












COVID-19 pandemic and mental distress in multiple sclerosis: implications for clinical management

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Background and purpose: In multiple sclerosis (MS), disease-related factors and dysfunctional coping might favor the development of mental distress induced by COVID-19 containment measures. Aim of this study was exploring the relationship between disability, coping strategies, daily life reorganization and neuropsychiatric symptoms in an Italian MS population during the COVID-19 lockdown, in order to identify potentially modifiable factors that could inform clinical management of mental distress in people with MS.

Methods: We explored the relationship between mental distress, disability and coping strategies in the Italian MS population under lockdown. Structural equation modeling was applied to information collected via web survey to identify modifiable factors that could account for mental distress.

Results: A total of 845 participants (497 with MS and 348 controls) were included in the study. The MS group had higher scores than the control group for depression ($P = 0.005$), but not for anxiety, emotional dyscontrol or sleep disturbances. The structural equation modeling explained 74% of the variance observed in depression score. Within the model, three latent factors were characterized from measured variables: motor disability and cognitive dysfunction contributed to disability ($\beta = 0.509$ and $\beta = 0.836$; $P < 0.001$); positive attitude and exercise contributed to active attitude ($\beta = 0.386$ and $\beta = 0.297$; $P < 0.001$); and avoidance, social support and watching television contributed to passive attitude ($\beta = 0.301$, $\beta = 0.243$ and $\beta = 0.212$; $P < 0.001$). With regard to the relationship between latent factors and their influence on depression, disability contributed to passive attitude ($\beta = 0.855$; $P < 0.001$), while both passive and active attitude significantly influenced depression ($\beta = 0.729$ and $\beta = -0.456$; $P < 0.001$).

Conclusion: As a practical implication of our model, favoring exercise would enhance active attitude and its positive impact on mental well-being while, at the same time, reducing the negative impact of disability on depression, representing a valuable tool in facing COVID-19-related mental distress.

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Introduction

Since the first cases reported in China in December 2019, COVID-19 has been spreading worldwide at an alarming rate, with the first Italian case recorded on February 21, 2020. As cases spiked in the country, in the attempt to

limit the diffusion of the virus and the pressure on the national healthcare service, a nationwide lockdown was enforced on March 9, 2020. The mental strain of containment measures, already described during previous infectious outbreaks [1,2], has been confirmed during the current pandemic in the general population [3,4] and in people with chronic conditions such as epilepsy and cancer [5,6]. Although first reports suggest that in multiple sclerosis (MS) no worsening in anxiety or depression was noted as a consequence of the lockdown [7,8], an increase in anxiety has been described in relation to disease management and access to healthcare services [9]. In addition to these factors, uncertainty about the risk related to immunotherapy might favor mental distress, which will ultimately depend also on the applied coping strategy [10]. Two general coping strategies have been distinguished so far: active coping strategies, namely, the efforts to change the nature of the stressor, and avoidant coping strategies, namely, the involvement in activities or mental states not focused on the stressful triggers [11]. People with MS adopt different coping strategies according to their level of disease activity and disability [12,13] and, while no coping strategy is, *per se*, maladaptive, a specific strategy might prove more effective than others to counterbalance mental distress.

In the present study, we explored the relationship between disability, coping strategies, daily life reorganization and neuropsychiatric symptoms in the Italian MS population during the COVID-19 lockdown, in order to identify potentially modifiable factors that could inform clinical management of mental distress in people with MS.

Methods

Study design

The survey of Italian-speaking people consisted of 69 items, with an estimated completion time of 15–20 min. To avoid missing data, in order to proceed from one section of the survey to the next, all questions had to be completed, and questionnaire answers could be submitted only if all fields had been filled. Participant recruitment was web-based: the survey, developed through the European Commission's official survey management tool (<https://ec.europa.eu/eusurvey>), was shared via SMSocialnetwork.com, a social Facebook-like network dedicated to people with MS [14], and the Facebook page of the MS Center of the University of Naples Federico II. Respondents were asked to share the link with family members and/or friends not affected by MS, in order to obtain a sociodemographically comparable control group. The version of the survey adapted for controls did not contain items specific to MS (i.e.,

ongoing immunotherapy, disability scales). Considering the difference in the prevalence of anxiety and depression between the MS and the control group [15], a sample size of 133 participants for depression and 149 participants for anxiety was determined, assuming 90% power and type 1 error $\alpha = 0.05$, with equal numbers of participants per group. Based on this estimate, a minimum target of 300 respondents was fixed and the enrollment period was set to 2 weeks (from April 22 to May 7, 2020), with a backup strategy to extend the enrollment period in case the target could not be reached.

