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Predicting improvement of quality of life and mental health over 18-months in multiple sclerosis patients

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Abstract:	Background : Multiple sclerosis (MS) is a chronic neurodegenerative disease that can negatively affect functioning across a wide spectrum of domains. This study aims to investigate the development of mental health and quality of life in MS patients over 18-months and to identify predictive factors. Method : 314 MS outpatients of Virgen Macarena University Hospital in Sevilla/Spain (mean age 45 years, 67.8% women, on average 12.1 years since diagnosis) participated in the study. Health-related quality of life (HRQOL) and mental health were assessed by the 12-Item Short Form Health Survey (SF-12) and the General Health Questionnaire-28 (GHQ-28) twice over an 18-months follow up period. Results : HRQOL and mental health significantly improved in almost all domains, except for a worsening of vitality. Mental and physical HRQOL improved by a large effect size. Binomial logistic regression models showed that disability status (Expanded Disability Status Scale) predicted both components of HRQOL and age the physical component of HRQOL. Sex, educational level, and disease duration predicted mental health. Conclusions : Our findings confirm the possibility of a significant large-sized improvement of HRQOL in the course of 18-months even 12 years after MS diagnosis on average. The study showed the importance of sociodemographic as well as clinical variables to predict HRQOL and mental health. Further longitudinal research is needed to better understand their impact on patients' outcomes.

Credict Authors Statement

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Predicting improvement of quality of life and mental health over 18-months in multiple sclerosis patients

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Highlights

-The improvement of HRQOL and mental health supports the adaptation theory in MS.

-Sociodemographic and clinical variables are predictors for HRQOL and mental health.

-Disability status and age are risk factors for HRQOL in MS.

-Female gender and lower formal education are risk factors in terms of mental health.

-More longitudinal research is needed to better understand MS patients´ outcomes.

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Background: Multiple sclerosis (MS) is a chronic neurodegenerative disease that can negatively affect functioning across a wide spectrum of domains. This study aims to investigate the development of mental health and quality of life in MS patients over 18-months and to identify predictive factors.

Method: 314 MS outpatients of Virgen Macarena University Hospital in Sevilla/Spain (mean age 45 years, 67.8% women, on average 12.1 years since diagnosis) participated in the study. Health-related quality of life (HRQOL) and mental health were assessed by the 12-Item Short Form Health Survey (SF-12) and the General Health Questionnaire-28 (GHQ-28) twice over an 18-months follow up period.

Results: HRQOL and mental health significantly improved in almost all domains, except for a worsening of vitality. Mental and physical HRQOL improved by a large effect size. Binomial logistic regression models showed that disability status (Expanded Disability Status Scale) predicted both components of HRQOL and age the physical component of HRQOL. Sex, educational level, and disease duration predicted mental health.

Conclusions: Our findings confirm the possibility of a significant large-sized improvement of HRQOL in the course of 18-months even 12 years after MS diagnosis on average. The study showed the importance of sociodemographic as well as clinical variables to predict HRQOL and mental health. Further longitudinal research is needed to better understand their impact on patients' outcomes.

Key words: Multiple Sclerosis; Quality of Life; Mental Health; risk factors.

1.Introduction

Multiple sclerosis (MS) is often associated with functional impairments hampering all aspects of daily life and severely affecting health-related quality of life (HRQOL) [1]. MS patients regularly report lower levels of HRQOL than the general population [2-5] and patients suffering from other chronic conditions [6,7]. There is growing evidence that HRQOL is influenced by a wide range of clinical and sociodemographic factors [8].

