Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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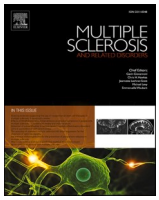

Original article

Impact of resilience, social support, and personality traits in patients with neuroinflammatory diseases during the COVID-19 pandemic

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ABSTRACT

Background and Objective: The COVID-19 pandemic negatively impacted the well-being of persons with neuroinflammatory diseases (pwNID). Identifying factors that influence the response to challenging conditions could guide supportive care.

Methods: 2185 pwNID and 1079 healthy controls (HCs) from five US centers completed an online survey regarding the effects of the COVID-19 pandemic on physical and psychological well-being. Survey instruments included resilience (Connor-Davidson Resilience Scale, CD-RISC), loneliness (UCLA Loneliness Scale), social support (modified social support survey, MSSS-5), personality traits (NEO-Five Factor Inventory, NEO-FFI), and disability (Patient-Determined Disability Steps (PDDS). Step-wise regression models and mediation analyses assessed whether the level of self-reported resilience, size of the social support, and specific personality traits (study predictors) were associated with self-reported disability and/or loneliness (study outcomes).

Results: The response rate varied significantly between the questionnaires. While, all pwNID completed the demographic questionnaire, 78.8% completed the loneliness questionnaire and 49.7% completed the NEO-FFI. Based on 787 responses, greater neuroticism (standardized β = 0.312, $p < 0.001$), less social support (standardized β = -0.242, $p < 0.001$), lower extraversion (standardized β = -0.083, p=0.017), lower agreeableness (standardized β = -0.119, $p < 0.001$), and lower resilience (standardized β = -0.125, p = 0.002) were associated with the feeling of loneliness. Social support and resilience modestly but significantly mediated the association between personality traits and loneliness. Older age (standardized β = 0.165, $p < 0.001$) and lower conscientiousness (standardized β = -0.094, p = 0.007) were associated with worse disability (higher PDDS scores). There were no differences in outcomes between pwNID and HCs.

Conclusion: Greater social support potentially attenuates the association between neuroticism and the feeling of loneliness in pwNID during the COVID-19 pandemic. Assessment of personality traits may identify pwNID that are in greater need of social support and guide targeted interventions.

1. Introduction

Neuroinflammatory diseases (NID) are chronic conditions that cause physical, psychological and cognitive manifestations with a significant impact on quality of life (QoL) (Garjani et al., 2021). The use of immune-modulating therapies that lower the SARS-CoV-2 vaccine response and presence of other risk factors such as cardiovascular comorbidities put persons with NID (pwNID) at increased risk for severe

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COVID-19 disease (Sormani et al., 2021). Beyond coping with the neurological disease, the necessary though negative social changes during the COVID-19 pandemic particularly affected pwNID (Garjani et al., 2021). Critical in-person support groups, rehabilitative interventions, and access to medical care were restricted during the pandemic. Taken together, pwNID are at greater risk for psychological stress and social isolation (Landi et al., 2020).

The Multiple Sclerosis Resilience to COVID-19 (MSReCOV) collaborative is a multi-center US-based effort that aims to understand the effects of the COVID-19 pandemic on the overall well-being of pwNID (Levin et al., 2021; Levit et al., 2022; Kever et al., 2022). Previous analyses showed that pwNID experienced significant worsening in their physical function and change in their standard of care (Levin et al., 2021). We further showed that pwNID with higher self-reported loneliness (perceived social isolation) had greater depressive symptoms (Levit et al., 2022). These associations may be moderated by resilience, defined as the capacity to cope, bounce back and flourish under stressful situations. Resilience was shown to be an important favorable modifier of QoL while living with chronic diseases (Silverman et al., 2015).

Personality traits can shape responses to life events and influence subjective well-being. Personality is commonly defined as an enduring pattern of characteristics, thoughts, feelings, and behaviors that differentiate people and their social interactions. Personality studies broadly describe five basic dimensions, including neuroticism, extraversion, agreeableness, openness and conscientiousness. For example, neuroticism is defined as a personality trait that predisposes people to experiencing greater negative affect, higher stress levels, and crisis preoccupation (Kroencke et al., 2020; Liu et al., 2021). Similarly, higher neuroticism is associated with significantly worse mental health that can be detected not only in survey respondents themselves but also in their families (Gadermann et al., 2021; Shokrkon and Nicoladis, 2021). Among pwNID, disease-induced damage can also cause personality changes resulting in higher neuroticism and/or lower conscientiousness (Roy et al., 2018). While extraversion (being enthusiastic, talkative and assertive) may have a protective role, neuroticism has a harmful role in patient-reported outcomes (Kever et al., 2022). Contrarily, presence of higher conscientiousness (defined as organized, responsible behavior that aims at completing long-range goals) is associated with better medical outcomes (Jokela et al., 2013). Agreeableness describes the desire to socialize, being honest and altruistic in relationships, whereas openness reflects one's desire for new experiences, knowledge and ideas (Benedict et al., 2001). Therefore, an examination of the effect of personality traits on the ability to cope with the pandemic are warranted.

In this study, we tested three hypotheses: (1) greater social support and higher resilience are associated with decreased loneliness among pwNID during the COVID-19 pandemic; (2) personality traits such as conscientiousness and neuroticism have differential effects on the feeling of loneliness; (3) higher resilience is associated with lower self-reported disability in pwNID.

2. Materials and methods

2.1. Study population

The MSReCOV Collaborative is comprised of five US-based clinical neuroimmunology centers (Jacobs MS Center at the University of Buffalo, Columbia University Irving Medical Center (CUIMC), MS Center at the University of Pittsburgh Medical Center (UPMC), University of Pennsylvania Comprehensive MS Center, and Yale University MS Center) that recruited study participants on a rolling basis (from the study initiation in April 2020 to July 2021). The institutional review board (IRB) of each center approved the study. All study participants provided written consent at the time of the survey. Participants did not receive financial compensation. The initial phase of the study aimed at collecting patient-reported data through several surveys up to 52 weeks. Each site retained the local participants' data, and data were shared among sites through data usage agreements.