Information on the following domains was collected: (i) sociodemographic features; (ii) general and MS-related health status; (iii) changes in lifestyle, including interference of lockdown with disease management, web usage and free-time activities; (iv) COVID-19 infection and risk perception; (v) physical disability, assessed via the Patient-Determined Disease Steps (PDDS) scale [16,17,18,19] and the Upper Extremity Function – Short Form (UEF) from the Quality of Life in Neurological Disorders (Neuro-QoL) measurement system [20]; (vi) cognitive function, investigated using the Cognition Function – Short Form from the Neuro-QoL, and abstract reasoning, logical thinking and, in part, sustained attention, measured using six Raven-like matrices; (vii) mental distress: four domains from the Neuro-QoL were explored, specifically, sleep disturbances, anxiety feelings, depressive symptoms, emotional dyscontrol; and (viii) coping strategies: individual response to lockdown was assessed using 18 items from the COPE-NVI-25 [21], evaluating five independent coping strategies: avoidance; social support; positive attitude; problem solving; and turning to religion. Scores were computed as ratios of number of items indicating the application of a specific strategy/total number of items exploring application of that specific strategy.

Further details about the content of the survey can be found in Appendix S1.

Standard protocol approvals, registrations and patient consents

The study was approved by the Carlo Romano ethics committee of the University of Naples Federico II (n.160/20), and was performed in accordance to the Declaration of Helsinki, UE regulations 2016/679 and 2018/1725. All patients and controls gave informed consent before participating in the online survey.

Statistical analysis

Differences in sociodemographic features and coping strategies between people with MS and controls were

assessed with Fisher's test, the chi-squared test and the *t*-test, as appropriate. Differences in daily habits and Internet usage were investigated via ANCOVA, accounting for age and gender. Differences in mental distress between the MS and the control group were additionally adjusted for pre-existent psychiatric conditions, while differences in cognitive status were additionally controlled for education. Each comparison was considered significant for $P < 0.05$ (Bonferroni-corrected at 0.05/number of tested variables).

Data analysis was performed using structural equation modeling with maximum likelihood estimation. Preliminary correlations were run to assess relationships between depression, disability, time organization and coping strategies. Variables that significantly correlated with the outcome of interest (Bonferroni-corrected $P < 0.001$, considering 0.05/41 as the number of considered variables) were selected to be entered in the final model. Specifically, the measurement model tested the adequacy of the measured independent variables as indicators of the latent variables hypothesized in the framework of the engagement/disengagement coping theory, while the structural model examined relationships among the latent variables as well as with depression. The following goodness-of-fit statistics were applied to the final estimated model: root mean square error of approximation; goodness-of-fit index; comparative fit index; and minimal discrepancy. Statistical analysis was conducted in SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp and Amos (Version 24.0). Chicago: IBM SPSS.

Results

Characteristics of the study population

From April 22 to May 7, 2020, 856 people completed the online survey. Of these, seven who were residing abroad, one who had amyotrophic lateral sclerosis, and three controls whose age fell outside the age range of the people with MS were excluded from the analysis. The final study population included 497 people with MS and 348 controls. Response rate by region is shown in Fig. 1 next to the number of COVID-19 cases per region.

Sociodemographic features of the study population are summarized in Table 1 and Fig. 2.

General health status

People with MS showed no significant differences in terms of comorbidities in comparison with controls ($P = 0.029$), while they presented a higher frequency of pre-existing psychiatric conditions ($P = 0.002$; Table 1). Before the pandemic, 30% of the control group and 28% of the MS group affected by psychiatric disorders were receiving psychotherapeutic treatment ($P = 0.853$). During the lockdown, 55.6% of the controls interrupted therapy versus 40.9% of the MS group, while 44.4% versus 36.4% continued via video counseling; none of the controls continued psychotherapy regularly, while 22.7% of the people with MS did ($P = 0.293$).