In a recent systematic review our research group analysed the literature on HRQOL in adult MS patients in a five year time-span up to February 2019 [9]. The search identified 4886 records, 106 articles met the inclusion and exclusion criteria for qualitative synthesis. Disability, fatigue, depression, cognitive impairment and unemployment were consistently identified as risk factors for HRQOL, whereas higher self-esteem, self-efficacy, resilience and social support proved to be protective. These findings are confirmed by more recent studies. Thus, Schmidt and Jöstingmeyer [10] found depression, fatigue, unemployment, and additionally lack of physical activity to be closely associated with lower HRQOL. A greater level of disability [11] and older age [11,12] were relevant factors negatively affecting HRQOL. Other studies showed that University education, relapsing-remittent MS type (RRMS), and shorter disease duration were connected to higher levels of HRQOL. Respective factors may play a different role depending on MS stage [13]. Particularly in the initial stages of the disease patients are deeply affected by the shock of the diagnosis, which might contribute to a greater impact of accompanying factors [9,14]. However, the vast majority of above mentioned results is based on cross-sectional studies, which limits the validity of findings. From 81 studies on a wide range of risk and protective factors for QOL analysed in our systematic review only 8 trials (9.9%) showed a longitudinal study design and all of the above cited more recent studies applied a cross-sectional approach.

It is important to note that HRQOL in conjunction with other variables has also demonstrated to be a strong predictor of disability progression. Therefore, one might regard the relationship between disability and HRQOL as a vicious circle mutually fueling each other [9].

Obviously, there is a close relationship between HRQOL and mental health. There is growing evidence from recent studies of increased prevalence of depression and anxiety in MS [15,16]. Further studies revealed that newly diagnosed patients have significantly higher levels of anxiety and depression [17,18]. An up to date meta-analysis showed that 13% of MS patients worldwide suffer from suicidal ideation. Interestingly, the percentage in industrialized countries was particularly high (15%) [19]. A systematic review of prospective studies found limited evidence that age, gender, ethnicity or educational level were predictors of emotional distress and concluded that more longitudinal research is needed [20].

Identifying the factors, which influence HRQOL and mental health in MS patients helps to optimize treatment and mitigate suffering [21]. With regard to rehabilitation a stabilization of mental health and HRQOL facilitates the participation of patients in rehabilitation programs and their therapeutic efficacy [22]. Against this backdrop our longitudinal study aims to investigate changes in HRQOL and mental health in a large sample of MS patient over an 18-months follow-up period, and (2) to identify clinical (EDSS, MS subtype, time since diagnosis and time since first relapse) and sociodemographic (sex, age, marital status, educational level and employment status) predictors of the physical and mental component of HRQOL and mental health.

2.Materials and method

2.1.Participants and procedures

Between June 2017 and May 2018 (T1), a total of 469 MS outpatients from Virgen Macarena University Hospital, were asked to take part in the study; 397 of them participated at T1, after the routine neurological consultation, which assesses orientation, attention, memory, language, executive function, apraxia and visuospatial function in the context of the anamnesis and examination [23]. Of those, 314 patients completed the questionnaires 18 months after the first evaluation between December 2018 and December 2019 (T2). As described in Table 1, the final T2 sample consisted of 314 MS patients (drop out rate 20.9%), 213 (67.8%) women and 101 (32.2%) men. The mean age was 45.31 years (SD=10.68) ranging, from 19 to 78 years. No differences in terms of sex and age were found between the final sample and dropouts at T1. However, drop outs showed worse physical (p=0.013) and mental (p=0.01) HRQOL as well as mental health (p=0.013). Most of the patients were under neurological medication, in the majority of cases selective immunosuppressants were prescribed, 177 (56.4%) at baseline and 203 (64.6%) at follow-up. Comparing the number of patients in terms of different types of neurological medications at baseline and follow-up (see Table 2) there was no significant difference (chi^2=5.41; p=0.248).

-Insert Table 1-

-Insert Table 2-

All participants met the following inclusion criteria: a) confirmed MS diagnosis according to McDonald criteria; b) aged over 18; and c) mental, physical and cognitive

capability to sign the informed consent. Figure 1, shows details of the sample selection process.

Exclusion criteria were as follows: a) relative with MS, b) mental disorder comorbidity, and c) cognitive deterioration in the previous routine neurological assessment.