Participants had one of the following neurologist-confirmed diagnoses: persons with multiple sclerosis (pwMS) or another inflammatory neurological disease, including clinically isolated syndrome (CIS), radiologically isolated syndrome (RIS), neuromyelitis optica spectrum disorders (NMOSD), myelin oligodendrocyte glycoprotein antibody-associated syndrome (MOG), autoimmune encephalitis (AIE), neurosarcoidosis, and CNS vasculitis. For comparison purposes, we also enrolled healthy controls (HCs). The HCs group included relatives of pwNID, controls from local registries, and people responding to local advertising at each of the recruiting centers. The inclusion criteria for the pwNID and HCs was: (1) at least 18 years of age, (2) able to provide informed consent, (3) proficient in English.

Participants completed standardized surveys using the Research Electronic Data Capture (REDCap) platform at multiple time points. Collected data included demographic (*i.e.,* age at survey response, sex, race and ethnicity), and clinical features (*i.e.,* age at first symptom onset, age at diagnosis, disease-modifying treatment or DMT usage) as well as patient-reported outcomes. For this study, we analyzed available data at study entry and at 24-week follow-up.

2.2. Questionnaires and Patient-Reported Outcomes (PRO)

Neurological disability was determined using patient-determined disease steps (PDDS). PDDS is a validated PRO with strong correlation with rater-determined Expanded Disability Status Scale (EDSS) (Learmonth et al., 2013). The scale ranges from 0 (Normal activity without limitation) to 8 (Bedridden) (see Supplemental Material).

The modified social support survey (MSSS-5) is a short 5-question Likert questionnaire that assesses the level of available social support (Ritvo et al., 1997). Questions included how often someone is *"available to take you to the doctor", "have a good time with you", "prepare meals if you are unable to do it", "understand your problems"* and/or *"hug you"* that can be answered in a range between 1 (none of the time) and 5 (all of the time). An average score combining all 5 questions is calculated. Higher MSSS-5 scores indicate greater social support.

The University of California Los Angeles (UCLA) loneliness scale (version 3.0) is a 20-item survey that assesses a person's subjective feelings of loneliness and feelings of social isolation (Russell, 1996). Each question has a response that ranges from 1 (never) to 4 (always) and a total score from 0 to 80 is calculated. Higher scores reflect greater subjective feeling of loneliness.

The Connor-Davidson Resilience Scale (CD-RISC) is a 25-item questionnaire that assesses the level of resilience, defined as an ability to thrive in the setting of adversity (Connor and Davidson, 2003). Each question has a response ranging from 1 (not true at all) to 4 (true, nearly all of the time) as applicable for the preceding month. A total score between 0 and 100 is calculated with higher scores indicating greater resilience. CD-RISC data were available from 4 of the 5 sites.

The NEO - Five-Factor Inventory (FFI) is a validated 60-item questionnaire that assesses five personality domains: neuroticism, extraversion, openness (to experience), agreeableness, and conscientiousness (Schwartz et al., 2011). Response to each question ranges from 1 (strongly disagree) to 5 (strongly agree). Scoring of the questionnaire was performed using sex-based T-score calculations (see Supplement Material). NEO-FFI data were available from 4 of the 5 sites. Higher scores in each of the personality domain indicate greater representation of the given personality in the participant.

The study additionally employed all components from the National Institute of Health Patient-Reported Outcomes Measurement Information System (PROMIS), including the depression and physical function versions. The results from the PROMIS-based findings is reported elsewhere (Levit et al., 2022).

2.3. Statistical analysis

All statistical analyses were performed using SPSS version 28.0 (IBM, Armonk, NY, USA). Data distribution was assessed through visual inspection of histograms and Q-Q plots. Data across sites were compared using one-way analysis of variance (ANOVA) and Kruskal Wallis H test for parametric and non-parametric data, respectively. Associations between measures were performed using non-parametric Spearman's correlation. We used a stepwise, multi-variate linear regression to determine the factors associated with PDDS. These predictors consist of age (at survey response), CD-RISC scores, MSSS-5 score, and NEO-FFI personality traits. A similar model was used to assess the relationship between social support and personality traits with the subjective feeling of loneliness. Additional models were further included the study site and the use of DMT. (Supplement Table 1) We used Wilcoxon Signed Ranks Test and Spearman's correlation to assess whether baseline age, CD-RISC scores, and personality traits are associated with change in PDDS scores during the follow-up period. We performed mediation analysis using PROCESS macro for SPSS (plugin version 4.0) where resilience/personality traits were the independent variables, loneliness was the dependent variable, and resilience or social support was the mediator (Hayes, 2017). Total, direct, and indirect effects were recorded, and 5000-sample bootstrapped 95% confidence intervals for the mediating effect were reported. We corrected the regression and mediation analyses for false discovery rate (FDR) using the Benjamini–Hochberg procedure (Benjamini and Hochberg, 1995). *P*-values $\leq$0.01 were considered statistically significant.

3. Results

3.1. Participant characteristics

Among the 3,264 participants who completed surveys, 2185 were pwNID and 1079 were HCs. All sites recruited pwNID (549 (25.1%) by Buffalo, 332 (14.7%) by CUIMC, 419 (19.2%) by UPenn, 620 (28.4%) by UPMC and 275 (12.6%) by Yale) and HCs 98 (9.1%) by Buffalo, 445 (41.2%) by CUIMC, 36 (3.3%) by UPenn, 324 (30.0%) by UPMC and 176 (16.3%) by Yale. The demographic and clinical characteristics of the pwNID and HCs are shown in Table 1. There are significant differences in age across the sites, with the oldest patients at University at Buffalo and youngest patients at Yale University (one-way ANOVA, $p < 0.001$). Similarly, the Buffalo patients reported on average significantly greater PDDS scores when compared to the remaining sites (Kruskal Wallis, $p < 0.001$). The HCs were significantly younger when compared to the pwNID (45.8 vs. 50.2 years old, $p < 0.001$). All participants completed at least the demographic questionnaire. The rate of missing information for each questionnaire/analysis is specified and described in Fig. 1.

