022.02.010.
30. Bell ML, Catalfamo CJ, Farland LV, et al. Post-acute sequelae of COVID-19 in a non-hospitalized cohort: Results from the Arizona CoVHORT. PLoS One. 2021; 16(8): e0254347, doi: 10.1371/journal.pone.0254347, indexed in Pubmed: 34347785.
31. Asadi-Pooya AA, Akbari A, Emami A, et al. Long COVID syndrome-associated brain fog. J Med Virol. 2022; 94(3): 979–984, doi: 10.1002/jmv.27404, indexed in Pubmed: 34672377.
32. Michelutti M, Furlanis G, Buoite Stella A, et al. Sex-dependent characteristics of Neuro-Long-COVID: Data from a dedicated neurology ambulatory service. J Neurol Sci. 2022; 441: 120355, doi: 10.1016/j.jns.2022.120355, indexed in Pubmed: 35994869.
33. Jiménez-Rodríguez BM, Gutiérrez-Fernández J, Ramos-Urbina EM, et al. On the single and multiple associations of COVID-19 post-acute sequelae: 6-month prospective cohort study. Sci Rep. 2022; 12(1): 3402, doi: 10.1038/s41598-022-07433-8, indexed in Pubmed: 35233062.
34. Righi E, Mirandola M, Mazzaferri F, et al. Determinants of persistence of symptoms and impact on physical and mental wellbeing in Long COVID: A prospective cohort study. J Infect. 2022; 84(4): 566–572, doi: 10.1016/j.jinf.2022.02.003, indexed in Pubmed: 35150765.
35. Evans RA, McAuley H, Harrison EM, et al. PHOSP-COVID Collaborative Group. Physical, cognitive, and mental health impacts of COVID-19 after hospitalisation (PHOSP-COVID): a UK multicentre, prospective cohort study. Lancet Respir Med. 2021; 9(11): 1275–1287, doi: 10.1016/S2213-2600(21)00383-0, indexed in Pubmed: 34627560.
36. Taquet M, Dercon Q, Luciano S, et al. Incidence, co-occurrence, and evolution of long-COVID features: A 6-month retrospective cohort study of 273,618 survivors of COVID-19. PLoS Med. 2021; 18(9): e1003773, doi: 10.1371/journal.pmed.1003773, indexed in Pubmed: 34582441.
37. Hedberg P, Granath F, Bruchfeld J, et al. Post COVID-19 condition diagnosis: A population-based cohort study of occurrence, associated factors, and healthcare use by severity of acute infection. J Intern Med. 2023; 293(2): 246–258, doi: 10.1111/joim.13584, indexed in Pubmed: 36478477.
38. Wulf Hanson S, Abbafati C, Aerts JG, et al. Global Burden of Disease Long COVID Collaborators. Estimated Global Proportions of Individuals With Persistent Fatigue, Cognitive, and Respiratory Symptom Clusters Following Symptomatic COVID-19 in 2020 and 2021. JAMA. 2022; 328(16): 1604–1615, doi: 10.1001/jama.2022.18931, indexed in Pubmed: 36215063.
39. Titze-de-Almeida R, da Cunha TR, Dos Santos Silva LD, et al. Persistent, new-onset symptoms and mental health complaints in Long COVID in a Brazilian cohort of non-hospitalized patients. BMC Infect Dis. 2022; 22(1): 133, doi: 10.1186/s12879-022-07065-3, indexed in Pubmed: 35135496.

40. Sarabadani S, Baruah G, Fossat Y, et al. Longitudinal changes of COVID-19 symptoms in social media: observational study. J Med Internet Res. 2022; 24(2): e33959, doi: 10.2196/33959, indexed in Pubmed: 35076400.
41. Del Brutto OH, Rumbea DA, Recalde BY, et al. Cognitive sequelae of long COVID may not be permanent: A prospective study. Eur J Neurol. 2022; 29(4): 1218–1221, doi: 10.1111/ene.15215, indexed in Pubmed: 34918425.
42. De Lorenzo R, Conte C, Lanzani C, et al. Residual clinical damage after COVID-19: A retrospective and prospective observational cohort study. PLoS One. 2020; 15(10): e0239570, doi: 10.1371/journal.pone.0239570, indexed in Pubmed: 33052920.
43. Méndez R, Balanzá-Martínez V, Luperdi SC, et al. Short-term neuropsychiatric outcomes and quality of life in COVID-19 survivors. J Intern Med. 2021; 290(3): 621–631, doi: 10.1111/joim.13262, indexed in Pubmed: 33533521.