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Participants were provided with oral and written information about the study. The implementation of the study was approved by the responsible Ethics Committee (0846-N-18).

2.2. Instruments

All participants filled in a standardized questionnaire on sociodemographic characteristics. Relevant clinical and diagnostic information were collected from the medical data base.

2.2.1. Health related Quality of life

The 12-Item Short Form Health Survey (SF-12) contains 12 items scored on a 3 or 5-point Likert scale. The SF-12 includes eight domains: physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional and mental health. The score for each subscale ranges from 0 (worst) to 100 (best). These subscales can be collapsed into two summary component scores: the Physical Component Summary Score (PCS) and the Mental Component Summary Score (MCS). QualityMetric SF Health Outcomes Scoring Software was used to calculate the component summary scores [24,25]. In our sample, the Cronbach's alpha for the above mentioned dimensions ranged from 0.699 to 0.960 at T1 and from 0.644 to 0.962 at T2. Cronbach's alpha was 0.92 and 0.88 for the PCS and MCS, respectively [26].

2.2.2.Mental health

The General Health Questionnaire (GHQ-28) comprises 28 items, which are scored on a 4-point Likert scale. The four subscales are somatic symptoms, anxiety/insomnia, social dysfunction and depression. Scores for every subscale vary from 0 to 21, the total GHQ-28 score varies from 0 to 84, higher scores indicate worse mental health [27,28]. The GHQ-28 Spanish version has demonstrated an acceptable degree of validity [29] and reliability in chronic health condition studies [30]. In our sample Cronbach's alpha varied from 0.856 and 0.937 at T1 and from 0.874 and 0.933 at T2, for the various subscales. Cronbach's alpha for the total scale was 0.949 and 0.952 at T1 and T2, respectively.

2.3.Statistical Analysis

Firstly, descriptive analysis (means, standard deviation and frequencies) were calculated to summarize clinical and sociodemographic sample characteristics. Unpaired t-test and Chi-squared test were used to analyse age, sex, HRQOL and GHQ-28 scores at T1.

To study potential mean differences between T1 and T2 in HRQOL and mental health, paired t-tests were applied.

Unpaired t-tests examined mean differences between HRQOL in MS patients and the general Spanish population [5] at T1 and T2. To evaluate the effect size of differences we calculated Cohen's *d*, effect sizes were interpreted according to recommendations as small (0.2 to <0.5), moderate (0.5 to <0.8), or large (≥0.8).

To identify baseline predictors of HRQOL and mental health at T2, three different logistic binomial logistic regression models were calculated with PCS, MCS or GHQ-28 total as dependent variables. In the three models, the dependent variable was dichotomized. Patients who scored higher were assigned the label 1, those who scored lower the label 0.

Sociodemographic (sex, age, marital status, educational level and employment status) and disease characteristics (EDSS, MS subtype, time since diagnosis and time since first relapse) were considered as predictors. Data analysis was conducted using SPSS version 26. For all test, $p<0.05$ was considered statistically significant.

3.Results

The analysis of differences in HRQOL between T1 and T2 showed a significant increase in the following domains: physical functioning ($p=0.008$), role-physical ($p<0.0001$), bodily pain ($p=0.015$), and role-emotional ($p<0.0001$). In contrast, the subscale vitality significantly decreased ($p=0.002$). Effect sizes were small for all domains, only the role-emotional domain reached a medium effect size. No significant changes were observed on the subscales general health, social functioning, and mental health. Additionally, the Physical Composite Score ($p=0.016$) and the Mental Composite Score ($p=0.048$) significantly increased resulting in a large effect size (see Table 3).

-Insert Table 3-

Table 4 presents the results for the comparison of HRQOL in our study sample with the General Spanish Population by unpaired t-tests. Mean scores of all SF-12 domains were significantly lower in the MS group, especially at T1. At T2 differences were diminished in all domains, except for vitality (see Figure 2).