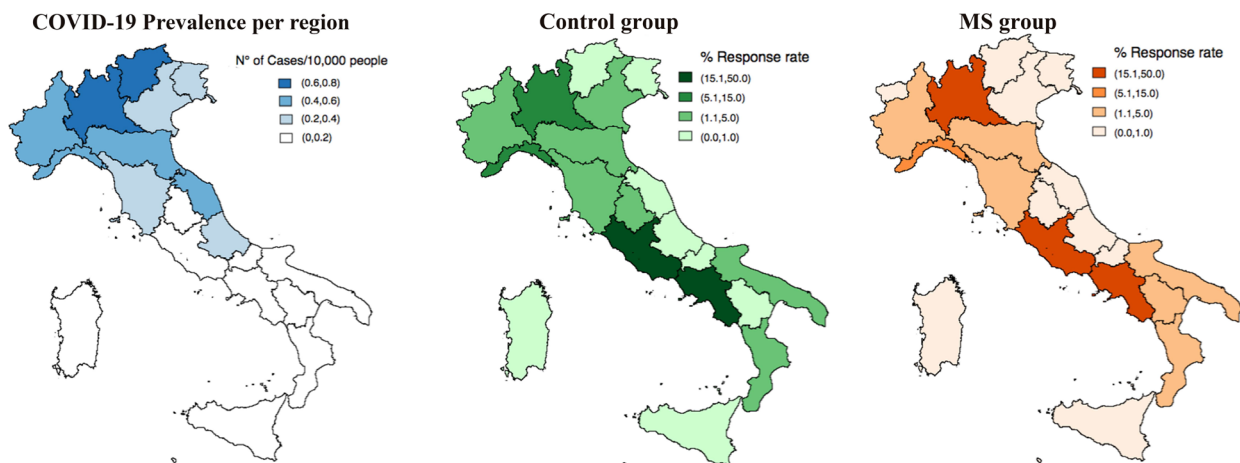


Figure 1 Prevalence of COVID-19 cases and percentage of responses per Italian region. The prevalence of COVID-19, calculated as number of cases over 10 000 people, is graded on a blue color scale. Data extracted from Protezione Civile website on April 30, 2020 (<http://www.protezionecivile.gov.it/>). The survey response rate is graded on a green color scale for control group and an orange color scale for the multiple sclerosis (MS) group.

Table 1 Sociodemographic features and general health status of the study population

	MS group	Control group	<i>P</i>
Participants, <i>n</i>	497	348	
Men, <i>n</i> (%)	146 (29.4)	84 (24.1)	0.06 ^b
Age, years	42.41 ± 10.72	40.84 ± 11.92	0.05
Education, years	14 ± 3.33	16.61 ± 2.80	<0.0001
Number of rooms	5.58 ± 2.01	5.95 ± 2.44	0.02
Access to garden/balcony, %	92	91	0.706 ^b
Number of cohabitants	2.23 ± 1.34	2.04 ± 1.27	0.038
Number of underage cohabitants	0.58 ± 0.85	0.53 ± 0.81	0.375
Number of comorbidities	0.59 ± 1.09	0.44 ± 0.94	0.029
Pre-existing psychiatric conditions, %	16.5	9.2	0.002^b

MS, multiple scl. Unless otherwise specified, *P* values refer to *t*-test. Values are mean ± SD, unless otherwise specified. ^aFisher's test. ^bChi-squared test. Significant results after Bonferroni correction are reported in bold.

Multiple sclerosis-related features

The distribution of disease duration in the MS group was as follows: fewer than 2 years, 8.7%, between 2 and 5 years, 16.3%, between 5 and 10 years, 21.5%, between 10 and 15 years, 33%, more than 20 years, 20.5%. The median (range) PDDS score in MS patients was 1 (0–8), the median (range) UEF score

was 8 (8–40). Ongoing disease-modifying therapies were, in order of frequency: ocrelizumab, 20.1%; dimethyl fumarate, 14.7%; fingolimod, 13.1%; natalizumab, 12.5%; no therapy, 11.1%; interferon-β, 9.6%; alemtuzumab, 5.8%; terifunomide, 4%; glatiramer acetate, 3.8%; cladribine, 3.2%; siponimod, 0.8%; blinded clinical trial, 0.4%; rituximab, 0.4%; azathioprine, 0.2%; and cyclophosphamide, 0.2%.

