Original article

Fear and anxiety in patients with multiple sclerosis during COVID-19 pandemic; report of an Iranian population

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A B S T R A C T

Background: There are reports that stress-related disorders are increasing during coronavirus disease 2019 (COVID-19) pandemic. Patients with Multiple Sclerosis (MS) are at higher risk of developing psychiatric disorders, which result in worsening of their disability. There are concerns about the mental health of MS patients during this pandemic.
Objective: We aimed to evaluate the prevalence of anxiety, depression, and levels of fear about Corona in MS patients during the COVID-19 pandemic.
Materials and methods: This was a cross-sectional study on MS patients who were admitted to the MS clinics affiliated with Isfahan University of medical sciences from May to June 2020. Anxiety and depression were evaluated according to the Hospital Anxiety and Depression Scale (HADS). The Corona Fear Questionnaire developed by Ahorsu et al. was applied to evaluate the state of fear about COVID-19. Chi-square tests were used to compare depression and anxiety between different groups, Kruskal-Wallis was used for fear scores, Spearman correlation coefficient was also reported for correlations.
Results: 410 MS patients with a mean age of 38.6 years (±10.35) were enrolled in the study. Among those patients who answered the HADS questionnaire completely (n=399, n=388, for anxiety and depression subscales respectively) the prevalence of anxiety and depression were 31.2% (n=128) and 39.3% (n=161), respectively. There was no significant relationship between anxiety and depression with any of the following variables: sex, marital status, history of drug abuse, smoking, duration of taking psychiatric medication, being tested for COVID-19, being quarantined. Regarding fear about COVID-19, patients with depression or anxiety showed higher scores on the fear questionnaire (p-value=0.03, p-value=0.008 respectively).
Conclusions: The prevalence of anxiety and depression in MS patients was higher than previously reported. Fear about COVID-19 was correlated with anxiety and depression. Multicenter studies are required to develop specific recommendations for screening mental health problems in MS patients during COVID pandemic.

1. Introduction

Multiple sclerosis (MS) is a chronic disease of the central nervous system and the most common cause of neurological disability in young adults (Koch-Henriksen and Sørensen, 2010). It has a prevalence of about 112.0 per 100000 population in the world and of 51.52 per 100 000 population in Iran (Mohebi et al., 2019). Beside physical comorbidities, MS patients are at higher risk of developing different psychiatric comorbidities (Hoang et al., 2016, Scherder et al., 2018) among which depression and anxiety disorders are more common (Paparrigopoulos et al., 2010). These disorders may be present even at the onset of MS and increase over the course of the disease (Marrie et al., 2015), so that about 95% of MS patients may experience psychiatric comorbidities during their lifetime (Paparrigopoulos et al., 2010).

Since December 2019 we are experiencing an unprecedented time, as the Coronavirus Disease 2019 (COVID-19) pandemic is causing stress

and fear all over the world. There are increasing reports of stress- related disorders, including anxiety and depression, as well as alcohol and tobacco abuse (Ozamiz-Etxebarria et al., 2020). There will be more concerns about mental health of patients with chronic diseases, such as MS. They are also more vulnerable to consequences of psychiatric disorders. Psychiatric disorders (i.e. anxiety) can increase disability, relapse rate, MRI activity, and suicidal thoughts and behaviors in MS patients (Seyed Ahadi et al., 2020, McKay et al., 2018, Artemiadis et al., 2011).

It is reasonable that anxiety has a negative effect on self-rated quality of life in MS patients (Chertcoff et al., 2020). The extent to which quarantine, social distancing and pandemic related fears can influence MS patients' health should be addressed more explicitly. The aim of this study was to investigate the prevalence of anxiety, depression, and levels of fear about COVID-19, in MS patients during COVID-19 pandemic.

2. Method

This was a cross-sectional study on MS patients, diagnosed by recent Mc Donald criteria (Thompson et al., 2018), who were admitted to the MS clinic affiliated with Isfahan University of medical sciences from May to June 2020. The study was approved by the Ethics Committee of Isfahan University of Medical Sciences with the ethics code of IR.MUI. MED.REC.1399.379. Demographic information and clinical course descriptions (e.g. age, sex, age at the onset of MS, history of relapse within last one year, history of moderate to severe MS relapse (which required high dose steroid therapy)) were recorded for each patient (Table 1).