-Insert Table 4-

-Insert Figure 2-

Paired t-test results yielded that almost every GHQ-28 subscale significantly decreased from T1 to T2, except for social dysfunction. Effect sizes were mainly small, only the differences in the GHQ-28 total score showed a moderate effect size (see Table 5).

-Insert Table 5-

In the final step of analysis the impact of clinical and sociodemographic characteristics at baseline on physical HRQOL, mental HRQOL and mental health after 18 months was investigated. The binomial logistic regression models are presented in Table 6. EDSS was negatively related to physical HRQOL with 1-unit increase in EDSS corresponding to a 39.2% (0.506-0.731) decrease of physical HRQOL (p<0.0001). Similarly, aging by one year was associated with a 3.2% (0.939-0.997) decrease in physical HRQOL (p=0.032).

For mental HRQOL, EDSS was the only predictive variable. A 1-unit EDSS increase was associated with a 15% (0.729-0.991) decrease of mental HRQOL (p=0.038).

With regard to mental health predictors, being a man was related with a 59.2% (0.237-0.702) decrease of GHQ-28 score (p=0.001). On the contrary, having undergone primary education was associated with a 269.7% (1.238-5.875) increase in GHQ-28 score (p=0.013). A 1-unit EDSS increase was related with an 34.9% (1.145-1.591) increase of the GHQ-28 score (p<0.0001). Also, a 1-unit increase in months since outbreak was related with a 0.5% (0.991-1.000) increase of the GHQ-28 score (p=0.048).

-Insert Table 6-

4. Discussion

The overarching objective of this longitudinal study was to explore HRQOL and mental health in a sample of MS patient over an 18-months follow-up period.

Interestingly, the results showed that physical and mental HRQOL significantly increased with a large effect size over the period of 18 months. Similarly, all mental health domains improved, except for social dysfunction. With regard to neurological treatment in terms of prescribed immune medications there was no significant change between both time points. Nonetheless, in keeping with previous studies MS patients showed significantly lower HRQOL compared to the general population at T1 and T2 [2-5]. In line with the significant increase in HRQOL over 18 months the difference to the GSP diminished at follow up, which corresponded to smaller effect sizes particularly for the subscale role-emotional.

In our sample patients had a mean age of 45 years and had been diagnosed with MS 12 years ago on average. Two thirds were female, most of the patients suffered from the remittent subtype. Thus, our study did not focus on newly diagnosed patients, but on patients which already had experienced the chronicity of the illness.

Previous studies have shown high emotional distress in the early phases of MS [19,21] but in the course of time the majority of patients and their families successfully accommodate to living with this chronic illness [31]. One could argue, that after having been diagnosed with MS for some years most patients have learned to cope with the illness and its unpredictability, which results in a stabilization of HRQOL. In line with this assumption a previous study investigating over 1-year a smaller sample of 55 patients in their thirties 4.8 year after the MS diagnosis found no significant differences in HRQOL between baseline and follow up [32]. Schreiber et al. [33] also found that HRQOL measured with SF-12 remained stable over a 2-year follow up period in a group of RRMS patients 7.46 years after MS diagnosis undergoing fingolimod treatment. However, our findings contradict this assumption insofar, as physical and mental HRQOL not only remained stable but even improved by a large effect size in the course of 18-months. We think this result to be very encouraging, as it points to