The outcomes from the survey questionnaires are shown in Table 2. The level of loneliness was reported in 1721 out of 2185 (78.8%) pwNID and 907 out of 1079 (84.1%) HCs. PwNID from UPMC reported significantly greater loneliness when compared to the remaining four sites (one-way ANOVA, $p < 0.001$). There was no difference in social support and resilience across the sites. The personality questionnaire (NEO-FFI) was completed by 1087 out of 2185 (49.7%) pwNID and 331 out of 1079 (30.7%) HCs. When comparing personality traits (from the four sites with available data), we found pwNID from Yale had greater Neuroticism scores when compared to the lowest Neuroticism scores at UPenn (Bonferroni-adjusted post-hoc pair analysis $p < 0.001$).

3.2. Factors associated with PDDS in pwNID during the COVID-19 pandemic

The relationship between resilience, social support and personality traits with baseline PDDS scores are shown in Table 3. The full data set required for this analysis was available in 818 pwNID. In a stepwise regression model, baseline age and conscientiousness were associated with baseline neurological disability (based on PDDS scores). Specifically, higher age ($B = 0.36$, standardized $\beta = 0.165$, $p < 0.001$) and lower conscientiousness ($B = -0.23$, standardized $\beta = -0.0094$, $p = 0.007$) were associated with higher PDDS scores. Social support (MSSS-5), resilience levels (CD-RISC), and the remaining four personality traits were not associated with neurological disability as measured by the baseline PDDS scores. Additional regression models which included the study site and DMT as predictor did not change the findings (Supplemental Table 1).

While each participant only completed the loneliness survey once, we analyzed the loneliness scores of the cohort as they were reported through the evolution of the pandemic, starting with April 2020 to July 2021 (local polynomial regression; LOESS analysis Fig. 2A for pwHC and Fig. 2B for PwNID). There was a significant increase in loneliness scores among both pwNID and HC respondents who completed the questionnaire during the early pandemic (UCLA scores for April vs. May 2020; 39.0 vs. 48.6, $p < 0.001$ for HCs and 39.9 vs. 50.8, $p < 0.001$ for pwNID). Slight differences in the best LOESS fit through the loneliness data can be visualized in Fig. 2. The scores remained relatively stable after July 2020 for both pwNID and HCs.

3.3. Factors associated with loneliness in pwNID during the COVID-19 pandemic

We next examined the associations between resilience, social support, and personality traits with the subjective feeling of loneliness. The

Table 1
Demographic and clinical characteristics of the study population.

Study population	Buffalo (n=549)	CUIMC (n=322)	UPenn (n=419)	UPMC (n=620)	Yale (n=275)	Total pwNID (n=2185)	HCs(n = 1079)
Female, n (%)	418 (76.1)	263 (81.7)	326 (77.8)	516 (83.2)	210 (76.4)	1733 (79.4)	782 (72.5)
Age at first survey response, mean (SD)	51.8 (15.2)	48.5 (12.2)	50.1 (15.2)	50.4 (12.6)	48.5 (14.4)	50.2 (13.9)	45.8 (15.3)
White, n (%)	485 (88.3)	282 (87.6)	371 (88.5)	578 (93.7)	237 (86.2)	1953 (89.4)	983 (91.1)
Non-Hispanic, n (%)	505 (92.3)	299 (92.9)	394 (94.0)	588 (94.8)	254 (92.4)	2040 (93.4)	1026 (95.1)
Age of symptom onset, mean (SD)	32.8 (12.7)	31.8 (10.7)	34.9 (11.4)	32.5 (11.2)	34.1 (12.4)	33.2 (11.7)	–
Age at diagnosis, mean (SD)	37.3 (12.3)	36.2 (10.3)	38.8 (10.9)	36.9 (10.8)	37.3 (12.5)	37.3 (11.3)	–
Disease duration, mean (SD)	20.7 (14.2)	16.5 (12.4)	15.3 (14.7)	18.0 (16.1)	14.4 (12.4)	17.2 (14.5)	
PDDS, mean (SD)	4.1 (3.6)	1.8 (2.3)	1.9 (2.5)	2.2 (1.9)	1.9 (2.6)	2.5 (2.9)	–
Use of DMT, yes (%)	237 (73.1)	295 (91.6)	346 (83.2)	500 (80.6)	215 (78.2)	1593 (81.6)$^{+}$	–

pwNID – persons with neuroinflammatory diseases, DMT – disease modifying therapy, PDDS – patient determined disease steps. *- Age at symptom onset was available in 1901 patients. Age at diagnosis was available in 1876 patients. $^{+}$ - DMT status was available in 1953 patients.
There were significant differences in the age of HCs based on the site of recruitment with UPMC enrolling the oldest and Yale University the youngest controls (51.2 vs. 43.1 years old, one-way ANOVA, $p < 0.001$). The mean age of the HCs were 49.1 (16.2) for Buffalo, 41.5 (9.9) for CUIMC, 50.7 (17.2) for UPenn, 51.6 (17.2) for UPMC and 43.1 (17.9) for Yale. There were site-specific age differences (one-way ANOVA p<0.001).
The remaining non-white MS population was separated as follows: 117 African-American (5.4%), 41 multi-racial (1.9%), 19 Asian (0.9%), 9 Native American (0.4%) and 44 (2.1%) did not provide response.