We applied Hospital Anxiety and Depression Scale (HADS) to assess the state of anxiety and depression. The HADS questionnaire is a reliable self-assessment tool for detecting severity of anxiety and depression in outpatient clinics. It has seven items each for depression and anxiety subscales. Each item is scored on a 0 to 3 range. The total score (e.g. sum of the respective 7 items for each subscale and 14 items for overall score). A total subscale score of $\geq$8 points out of a possible 21 in the HADS questionnaire was considered as positive for anxiety and the same cut-off was applied for depression. The reliability and validity of the Persian version of the HDAS questionnaire were reported previously (Montazeri et al., 2003).

The Corona Fear Questionnaire was applied to evaluate the fear about COVID-19. This tool consists seven items with a 1 to 5 scale (1= strongly disagree, 5= strongly agree). The total score is from 5 to 35, the higher the total score the more the fear of coronavirus. The validity and reliability of this scale was studied and established in different populations as well as in the Iranian population (Ahorsu et al., 2020).

Table 1
Demographic and clinical characteristics of patients (n=410)

	characteristic	n (%)
Sex	Female	326 (79.5)
	Male	84 (20.5)
	Age, in years	38.60 (±10.35)*
Education	Without Academic degree	224 (54.6)
	With Academic degree	186 (45.4)
Occupation	Unemployed	288 (70.2)
	Employed	112 (27.3)
Marital status	Single	97 (23.6)
Married		311 (75.7)
Age at the onset of MS		29.2 (±9.39)*
History of drug abuse		9 (2.2)
Smoking		37 (9.0)
History of psychiatric disorders		114 (27.8)
History of taking psychiatric medication		102 (24.9)
Being tested for COVID-19		38 (9.3)
Being quarantined		224 (56.3)
Being hospitalized in the last two months		65 (15.9)
History of MS relapse within last 1 year		157 (38.3)
History of moderate to severe MS relapse (which required high dose steroid therapy)		72 (17.6)

* Mean (standard deviation)

Chi-square tests were performed to compare depression and anxiety status between different groups. The global score of fear questionnaire were analyzed using Mann-Whitney and Kruskal-Wallis tests. Spearman correlation coefficient was also reported for correlations. Significant level for tests was considered at 0.05. Statistical analysis was performed with SPSS version 25.0.

3. Results

3.1. Participant Characteristics

Relevant demographic information for 410 participants with MS (326 females and 84 males) is summarized in Table 1. The mean age (±SD) of the patients was 38.60 (±10.35) years. Among all participants, 45.4% (n=186) had an academic degree. Also, 75.7% of the participants (n=311) were married, and 27.3% (n=112) were employed.

More than half of the patients (56.3%, n=224) were being quarantined at home during the COVID-19 pandemic, and 9.3% of patients (n=38) were being tested for COVID-19.

3.2. State of depression and anxiety

Among those patients who answered the HADS questionnaire completely, the prevalence of depression was 39.3% (n=161) and 31.2% (n=128) had symptoms of anxiety. Depressive subjects were significantly older than participants without depression (40.71±10.59, 37.37±9.94, p-value=0.002). Similar results were obtained regarding the mean age of patients with symptoms of anxiety in comparison to those without these symptoms (39.93±10.18, 37.75±10.28, p-value=0.034).

Patients with symptoms of depression and anxiety were without academic degree in comparison to those without these symptoms (50.2% vs 31.1%, p-value<0.001, 40.6% vs 22.0%, p-value<0.001 respectively). The history of COVID-19 in family (positive / suspicious cases), was reported more frequently by patients with depression (69.2% vs 30.8%, p-value=0.047) in comparison to those without these symptoms. The mean age at the onset of MS was higher in patients with symptoms of anxiety in comparison to those without these symptoms (30.80±10.26 vs 28.35±8.83, p-value=0.025; table 4). State of depression and anxiety in MS patients under different treatment are summarized in Table 2.

There was no significant relationship between either anxiety or depression with any of the following variables: sex, marital status, history of drug abuse, smoking, duration of taking psychiatric medication, being tested for COVID-19, being quarantined.