essential adaptation processes and an optimization of coping more than a decade after the diagnosis of MS. In the long run even further improvements might be possible. In accordance with this, Foley et al. [34], investigated HRQOL changes over 3 years in RRMS patients medicated with natiluzumad. Patients mean age was 48 years. The sample was stratified by years since diagnosis: ≤10 years and >10 years. SF-12 PCS significantly increased in the subgroup ≤10 years and remained stable in the subgroup >10 years, while MCS significantly increased in both groups. How can the improvements in those patients diagnosed with MS for over a decade as in our sample and in the study by Foley et al. [34] be explained? First, improvements in mental HRQOL in MS patients during their forties more than a decade after diagnosis can suggest a delayed process of adaptation, because patients need more time to come to terms with the disease. More longitudinal research is required to further understand these long term coping processes in MS. Second, it might be possible that even though our study was merely observational, the mere focus on HRQOL in the framework of a scientific study contributed to this positive development as it raised positive expectations in the sense of a placebo effect. This possibility underlines the fact that any therapy should increase patients' awareness of their own resources in dealing with this challenging disease and improving their HRQOL. Third, there have been important pharmacological developments in recent years. The introduction of new Disease Modifying Drugs (DMDs) beyond the traditional medications might have a positive influence on HRQOL. The prescribed DMD agents (fingolimod, aletuzumab, natalizumab) have selective points of action in the immune system. A more selective medication can reduce disease severity and relapse rate. In our sample, 54.6% of participants were prescribed selective immunosuppressant at T1 and 64.6% at T2, which may also have been a contributing factor to HRQOL improvement. In keeping with this fact, patients with RRMS treated with Alemzutumad experienced an improvement

in mental and physical HRQOL measured by SF-36 over 6 years [35]. Several other studies examined HRQOL development in MS samples treated with novel DMDs. Results showed improvements of HRQOL [34,36] or stability at high levels [33].

With regard to the inconsistency of findings on changes in HRQOL, differences in study designs and methodological approaches are further factors, which have to be considered. A study using EuroQoL found a decrease of HRQOL [37], while results from other studies using SF-36 [35,36] and SF-12 [34] showed improvements in the 1 year [36] as well as 3 [34] and 6 [35] years follow-up period. Obviously, above mentioned assessment tools underly different psychological constructs of HRQOL, which greatly affects outcome.

With regard to HRQOL subscales, it is noteworthy that physical functioning, role-physical, and bodily pain significantly increased by a small effect size, and role-emotional by a medium effect size. The role emotional subscale specifically asks for limitations in work or other regular activities due to emotional problems such as depression or anxiety. The greater improvement on this particular domain in the course of 18-months corroborates the assumption of an optimized emotional adaptation and coping [31]. Akman-Demir et al. [36] also found improvements on this subscale in the SF-36 in the course of 12 months in patients with RRMS on fingolimod. The lack of improvement in social functioning points to the fact that physical limitations impair the capacity of MS patient to participate in social activities and bear the danger of social isolation and mental health problems [12]. Against this backdrop social support and the participation in social activities is a major protective factor for HRQOL in MS [9,38]. Vitality was the only subscale to significantly decrease, which emphasizes the relevance of fatigue in MS. Our above mentioned systematic review identified fatigue as a major physical risk factor for HRQOL [9].

According to previous studies the following sociodemographic and clinical variables were expected to significantly influence changes in HRQOL: disease duration [9,38,13], employment [8,9,39], marital status [9], educational level [9,13], MS type [9,13]. However, in our study only two variables predicted HRQOL: EDSS score and age. One might argue that this can be explained by major differences between our study and previous studies regarding study design and study samples. As outlined before, most of the above cited evidence is based on cross-sectional studies. Furthermore, it is important to note, that the influence of psychosocial factors probably largely depends on specific sample and study characteristics such as age, time since diagnosis or outbreak and duration of follow up. To demonstrate relevant differences in study design and sample characteristics, one might compare our longitudinal study to one of the few previous longitudinal studies [40], which also was included in our previous systematic review. Both studies show significantly different sample characteristics with regard to mean age (45 years in our study versus 40 years) and mean time since diagnosis (12 years in our study versus 7 years). Study design differed with regard to the duration of follow up: 18 months in our study versus 24 months. Thus, to better understand the influence of specific factors on QOL these differences have to be taken into account.

Not surprisingly, EDSS was the strongest predictor of physical HRQOL in our study. From a methodological perspective the SF-12 items on physical HRQOL specifically asks for limitations due to a lack of mobility, which implies a certain overlap between the psychological constructs of disability status as measured by the EDSS and physical HRQOL as measured by the SF-12. A higher level of disability is related to more helplessness, dependence on others, and limitations in daily life [1]. Disability, particularly lack of

mobility, has been identified consistently as the major risk factor for HRQOL worsening [9-12,14,41-43].