Cognition

Accounting for age, gender and education, people with MS showed higher cognitive dysfunction than controls (15.24 ± 6.78 vs. 12.25 ± 4.40; *P* < 0.0001), with no difference in abstraction and logical abilities (3.54 ± 1.44 vs. 4.01 ± 1.24; *P* = 0.1).

COVID-19 infection and risk perception

Overall, 1% of the people with MS and 1.1% of the controls received a diagnosis of COVID-19 infection confirmed via nasopharyngeal swab, while 8.2% of the MS group versus 15.8% of the control group underwent fiduciary isolation (*P* = 0.001). In the MS group, 16.7% had cases of COVID-19 infection among family and friends, in comparison with 23.3% of the control group (*P* = 0.021) and 71.6% of the MS group believed their risk of infection to be higher because of MS and/or because of MS therapy.

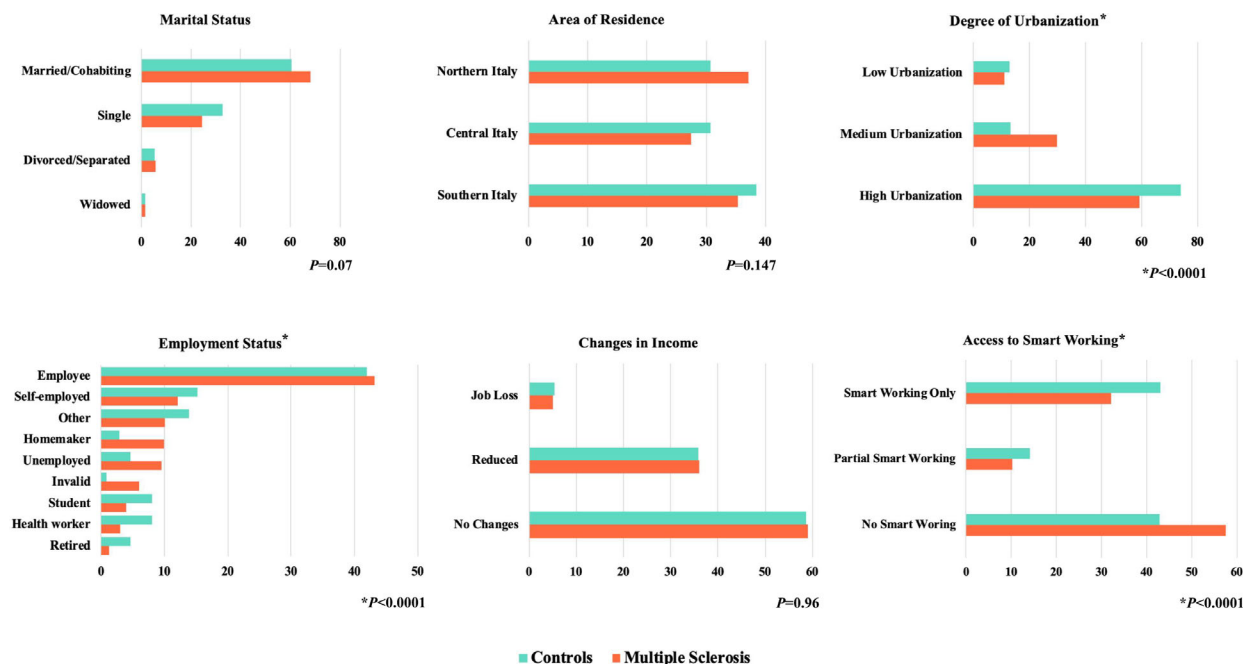


Figure 2 Sociodemographic features of the study population. x-axis represents percentage.