3.3. State of fear about COVID-19

Regarding fear about COVID-19, patients with depression or anxiety showed higher scores on the fear questionnaire, in comparison to those without depression or anxiety (18.16±5.71 vs 16.73±5.93, p-value=0.030,18.50±5.94 vs 16.77±5.67, p-value=0.008, respectively)

Married individuals reported higher levels of fear about COVID-19

Table 2
State of depression and anxiety in MS patients under different treatment

Medication	Depression (n=354)		Anxiety (n=358)	
	No	Yes	No	Yes
Immunomodulator	79 (59.8)	53 (40.2)	53 (66.3)	27 (33.7)
Immunosuppressor	83 (60.1)	55 (39.9)	92 (67.2)	45 (32.8)
Others	42 (50.0)	42 (50.0)	96 (68.1)	45 (31.9)
P-value	0.269		0.960	

NOTE: data are number of patients, and data in parenthesis are percentages. P-values are for comparison of frequency of depression/ anxiety between groups.
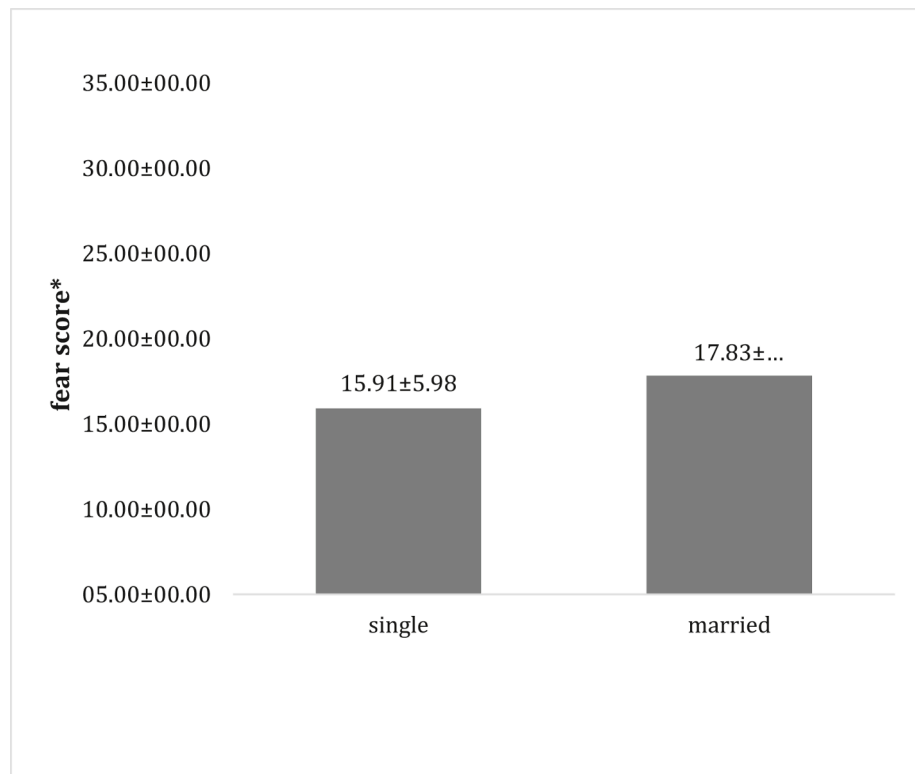
Fig. 1. Mean score of fear about corona in married and single patients (p-value=0.027)

(Figure 1, 17.83±5.72 vs 15.91±5.98, p-value=0.027). There was no significant relationship between fear about COVID-19 with any of the following variables: age, sex, academic degree, occupation, history of drug abuse, smoking, history of taking psychiatric medication, duration of taking psychiatric medication, being tested for COVID-19, being quarantined, age at the onset of MS, number of hospitalizations in the last two months, history of MS relapse within last one year, comorbidities, history of psychiatric disorders, history of moderate to severe MS relapse (which required high dose steroid therapy), history of COVID-19 in family (positive / suspicious cases), history of death due to corona in family.