44. Shang YF, Liu T, Yu JN, et al. Half-year follow-up of patients recovering from severe COVID-19: Analysis of symptoms and their risk factors. J Intern Med. 2021; 290(2): 444–450, doi: 10.1111/joim.13284, indexed in Pubmed: 33904618.
45. Ortelli P, Ferrazzoli D, Sebastianelli L, et al. Altered motor cortex physiology and dysexecutive syndrome in patients with fatigue and cognitive difficulties after mild COVID-19. Eur J Neurol. 2022; 29(6): 1652-–1662, doi: 10.1111/ene.15278, indexed in Pubmed: 35138693.
46. Scherer PE, Kirwan JP, Rosen CJ. Post-acute sequelae of COVID-19: A metabolic perspective. Elife. 2022; 11, doi: 10.7554/eLife.78200, indexed in Pubmed: 35318939.
47. Bratosiewicz-Wąsik J. Neuro-COVID-19: an insidious virus in action. Neurol Neurochir Pol. 2022; 56(1): 48–60, doi: 10.5603/PJNNS.a2021.0072, indexed in Pubmed: 34642927.
48. Stefano GB, Büttiker P, Weissenberger S, et al. Editorial: The Pathogenesis of Long-Term Neuropsychiatric COVID-19 and the Role of Microglia, Mitochondria, and Persistent Neuroinflammation: A Hypothesis. Med Sci Monit. 2021; 27: e933015, doi: 10.12659/MSM.933015, indexed in Pubmed: 34016942.
49. Pratt J, Lester E, Parker R. Could SARS-CoV-2 cause tauopathy? Lancet Neurol. 2021; 20(7): 506, doi: 10.1016/S1474-4422(21)00168-X, indexed in Pubmed: 34146504.
50. Ortona E, Malorni W. Long COVID: to investigate immunological mechanisms and sex/gender related aspects as fundamental steps for tailored therapy. Eur Respir J. 2022; 59(2), doi: 10.1183/13993003.02245-2021, indexed in Pubmed: 34531277.
51. Davis LK, Stranger BE. The new science of sex differences in neuropsychiatric traits. Am J Med Genet B Neuropsychiatr Genet. 2019; 180(6): 333–334, doi: 10.1002/ajmg.b.32747, indexed in Pubmed: 31237066.
52. Conti P, Younes A. Coronavirus COV-19/SARS-CoV-2 affects women less than men: clinical response to viral infection. J Biol Regul Homeost Agents. 2020; 34(2): 339–343, doi: 10.23812/Editorial-Conti-3, indexed in Pubmed: 32253888.
53. Shansky RM. Sex differences in mechanisms of disease. Genes Brain Behav. 2020; 19(3): e12646, doi: 10.1111/gbb.12646, indexed in Pubmed: 32141220.
54. Cristillo V, Pilotto A, Piccinelli SC, et al. Predictors of "brain fog" 1 year after COVID-19 disease. Neurol Sci. 2022; 43(10): 5795–5797, doi: 10.1007/s10072-022-06285-4, indexed in Pubmed: 35930181.
55. Rabaan AA, Al-Ahmed SH, Garout MA, et al. Diverse Immunological Factors Influencing Pathogenesis in Patients with COVID-19: A Review on Viral Dissemination, Immunotherapeutic Options to Counter Cytokine Storm and Inflammatory Responses. Pathogens. 2021; 10(5), doi: 10.3390/pathogens10050565, indexed in Pubmed: 34066983.
56. Cull WL, O'Connor KG, Sharp S, et al. Response rates and response bias for 50 surveys of pediatricians. Health Serv Res. 2005; 40(1): 213–226, doi: 10.1111/j.1475-6773.2005.00350.x, indexed in Pubmed: 15663710.
57. Efstathiou V, Stefanou MI, Demetriou M, et al. Long COVID and neuropsychiatric manifestations (Review). Exp Ther Med. 2022; 23(5): 363, doi: 10.3892/etm.2022.11290, indexed in Pubmed: 35493431.
58. Taskiran-Sag A, Eroglu E, Ozulken K, et al. Headache and cognitive disturbance correlate with ganglion cell layer thickness in patients who recovered from COVID-19. Clin Neurol Neurosurg. 2022; 217: 107263, doi: 10.1016/j.clineuro.2022.107263, indexed in Pubmed: 35525105.
59. González-Herazo MA, Silva-Muñoz DC, Guevara-Martínez PA, et al. Post-COVID 19 Neurological Syndrome: a fresh challenge in neurological management. Neurol Neurochir Pol. 2021; 55(4): 413–414, doi: 10.5603/PJNNS.a2021.0052, indexed in Pubmed: 34346051.