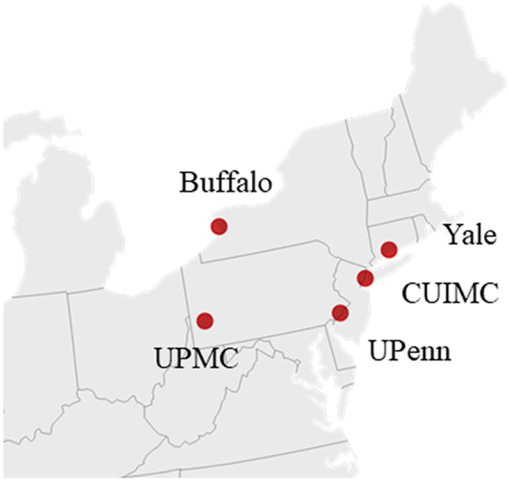

Fig. 1. MSReCOV Collaborative sites and the pwNID response rate to each study questionnaire.
MSReCOV - Multiple Sclerosis Resilience to COVID-19, pwNID – persons with neuroinflammatory diseases, PDDS - patient determined disease steps, UCLA-L – University of California, Los Angeles – Loneliness questionnaire, MSSS-5 – Modified social support survey, CD-RISC - Connor-Davidson Resilience Scale, NEO-FFI - The NEO Five-Factor Inventory-3.
Data is shown as the number of responses and percentage of responses.

PwNID	Demographics	PDDS	UCLA-L	MSSS-5	CD-RISC	NEO-FFI
Buffalo	549	517 (94.2)	404 (73.6)	507 (92.3)	440 (80.1)	383 (69.8)
CUIMC	322	311 (96.6)	279 (86.6)	301 (93.5)	-	-
UPenn	419	394 (94)	349 (83.3)	366 (87.4)	213 (50.8)	239 (57)
UPMC	620	620 (100)	460 (74.2)	479 (77.3)	308 (49.7)	306 (49.4)
Yale	275	258 (93.8)	229 (83.3)	257 (93.5)	124 (45.1)	159 (57.8)
Total	**2185**	**2100 (96.1)**	**1721 (78.8)**	**1910 (87.4)**	**1085 (49.7)**	**1087 (49.7)**

Table 2
Social history and personality traits of the study population.

Social history and personality traits	Buffalo	CUIMC	UPenn	UPMC	Yale	Total pwNID	Site comparison p-value	HCs	pwNID vs. HCsp-value*
UCLA Loneliness, mean (SD)	41.2 (12.8)	39.5 (11.7)	39.6 (11.2)	50.6 (8.6)	41.4 (11.2)	43.1 (11.9)	**<0.001**	41.3 (10.8)	**<0.001**
MSSS-5, mean (SD)	3.9 (1.1)	3.9 (1.0)	4.0 (1.1)	3.9 (1.0)	3.9 (1.1)	3.9 (1.1)	0.15	3.9 (1.1)	0.525
CD-RISC, mean (SD)	73.1 (17.0)	.	73.6 (13.8)	72.9 (15.9)	69.1 (15.9)	72.7 (16.0)	0.062	73.9 (15.0)	0.346
NEO-FFI, mean (SD)									
Neuroticism	50.1 (12.3)	.	46.9 (12.0)	48.7 (12.4)	51.9 (11.6)	49.3 (12.3)	**<0.001**	49.3 (12.3)	0.069
Extraversion	46.3 (11.9)	.	48.0 (12.3)	46.2 (11.6)	44.9 (11.6)	46.5 (11.9)	0.07	46.5 (11.9)	0.037
Openness	51.1 (10.8)	.	52.9 (11.9)	50.7 (11.2)	54.2 (11.1)	51.8 (11.3)	0.003	51.8 (11.3)	**0.001**
Agreeableness	51.9 (12.7)	.	52.9 (13.5)	52.0 (11.4)	51.2 (11.2)	52.1 (11.3)	0.595	52.1 (12.3)	0.83
Conscientiousness	46.4 (13.8)	.	49.0 (12.7)	48.1 (11.5)	46.6 (10.9)	47.5 (12.6)	0.045	47.5 (12.6)	0.02

pwNID – persons with neuroinflammatory diseases, HCs – healthy controls, UCLA – University of California, Los Angeles, MSSS-5 – Modified social support survey, CD-RISC - Connor-Davidson Resilience Scale, NEO-FFI - The NEO Five-Factor Inventory-3. UCLA was available in 1721 pwNID and 907 HCs. CD-RISC was available in 1085 pwNID and 312 HCs. NEO-FFI was available in 1087 pwNID and 331 HCs. The response rate for each category is shown in Fig. 1.
The comparison between sites was performed using one-way analysis of variance (ANOVA). * Age-adjusted analysis of covariance (ANCOVA) was used. All values are presented as mean (standard deviation). *P*-values lower than 0.01 were considered statistically significant and shown in bold., whereas *p*-values lower than 0.05 were considered as trending.

full data set required for this analysis was available in 787 pwNID. When utilizing data from all centers, higher levels of social support were significantly associated with less loneliness both in the pwNID (n = 1721, r = -0.383, $p < 0.001$) and HCs (n = 664, r = -0.376, $p < 0.001$). Similarly, higher resilience scores were significantly associated with less loneliness in the pwNID (n = 942, r = -0.459, $p < 0.001$) and HCs (n = 284, r = -0.381, $p < 0.001$). All relationships remained significant after Benjamini-Hochberg correction. Among pwNID with all available measures (n = 787), the UCLA loneliness regression model included resilience, social support, agreeableness, extraversion, and neuroticism as five significantly associated factors (Table 3). In particular, lower resilience scores (B = -0.99, standardized β = -0.125, p = 0.002), lower social support (B = -2.777, standardized β = -0.242, $p < 0.001$), lower agreeableness (B = -0.118, standardized β = -0.119, $p <= 0.001$), lower extraversion (B = -0.086, standardized β = -0.083, p = 0.017), and higher neuroticism scores (B = 0.313, standardized β = 0.312, $p <$ 0.001) were associated with loneliness. Age and sex were not associated with loneliness. Disease duration was excluded due to its high collinearity with age. A regression model with study site included as predictor and DMT use is also shown in Supplement Table 1. The study site was additionally associated with loneliness (B = 1.92, standardized β = 0.237, $p < 0.001$), while the resilience association was rendered non-significant. Similar findings were seen in the HCs: lower resilience (B = -0.234, standardized β = -0.279, p = 0.001), agreeableness (B = -0.227, standardized β = -0.192, p = 0.010) and extraversion (B = -0.317, standardized β = -0.33, $p < 0.001$) were associated with greater

Table 3
Regression model predicting baseline PDDS scores and baseline loneliness in the pwNID population.