Mental distress and coping strategies

Accounting for age, gender and pre-existing psychiatric conditions, the MS group had significantly higher scores than controls for depression (15.54 ± 6.99 vs. 13.87 ± 5.85 ; $P = 0.005$), but not for anxiety (19.61 ± 7.25 vs. 18.26 ± 6.05 ; $P = 0.064$), emotional dyscontrol (17.94 ± 7.04 vs. 16.53 ± 6.28 ; $P = 0.015$) or sleep disturbances (16.68 ± 6.02 vs. 15.40 ± 5.49 ; $P = 0.017$).

Coping strategies application differed between the MS and the control group ($P = 0.005$), with people with MS having a higher turning to religion ratio (0.46 ± 0.25 vs. 0.38 ± 0.20 ; $P < 0.0001$) and a lower social support ratio (0.43 ± 0.16 vs. 0.45 ± 0.15 ; $P = 0.013$) than controls. The frequency of prevalent coping strategies in the two groups is shown in Fig. 3.

Changes in lifestyle

On average, people with MS had to cancel more health-related appointments than controls, even when accounting for the number of comorbidities (median [range] 1 [0–12] vs. 0 [0–6]; $P < 0.0001$). When investigating time spent daily in different activities, people with MS spent less time than controls surfing the Internet ($P = 0.002$), smart working ($P < 0.0001$), studying ($P < 0.0001$) and sleeping ($P = 0.002$), and more time than controls watching television ($P = 0.001$). No difference was detected for any other activity. With regard to Internet usage, people with MS resorted less frequently to instant messaging ($P = 0.002$), work video calling ($P < 0.0001$), searching for general information ($P < 0.0001$) and online learning ($P < 0.0001$), and more frequently to searching for information about

COVID-19 and MS ($P < 0.0001$). For a graphical display of daily activities and Internet usage under lockdown see Fig. 4.

Relationships among measured variables, latent variables and neuropsychiatric symptoms

As only depression significantly differed between the MS and the control group, our further analyses focused on depression as an outcome of interest. In the preliminary analysis, the following variables showed significant correlations with depression in people with MS: PDDS score, online search for information about COVID-19, watching television, exercise, UEF score, cognitive dysfunction, avoidance ratio, positive attitude ratio, social support ratio ($r = -0.257$ to 0.555 , $P < 0.001$ for all). As PDDS and UEF scores were highly intercorrelated ($r = 0.655$, $P < 0.001$), and UEF score was more strongly related to depression than PDDS score, only UEF score was retained in the final analysis. Considering these variables in the framework of the engagement versus disengagement theory of coping [11], we built a model in which three latent factors (disability, active and passive attitude) would explain the variance observed in depression score. In detail, we hypothesized that UEF score and cognitive dysfunction would contribute to the latent factor disability; positive attitude ratio, online search for information about COVID-19 and exercise would contribute to the latent factor active attitude and social support ratio, avoidance ratio and watching TV would contribute to the latent construct passive attitude, with passive attitude mediating the effects of disability. Results of the structural equation model are reported in Fig. 5. Briefly,