4. DISCUSSION

In this cross-sectional study, we examined prevalence of anxiety, depression, and levels of fear about COVID-19 in patients with MS during the COVID-19 pandemic. Our results showed that, during the COVID-19 pandemic, the prevalence of anxiety and depression was (31.2%) and (39.3%), respectively in our MS patients. Previous studies have reported 22.1% for anxiety and 30.5% for depression (Boeschoten et al., 2017). Anxiety in MS patients is associated with lower self-efficacy, higher levels of disability, and stress (Ahmadi et al., 2018). Mental health issues are of great concern during the current COVID-19 pandemic, as psychological distress and anxiety were increasingly reported even in the healthy general population (Serafini et al., 2020, Wang et al., 2020). MS patients are more vulnerable to develop depression and anxiety disorders in comparison to healthy populations (Beiske et al., 2008) and need more attention as mental health issues can deteriorate their physical disability as well (Marrie et al., 2015). Our results showed that fear about COVID-19 correlates with state of anxiety as well as of depression. Accordingly, MS patients should be well informed about effective coping strategies such as fostering self-efficacy as well as maintaining a healthy lifestyle and social contacts to avoid anxious and depressive symptoms. These coping strategies can consequently avoid new progression or worsening of the disease.

The present study showed that MS patients with academic degree, have experienced less anxiety during the COVID-19 pandemic. This was similar to the findings of another study on factors associated with anxiety in MS patients before the COVID-19 pandemic (Pham et al., 2018, Tsivgoulis et al., 2007). Persons without academic degree may be less likely to gather required information such as relevant protocols for self-protections, clinicians should pay more attention to these patients and inform them more precisely about how and where to receive medical help or social support if needed. This may provide patients with more confidence and less anxiety.

According to our results, patients with a history of psychiatric disorder were more prone to depression during the COVID-19 pandemic, 58.6% of these patients had depression (Table 3). Pre-existing mental disorders are generally associated with higher risk of anxiety and depression in MS patients (Chertcoff et al., 2020). These patients require more support regarding coping with fear about COVID-19. The same recommendation is reasonable for patients with older age who were also according to our results, more susceptible to anxiety during the COVID-19 pandemic. They have also reported significantly higher depression scores than younger participants. In a previous study conducted on 7,786 MS patients; the lowest levels of depression were found in the youngest group of patients and the highest in the patients aged between 45-64 years old; however, people with older age had less risk for experiencing anxiety (Jones et al., 2012).The different results in our study can be due to higher death rate in people with older ages during COVID-19 pandemic, leading to high levels of anxiety in older MS patients. Moreover, we suppose that the age at the onset of MS seems to be more predictive than the current age of patients regarding developing anxiety. The patients who were diagnosed with MS at older ages have experienced more anxiety during the current pandemic in comparison to those with younger ages at the disease onset.

History of MS relapse within last one year and recent treatment with corticosteroids indicating a recent disease activity, were associated with fear about COVID-19 (Which was not statistically significant (. It is reasonable to recommend a close follow up of patients with active

Table 3
. Factors correlated with depression status in MS patients during the COVID-19 outbreak

Clinical and demographic parameters	Group	HADS-Depression (n=388)	
		No (n=227)	Yes (n=161)
Age, in years*		37.37 (±9.94)	40.71 (±10.59)
		p-value=0.002	
History of psychiatric disorders		42 (38.9%)	66 (61.1%)
		p-value <0.001	
History of taking psychiatric medication		41 (41.4%)	58 (58.6%)
		p-value <0.001	
History of COVID-19 in family**		4 (30.8%)	9 (69.2%)
		p-value=0.047	
Education	Without academic degree	105 (49.8%)	106 (50.2%)
	With Academic degree	122 (68.9%)	55 (31.1%)
		p-value<0.001	
Occupation	Unemployed	148 (53.8%)	127 (46.2%)
	Employed	72 (68.6%)	33 (31.4%)
		p-value=0.011	

Note: unless otherwise indicated, data are number of patients, and data in parenthesis are percentages.
P-values are for comparison of frequency of depression between groups.
 * Mean (standard deviation)
 ** Positive / suspicious cases

Table 4
Factors correlated with anxiety status in MS patients during the COVID-19 outbreak

Clinical and demographic parameters	Group	HADS-Anxiety (n=399)	
		No (n=271)	Yes (n=128)
Age, in years*		37.75 (±10.28)	39.93 (±10.18)
		p-value=0.034	
Age at the onset of MS		28.35±8.83	30.80±10.26
		p-value=0.025	
History of psychiatric disorders		59 (54.1%)	50 (45.9%)
		p-value<0.001	
History of taking psychiatric medication		58 (58.0)	42 (42.0%)
		p-value=0.015	
History of COVID-19 in family**		7 (53.8%)	6 (46.2%)
		p-value=0.363	
Education	Without academic degree	129 (59.4%)	88 (40.6%)
	With academic degree	142 (78%)	40 (22%)
		p-value <0.001	
Occupation	Unemployed	182 (64.3%)	101 (35.7%)
	Employed	81 (75.7%)	26 (24.3%)
		p-value=0.039	

Note: unless otherwise indicated, data are number of patients, and data in parenthesis are percentages.
P-values are for comparison of frequency of anxiety between groups.
 * Mean (standard deviation)
 ** Positive / Suspicious cases

disease regarding developing anxiety or depression and continuing routine clinical care to avoid disease activity during COVID-19 pandemic.