Baseline PDDS score (n=818)	Unstandardized Coefficients B	Std. Error	Standardized β	t	P-value
Age at first survey response	0.36	0.008	0.165	4.787	**<0.001**
Conscientiousness	-0.23	0.009	-0.094	-2.725	**0.007**
UCLA Loneliness score (n=787)	B	Std. Error	Standardized β	t	P-value
Neuroticism	0.313	0.038	0.312	8.289	**<0.001**
MSSS-5	-2.777	0.337	-0.242	-8.233	**<0.001**
Extraversion	-0.086	0.036	-0.083	-2.401	**0.017**
Agreeableness	-0.118	0.032	-0.119	-3.67	**<0.001**
CD-RISC	-0.99	0.031	-0.125	-3.164	**0.002**

pwNID – persons with neuroinflammatory diseases, PDDS - patient determined disease steps, UCLA – University of California, Los Angeles, MSSS-5 – Modified social support survey, CD-RISC - Connor-Davidson Resilience Scale.
Step-wise regression model was utilized. In the first regression model, the PDDS score was the dependent variable and sex, age, CD-RISC, average MSSS-5, and all five personality traits (Neuroticism, Extraversion, Openness, Agreeableness, and Conscientiousness) were included as independent predictors. Disease duration was excluded due to high collinearity with age. In the second regression model, the UCLA loneliness score was the dependent variable and sex, age, CD-RISC, average MSSS-5, and all five personality traits (Neuroticism, Extraversion, Openness, Agreeableness, and Conscientiousness) were included as independent predictors. The stepping method utilized F probability of 0.01 for entry and 0.05 for removal of variables.

feelings of loneliness.

We further assessed the mediating effect of social support and resilience on the association between the significant personality traits and feeling of loneliness. A modest amount of the association between neuroticism and loneliness (total effect coefficient of 0.511, $p < 0.001$) was mediated by social support (direct effect coefficients 0.46 vs. indirect effect coefficient 0.051) (Fig. 3A) for pwNID, and the indirect effect was statistically significant (95% confidence interval [CI]: 0.034-0.07). Social support mediated 10% of the association between neuroticism and loneliness. Contrarily, resilience significantly mediated the association between neuroticism and loneliness (indirect effect coefficient 0.174, 95% CI of 0.142 to 0.209) (Fig. 3B), accounting for 37.3% of the association. The same analyses regarding agreeableness and extraversion are shown in Figs. 4 and 5. Resilience was a significant mediator of the relationship between agreeableness and loneliness (39.3% of indirect effect). A much smaller part of the relationship was mediated through social support (11.8% of indirect effect; Fig. 4). Similarly, large portion of the total extraversion effect on loneliness was mediated through the resilience (58.7% of indirect effect; Fig. 5). Unlike the pwNID, social support was not associated with loneliness scores in the HCs. (data not shown) Lastly, higher resilience was associated with less loneliness in the HCs ($n = 284$, $r = -0.381$, $p < 0.001$).

Among the 1169 pwNID participants with 24-week follow-up survey data, there were no significant changes in PDDS score (Wilcoxon Signed Ranks Test $p = 0.232$, for paired analysis between baseline to 24 weeks).

4. Discussion

The key findings from this MSReCOV Collaborative analysis include the following. First, greater resilience, more social support, higher extraversion, higher agreeableness, and lower neuroticism are associated with less loneliness reported during the COVID-19 pandemic. Second, the association between higher neuroticism and greater loneliness in pwNID could be mediated by social support and resilience. Third, greater conscientiousness, as measured by NEO-FFI, may be associated with patient-reported disability (PDDS scores) in pwNID.

Higher psychological resilience has previously been identified as a non-disease-specific factor associated with better physical function in pwMS (Klineova et al., 2020; Swanepoel et al., 2020). For example, a recent longitudinal study examining the risk and protective factors for cognitive decline (Reserve against disability in early MS (RADIEMS)) showed that pwMS with greater CD-RISC scores had better objective functional outcomes, including both motor and cognitive indices (Klineova et al., 2020). When compared to more vulnerable counterparts, pwMS with greater resilience also exhibit less neurological symptoms (paresthesia, motor dysfunction, fatigue) within the 60 days after an adverse life event (Swanepoel et al., 2020). Therefore, resilience-targeted interventions may provide benefits to both mental and physical outcomes (Pakenham et al., 2018). PwMS with greater social support (*e.g.,* belonging to patient community) have significantly greater resilience and sense of coherence, and use more suitable coping strategies (Reguera-Garcia et al., 2020). Moreover, pwMS with more open social networks are, on average, less disabled when compared to pwMS with close-knit social networks (OR 0.87) (Levin et al., 2020). Importantly, these patients were also more likely to remain physically active during the COVID-19 lockdown periods, an important functional factor which correlates with lower patient-reported disability (Reguera-Garcia et al., 2020). Additional structured resilience training sessions performed by psychologists could lower feelings of anxiety and depression and improve health-related quality of life in pwMS (Giovannetti et al., 2021). For comparison, improving the knowledge regarding the neuroinflammatory diseases and COVID-19 is insufficient in improving resilience, self-efficacy (capability to perform a target behavior), or improve the overall health-related QoL (Claflin et al., 2021).