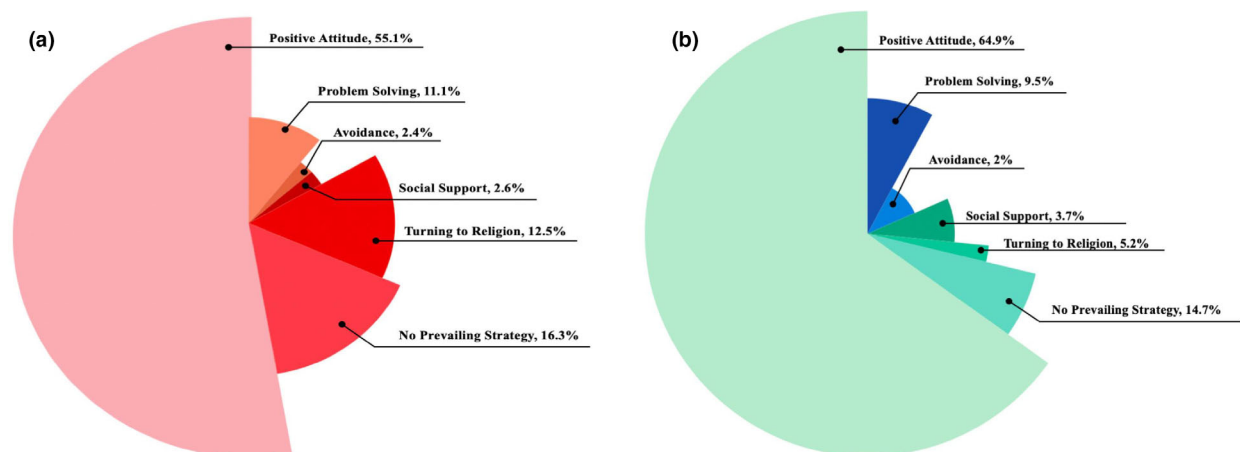


Figure 3 Coping strategies application in the study population. Percentages referring to the multiple sclerosis group are shown in (a), while percentages referring to the control group are shown in (b).

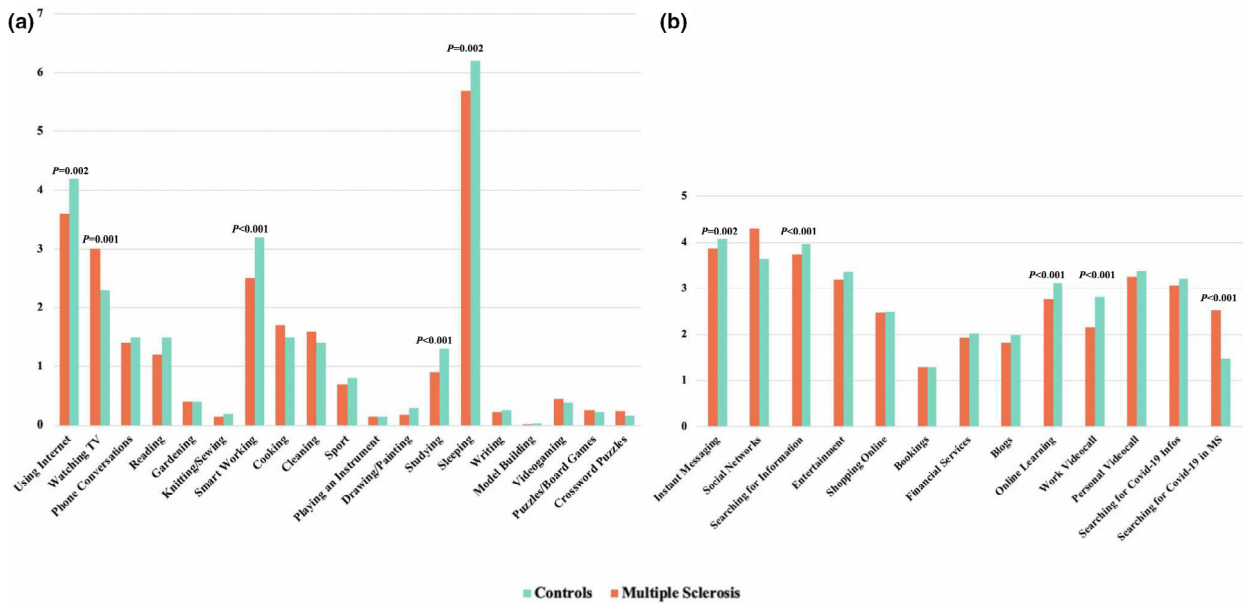


Figure 4 Lifestyle under lockdown. (a) Hours spent in daily activities and (b) frequency of Internet usage. Green bars represent the control group; orange bars represent the multiple sclerosis group.