Although our center is the only comprehensive center for MS in the province, data gathered from single-center studies has limited external validity and should be confirmed with future studies. At the beginning of the study (May 2020) there were 2577913 confirmed cases and 121696 deaths, which had 32.09% decrease amount of deaths compared to April. Also, at the end of the study (June 2020) confirmed cases and deaths were 5188670 and158533 (Organization WH 2020). Obviously, these numbers vary country to country. This changing of the epidemiologic pattern of the COVID-19 pandemic over the time, may alter the patient's behaviour and reaction as well.

5. Conclusion

This study showed that MS patients, especially those with a history of psychiatric comorbidities, recent disease activity, and patients without academic degree are more prone to psychiatric disorders during the COVID-19 pandemic. Data from multi-center studies are needed to achieve better recommendations regarding screening psychiatric problems and supportive strategies in clinical practice.

Ethical Considerations

Compliance with ethical guidelines Written informed consent was obtained from all participants and the research protocol was approved by the medical ethics committee of Isfahan University of Medical Sciences.

Authors contributions

All authors contributed in preparing this article.

CRediT authorship contribution statement

Neda Ramezani: Investigation, Resources, Data curation, Writing - review & editing. **Fereshteh Ashtari:** Supervision, Conceptualization, Methodology, Writing - review & editing. **Elahe Abdi Bastami:** Data curation, Writing - original draft. **Kimia Ghaderi:** Data curation, Writing - original draft. **Sayed Mohsen Hosseini:** Formal analysis. **Maryam Kazemi Naeini:** Formal analysis. **Fatemeh Rajabi:** Validation, Methodology. **Iman Adibi:** Supervision, Conceptualization, Methodology, Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

1 Koch-Henriksen, N, Sørensen, PS., 2010. The changing demographic pattern of multiple sclerosis epidemiology. The Lancet Neurology 9 (5), 520–532.
2 Mohebi, F, Eskandarieh, S, Mansournia, MA, Mohajer, B, Sahraian, MA., 2019. Multiple Sclerosis in Tehran: Rising Prevalence alongside Stabilizing Incidence - True Increase or Enhanced Diagnosis? Archives of Iranian medicine 22 (8), 429–434.
3 Hoang, H, Laursen, B, Stenager, EN, Stenager, E., 2016. Psychiatric co-morbidity in multiple sclerosis: The risk of depression and anxiety before and after MS diagnosis. Multiple sclerosis (Houndmills, Basingstoke, England) 22 (3), 347–353.
4 Scherder, R, Kant, N, Wolf, ET, Pijnenburg, B, Scherder, EJ., 2018. Psychiatric and physical comorbidities and pain in patients with multiple sclerosis. Journal of pain research 11, 325–334.

5 Paparrigopoulos, T, Ferentinos, P, Kouzoupis, A, Koutsis, G, Papadimitriou, GN., 2010. The neuropsychiatry of multiple sclerosis: focus on disorders of mood, affect and behaviour. International review of psychiatry (Abingdon, England) 22 (1), 14–21.

6 Marrie, RA, Reingold, S, Cohen, J, Stuve, O, Trojano, M, Sorensen, PS, et al., 2015. The incidence and prevalence of psychiatric disorders in multiple sclerosis: a systematic review. Multiple sclerosis (Houndmills, Basingstoke, England) 21 (3), 305–317.

7 Ozamiz-Etxebarria, N, Dosil-Santamaria, M, Picaza-Gorrochategui, M, Idoiaga-Mondragon, N., 2020. Stress, anxiety, and depression levels in the initial stage of the COVID-19 outbreak in a population sample in the northern Spain. Cadernos de saude publica 36 (4), e00054020.