Consistent with our results, a large COVID-19 survey of nearly 100,000 people in the general population also showed that neuroticism is significantly associated with loneliness in times of crises (Ikizer et al., 2022). In a prior study in MS, neuroticism was associated with depression and cognitive impairment (Kever et al., 2022). Based on the standardized coefficient in the stepwise regression models, greater social support can offset some of the feelings of loneliness associated with the neuroticism trait. Given that personality traits such as neuroticism are generally difficult to modify, greater focus on developing social and emotional support programs are warranted (Abdellaoui et al., 2019; Peerenboom et al., 2015). While the association between being outgoing/social (*i.e.,* higher extraversion) and lower feeling of isolation is possibly related to social support, our study did not find collinearity between MSSS-5 and extraversion while the variance inflation factor of both variables was below 2 (both factors providing independent significance). The beneficial effects of greater social support on lowering loneliness and depression has been reported even before the COVID-19 pandemic (Beal and Stuifbergen, 2007).

The association between conscientiousness and lower disability scores has been reported in the literature and are unlikely related to the COVID-19 circumstances. We previously reported that lower conscientiousness was associated with worse physical and cognitive outcomes in pwMS as well as structural and functional brain changes (Fuchs et al., 2021, 2020). While the organized, goal-driven behavior of persons with greater conscientiousness could lead to greater adherence to COVID-19 guidelines and health-oriented lifestyle, despite social and physical restrictions, the pandemic timeframe examined in this study is too short to meaningfully impact disability. Outside of special circumstances, the adherence to disease-modifying therapies, symptomatic therapy, and rehabilitation in the setting of higher conscientiousness, could potentially improve disability outcomes and prevent disease progression (Fuchs et al., 2020). Alternative explanations include: (1) people with higher disability might have physical and cognitive impairments that could interfere with conscientiousness behavior; (2) higher conscientiousness represents better cognitive function, which often correlate with lower physical disability. Indeed, the relationship between lower conscientiousness and higher disability could be directional. Future longitudinal or intervention studies would be more suitable to confirm

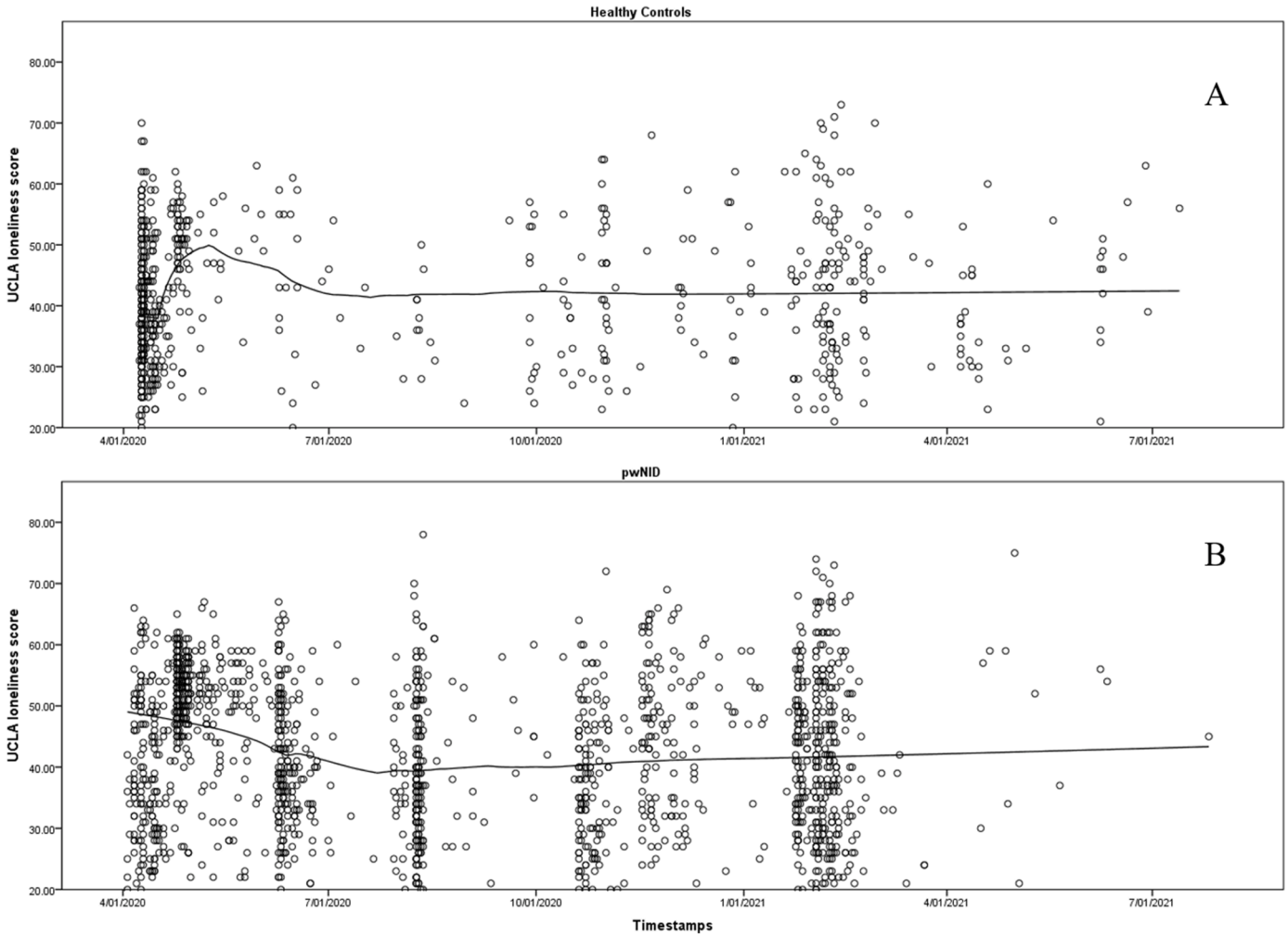

Fig. 2. Average feeling of loneliness as reported through the COVID-19 pandemic.
Panel A – feeling of loneliness in healthy control participants, Panel B – feeling of loneliness in pwNID participants. pwNID – persons with neuroinflammatory diseases, UCLA - University of California, Los Angeles.