UES score and cognitive dysfunction significantly contributed to the latent construct disability ($\beta = 0.509$ and $\beta = 0.836$, respectively; both $P < 0.001$); positive attitude ratio and exercise significantly contributed to the latent construct active attitude ($\beta = 0.386$ and $\beta = 0.297$; both $P < 0.001$), while online search for information about COVID-19 did not significantly contribute ($\beta = -0.126$; $P = 0.073$). Finally, avoidance ratio, social support ratio and watching television

significantly contributed to the latent construct passive attitude ($\beta = 0.301$, $\beta = 0.243$ and $\beta = 0.212$, respectively; $P < 0.001$ for all). Overall, the model explained 74% of the variance observed in depression score. Disability significantly contributed to passive attitude ($\beta = 0.855$; $P < 0.001$), while both passive and active attitude significantly contributed to the variance observed in depression score ($\beta = 0.729$ and $\beta = -0.456$, respectively; $P < 0.001$ for both). To

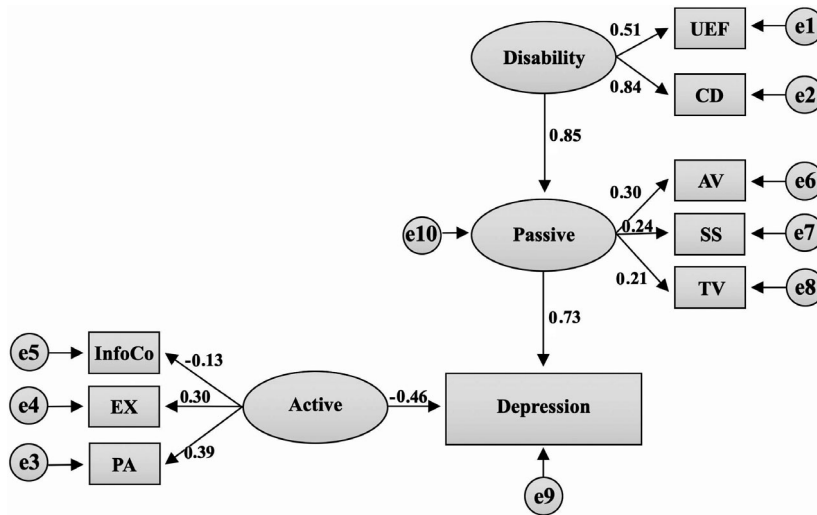


Figure 5 Model of the relationship between measured variables, latent variables and depression. Square boxes indicate measured variables; oval boxes indicate latent variables. Circles indicate error variables. Arrows indicate standardized regression weightings. AV, avoidance; CD, cognitive dysfunction; EX, exercise; InfoCo, information about COVID-19; PA, positive attitude; SS, social support; TV, television; UEF, upper extremity function.

better clarify the relationship between passive attitude and depression, a second model with passive attitude and disability as two independent predictors of depression was tested, but disclosed no significant contribution of passive attitude ($\beta = 0.331$; $P = 0.084$) to depression. The final model showed an overall good fit (root mean square error of approximation = 0.073, goodness-of-fit index = 0.961, comparative fit index = 0.857, minimal discrepancy = 3.624).

Discussion

A global and uncontrollable event, such as the pandemic that we are currently experiencing, inevitably takes a toll on mental distress. If this is true for the general population [3,4,22–24], in people with MS, whose vulnerability is presumably enhanced by the chronic condition with which they are living and by the high prevalence of psychiatric comorbidity [25,26], even more stressors are at play. Mood disorders represent risk factors for COVID-19-related mental distress [27] but, even when accounting for pre-existing psychiatric comorbidities, people with MS presented higher depression scores than controls, suggesting a higher susceptibility to stressors in comparison with the general population. With regard to daily life changes, people with MS experienced significant disruption to their management of the disease, with many health-related appointments being canceled, difficulties in continuing psychotherapy, and uncertainty about their individual risk. Seventy percent of the people with MS who participated in the survey reported a perceived risk of COVID-19 infection higher than that of the general population. To date, as no scientific evidence is yet available about risk increase in relation to MS or MS immunotherapy, patient concerns cannot be properly addressed and this might contribute to their uncertainty [28–31]. In fact, although the initial report from the Italian COVID-19 infection in MS program appears to be slightly reassuring, with 96% of the enrolled patients showing only mild symptoms [32], to date there is not enough information to speculate about the interaction between disease-modifying therapies and COVID-19. With regard to the reorganization of daily activities, a similar pattern emerged in patients and controls, with the only differences observed in work- and study-related activities, which might be explained by the higher frequency of unemployment and invalid status, and the lower frequency of students among patients, as well as by their limited access to smart working. The time spent daily watching television, which also emerged as a difference in comparison with controls, might be a further indicator of need for information and/or a sign of a more passive attitude among people with MS. The latter hypothesis might

also explain why a significantly lower number of people with MS underwent fiduciary isolation in comparison with controls. Patients with MS might engage less in social activities because of their disability or mood disorder, thus being less exposed to contacts with potentially infected people. Alternatively, this difference might be explained by the higher frequency of health workers observed in the control group.