8 Seyed Ahadi, M, Sahraian, MA, Rezaeimanesh, N, Naser Moghadasi, A, 2020. Psychiatric Advice During COVID-19 Pandemic for Patients with Multiple Sclerosis. Iran J Psychiatry Behav Sci 14 (2), e103243.

9 McKay, KA, Tremlett, H, Fisk, JD, Zhang, T, Patten, SB, Kastrukoff, L, et al., 2018. Psychiatric comorbidity is associated with disability progression in multiple sclerosis. Neurology 90 (15), e1316. -e23.

10 Artemiadis, AK, Anagnostouli, MC, Alexopoulos, EC., 2011. Stress as a risk factor for multiple sclerosis onset or relapse: a systematic review. Neuroepidemiology 36 (2), 109–120.

11 Chertcoff, A, Curbelo, MC, Bauer, J, Ferrandina, F, Martinez, A, Steinberg, J, et al., 2020. Anxiety in Argentinian patients with multiple sclerosis: Prevalence and associated factors. Multiple sclerosis and related disorders 41, 102042.

12 Thompson, AJ, Banwell, BL, Barkhof, F, Carroll, WM, Coetzee, T, Comi, G, et al., 2018. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. The Lancet Neurology 17 (2), 162–173.

13 Montazeri, A, Vahdaninia, M, Ebrahimi, M, Jarvandi, S., 2003. The Hospital Anxiety and Depression Scale (HADS): translation and validation study of the Iranian version. Health and quality of life outcomes 1, 14.

14 Ahorsu, DK, Lin, CY, Imani, V, Saffari, M, Griffiths, MD, Pakpour, AH., 2020. The Fear of COVID-19 Scale: Development and Initial Validation. International journal of mental health and addiction 1–9.

15 Boeschoten, RE, Braamse, AMJ, Beekman, ATF, Cuijpers, P, van Oppen, P, Dekker, J, et al., 2017. Prevalence of depression and anxiety in Multiple Sclerosis: A systematic review and meta-analysis. Journal of the neurological sciences 372, 331–341.

16 Ahmadi, AM, Mobini, A, Kabiri, F, Bidaki, R, Bozorg, B., 2018. Relationship Between Anxiety and Depression with Disability Over Multiple Sclerosis Patients in Rafsanjan. Iran. Archives of Neuroscience. 5 (2), 6.

17 Serafini, G, Parmigiani, B, Amerio, A, Aguglia, A, Sher, L, Amore, M., 2020. The psychological impact of COVID-19 on the mental health in the general population. QJM: An International Journal of Medicine 113 (8), 531–537.

18 Wang, C, Pan, R, Wan, X, Tan, Y, Xu, L, Ho, CS, et al., 2020. Immediate psychological responses and associated factors during the initial stage of the 2019 coronavirus disease (COVID-19) epidemic among the general population in China. International journal of environmental research and public health 17 (5), 1729.

19 Beiske, A, Svensson, E, Sandanger, I, Czujko, B, Pedersen, E, Aarseth, J, et al., 2008. Depression and anxiety amongst multiple sclerosis patients. European journal of neurology 15 (3), 239–245.

20 Marrie, RA, Elliott, L, Marriott, J, Cossoy, M, Blanchard, J, Leung, S, et al., 2015. Effect of comorbidity on mortality in multiple sclerosis. Neurology 85 (3), 240–247.

21 Pham, T, Jetté, N, Bulloch, AG, Burton, JM, Wiebe, S, Patten, SB., 2018. The prevalence of anxiety and associated factors in persons with multiple sclerosis. Multiple sclerosis and related disorders 19, 35–39.

22 Tsivgoulis, G, Triantafyllou, N, Papageorgiou, C, Evangelopoulos, ME, Kararizou, E, Sfagos, C, et al., 2007. Associations of the Expanded Disability Status Scale with anxiety and depression in multiple sclerosis outpatients. Acta neurologica Scandinavica 115 (1), 67–72.

23 Jones, KH, Ford, DV, Jones, PA, John, A, Middleton, RM, Lockhart-Jones, H, et al., 2012. A large-scale study of anxiety and depression in people with Multiple Sclerosis: a survey via the web portal of the UK MS Register. PloS one 7 (7), e41910.

24.Organization WH. Coronavirus disease (COVID-19) outbreak. 2020. URL https://www who int/emergencies/diseases/novel-coronavirus-2019. 2020.