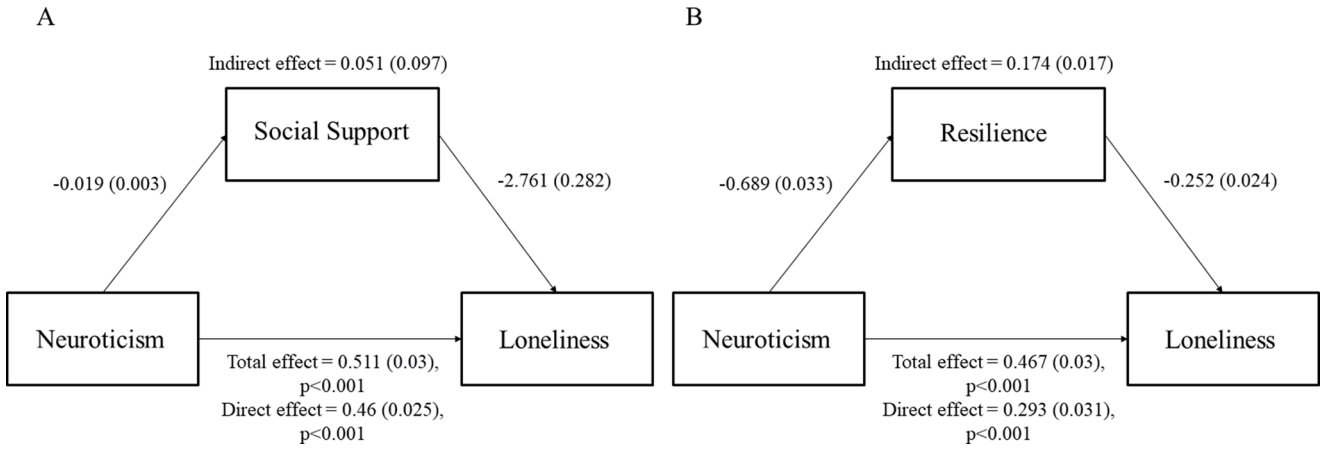

Fig. 3. The mediating effect of social support and resilience on the relationship between neuroticism and feeling of loneliness.
Each effect is shown as effect coefficient and (standard error). *P*-value lower than 0.01 was considered statistically significant. The analysis was performed using PROCESS macro tool for SPSS (plugin version 4.0).

the findings. In a pilot interventional trial, 11 pwMS with low baseline conscientiousness were randomized into 12-week-long behavioral treatment that utilized the motivational framework of expectancy value theory (Fuchs et al., 2021). Structured phone application helped patients identify personal values and goals, and how certain behaviors could help accomplish these goals. All patients reported benefits from the intervention and the treatment group had significantly more positive employment outcomes.

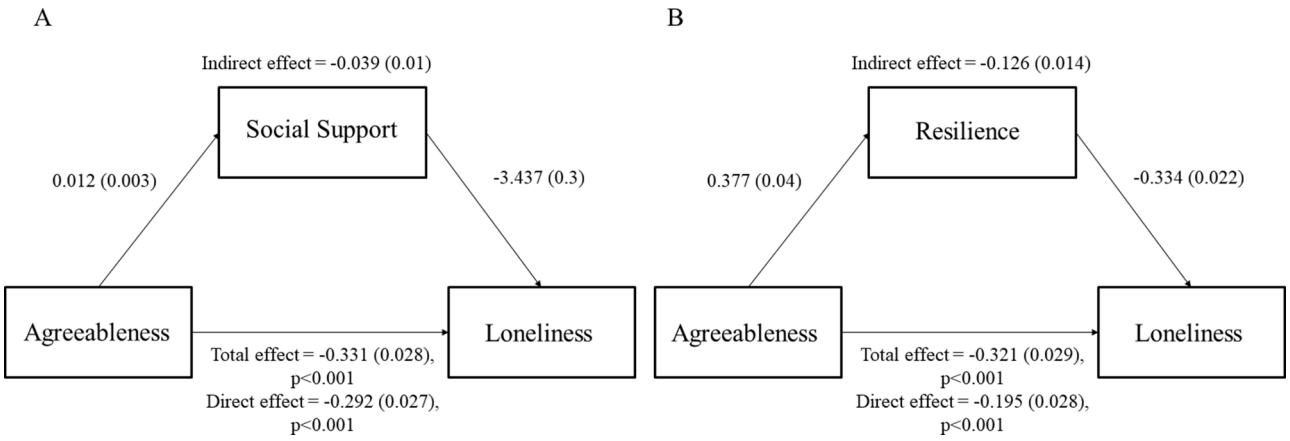

Fig. 4. The mediating effect of social support and resilience on the relationship between agreeableness and feeling of loneliness.
Each effect is shown as effect coefficient and (standard error). *P*-value lower than 0.01 was considered statistically significant. The analysis was performed using PROCESS macro tool for SPSS (plugin version 4.0).