Generally speaking, stress derives from experiencing events that interfere with goals and conditions of life, especially if they exceed one's ability to manage them [11]. Such ability can take many forms, and a known relationship exists between the application of specific coping strategies and well-being. Engagement coping usually relates to better physical and mental health than less volitional responses, but this relationship might be more complex when uncontrollable stressors are at play [11]. People with MS tend to adopt dysfunctional avoiding strategies [33], especially when significant concomitant cognitive and physical disability exist [12,34]. In the present study, positive attitude was the prevailing strategy in both groups, and this might be partially explained by the specific nature of the stressor (i.e., government-enforced lockdown), which prevented the application of other engagement strategies such as problem solving. Regarding other coping strategies, people with MS had higher scores for turning to religion and social support, confirming a tendency to resort to passive behavior. Our model, built by grouping factors related to depression according to the active/engagement–passive/disengagement theoretical framework, confirmed that both active and passive attitude influence the clinical manifestation of depressive symptoms. Specifically, while positive attitude played a direct protective role, passive attitude mediated the effects of disability on depression. This seems to suggest that, while trying to modify factors that contribute to passive attitude might not determine any substantial variation in depression, unless disability is not concurrently managed, favoring a positive attitude might determine a gain in terms of mental well-being regardless of disability status. A positive attitude might benefit from psychological support, that should always be considered as part of the multidimensional management of MS, especially when disease-related or external stressors amplify the disease burden. With regard to disability management, neurorehabilitation plays a well-established role in MS, with physical therapy methods improving mobility, fatigue and quality of life [35] and exercise exerting a beneficial effect on cognition [36]. Against this background, the results of our model suggest that exercise would enhance active attitude and its positive impact on mental well-being while, at the same time, reducing

the negative impact of disability on depression. From an operational standpoint, in the context of the ongoing pandemic, home-based telerehabilitation and exergaming could be suitable choices to promote physical activities, while routine care activities are restored [37,38], especially considering that hospital access will require cautionary measures for many months to come [39]. In parallel, remote psychological support should be proposed, via video or telephone call, and particular care should be taken to avoid interruptions in pre-existing psychotherapy.

In summary, our work highlights the relevance of exercise in the management of depressive symptoms. Such simple and transversal intervention might represent a valuable tool in facing COVID-19-related mental distress, both mitigating the negative role of disability and promoting the positive effect of active coping.

When interpreting our results, some methodological limitations should be acknowledged. First, our sample, although well distributed when considering division in geographic macroareas (Northern, Central and Southern Italy) and prevalence of COVID-19 cases per region, might not be representative of the whole MS population. Participation in the survey might have been biased by the relationship between individual patients and the recruiting centers, with patients who were more closely monitored than others by reason of the ongoing treatment being more likely to participate. More broadly, the present study might be subject to self-selection bias, which is an intrinsic issue of survey-based data collection. Second, severely disabled patients might have been less motivated to participate, and in this subgroup, the relationship between disability, passive attitude and depression might be different from the one described in our sample. Third, as only 1% of our MS group received a confirmed diagnosis of COVID-19, we were not able to perform a tailored subgroup analysis, and our results might not apply to these participants. Additionally, our cohort showed mild disability (median PDSS score 1.0). As such, rates of mental distress are probably under-estimated in comparison with patients presenting more severe disability, and the generalizability of some of the identified protective factors is limited.

Despite these limitations, we report, based on the comparison of two sociodemographically well matched groups of people with MS and controls, the presence of more severe depressive symptoms in people with MS who experienced lockdown during the COVID-19 pandemic and present a model of the relationship between disability, coping strategies and disability that has practical implications for the long-term management of COVID-19-related mental distress.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Content of the online survey.

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