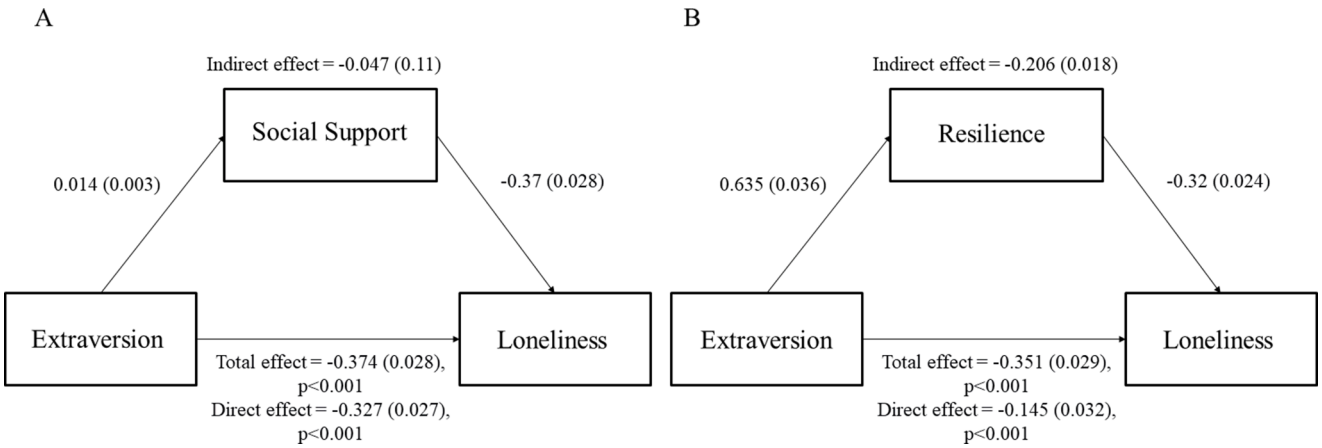

Fig. 5. The mediating effect of social support and resilience on the relationship between extraversion and feeling of loneliness.
Each effect is shown as effect coefficient and (standard error). P-value lower than 0.01 was considered statistically significant. The analysis was performed using PROCESS macro tool for SPSS (plugin version 4.0).

The study has several limitations. First, over the course of the longitudinal survey study, there was a decline in completed follow-up surveys and a more modest sample size for longitudinal analysis. Moreover, the length of follow-up (24-weeks) may not be sufficiently long enough to detect any disability changes as measured by PDDS. Second, internet-based survey might bias towards lower recruitment of patients with technological challenge, lower socioeconomic status, or non-English speaking. Due to the more modest sample size, we were unable to investigate the personality traits across different age categories and/or other demographic factors. Finally, participant recruitment occurred on rolling basis and might occur at different stages of the COVID-19 pandemic (*e.g.,* during lockdown at the time of recruitment), which could influence the subjective outcomes, especially the feeling of loneliness. As shown in the loneliness analysis, a significant increase in loneliness was seen among pwNID that responded to the survey during the first few months of the pandemic, contrasting with HC who did not have such increase during the same early period of the pandemic. This increase in loneliness among pwNID was only temporary and the average loneliness reports of participants joining the study later in the pandemic stabilized. The rise in loneliness during the first few months of the pandemic does not influence the overall finding between the personality traits and feeling of loneliness, which was analyzed using the entire data set across the whole length of the study. One caveat of the study design as a tradeoff to reduce survey burden to participants is the lack of follow-up loneliness questionnaire that would allow longitudinal analyses regarding the change in loneliness within the same participant over the period of the pandemic. Further, the study did not have pre-COVID-19 data on loneliness, personality traits and social support to allow baseline adjustment.

In conclusion, higher resilience is associated with lower loneliness in pwNID during the COVID-19 pandemic. The subjective feeling of loneliness is attributable to lack of social support as well as having certain personality traits (lower agreeableness, lower extraversion, and higher neuroticism). Greater resilience to stressors and greater social support both provide modest but significant mediating effect on the association between neuroticism and feeling of loneliness. These findings reinforce the need for social support for the vulnerable NID population and interventions that could compensate the potentially negative effects due to certain personality traits and improve resilience.

CRediT authorship contribution statement

Dejan Jakimovski: Conceptualization, Methodology, Formal analysis, Investigation, Data curation, Project administration, Visualization, Writing – original draft. **Katelyn S Kavak:** Investigation, Conceptualization, Formal analysis, Writing – review & editing. **Erin E. Longbrake:** Investigation, Project administration, Writing – review & editing. **Elle Levit:** Investigation, Project administration, Writing – review & editing.

Christopher M Perrone: Investigation, Project administration, Writing – review & editing. **Amit Bar-Or:** Investigation, Project administration, Writing – review & editing. **Ralph HB Benedict:** Investigation, Project administration, Writing – review & editing. **Claire S Riley:** Investigation, Project administration, Writing – review & editing. **Philip L De Jager:** Investigation, Project administration, Writing – review & editing. **Shruthi Venkatesh:** Investigation, Conceptualization, Project administration, Writing – review & editing. **Elizabeth L.S. Walker:** Investigation, Project administration, Writing – review & editing. **Zongqi Xia:** Investigation, Conceptualization, Supervision, Writing – review & editing. **Bianca Weinstock-Guttman:** Investigation, Conceptualization, Supervision, Writing – review & editing.

Declaration of Competing Interest

Dejan Jakimovski, Katelyn S Kavak, Elle Levit, Shruthi Venkatesh, and Elizabeth L.S. Walker have nothing to disclose.

Erin E. Longbrake has received honoraria for consulting for EMD Serono, Biogen, Alexion, Genzyme, Genentech, Janssen, NGM, Bristol Myers Squibb and TG Therapeutics. She has received research support from National Institutes of Health (NIH) K23107624, Race to Erase MS, Robert Leet and Clara Guthrie Patterson Trust, and UL1 TR001863.

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Amit Bar-Or has participated as a speaker in meetings sponsored by, and received consulting fees and/or grant support from, Accure, Atara Biotherapeutics, Biogen, BMS/Celgene/Receptos, GlaxoSmithKline, Gossamer, Janssen/Actelion, Medimmune, Merck/EMD Serono, Novartis, Roche/Genentech, and Sanofi Genzyme.

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Philip L De Jager serves on advisory board for: Biogen; Merck Serono; and Roche; he has sponsored research agreements with Roche, Biogen, and Puretech.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.msard.2022.104235.

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