Furthermore, older age predicted worse physical HRQOL. This finding is consistent with previous findings [9-12,38]. Apart from a worsening of MS symptoms, older age increases the likelihood of additional somatic comorbidities [9].

EDSS was the only predictor of mental HRQOL, emphasizing the significance of mobility and physical independence for patients' well-being. Impaired physical functioning often negatively affects the feeling of self-efficacy, which leads to mental health problems. Our findings are in line with previous studies, which identified EDSS as significant risk factor for mental and physical HRQOL [14,41].

Interestingly, disability status was no predictor for mental health as measured by the GHQ-28, even though it predicted mental HRQOL. This might have to do with the different construction of both questionnaires. In 28 items the GHQ asks far more differentiated for a wide spectrum of mental health aspects such as pain, depression, anxiety, and suicidality compared to the SF-12. However, it does not focus on limitations in working or other regular activities due to emotional problems. This is, on the contrary, the focus of the SF-12 mental HRQOL component: "Have you accomplished less?" or "Have you been working less careful?" are typical items in the SF-12. One might argue that the underlying construct of HRQOL is debatable as it implies that the interference with regular activities is the most important factor for HRQOL.

Regarding further predictors male gender was a protective factor for mental health. This result is consistent with the study by Khader et al. [44], which found greater mental health impairments in female MS patients. These findings points to the importance of psychodiagnostics and psychotherapeutic measures particularly in female MS patients.

Our study identified lower formal education as a highly relevant predictor for impaired mental health. Having undergone primary education was associated with a 269.7% increase in GHQ-28 score. This result supports the findings by Podda et al. [16], that showed lower educational level to be a significant predictor for anxiety at one-year follow up. This finding is in keeping with previous studies confirming the protective effect of higher formal education, which goes along with a higher employment rate and income as well as favorable health behavior. However, in a recent systematic review Fisher et al. [20] point out that there is limited evidence for the relevance of lower educational level for emotional distress in MS. Finally, a longer duration since outbreak of the disease measured in months was a weak predictor of worse mental health. Previous studies identified longer disease duration as a risk factor for HRQOL [13,38,40,43,45]. As mentioned above, it is highly important to specifically compare the results of respective studies with regard to the applied questionnaires and the underlying psychological constructs of mental health or HRQOL. Nevertheless, particularly with regard to the development of mental health more longitudinal research is needed.

The study presents some limitations and strength. The main weakness is the non-random selection of participants, which limits its external validity. Furthermore, only self-report instruments were applied, an assessment of mental health by a semi-structured interview, for example, may be more reliable. Besides, the SF-12 and SF-36 questionnaires present some limitations in evaluating HRQOL changes in MS patients with moderate to severe disability [46]. Using an additional disease specific HRQOL questionnaire, with higher sensitivity to changes, might have facilitated the preciser assessment of alterations. Furthermore, in future research other significant variables, such as number of relapses in the previous year and time since last relapse should be included. Nonetheless, sociodemographic

and clinical characteristics of our sample underline its heterogeneity. The longitudinal study design with an 18-months follow up, the large sample size and a relatively low drop out rate can be seen as major strengths.

5. Conclusions

Our study findings accentuate the great potential of favorable adaptation processes in MS patients leading to great improvements in HRQOL even over a decade after the diagnosis. In addition to disability status gender, formal education, and disease duration should be taken into account as relevant risk factors for patients' well-being in order to improve the efficiency of interventions. Future research should gain further insights into the impact of sociodemographic and clinical characteristics on HRQOL and mental health in specific subgroups of MS patients as defined, for example, by age, gender, and duration of disease. This could pave the path towards a more personalized medical approach in MS.

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Declaration of interest

The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Data availability statement

Due to the nature of this research, participants of this study did not agree for their data to be shared publicly, so supporting data is not available.

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Figure 1

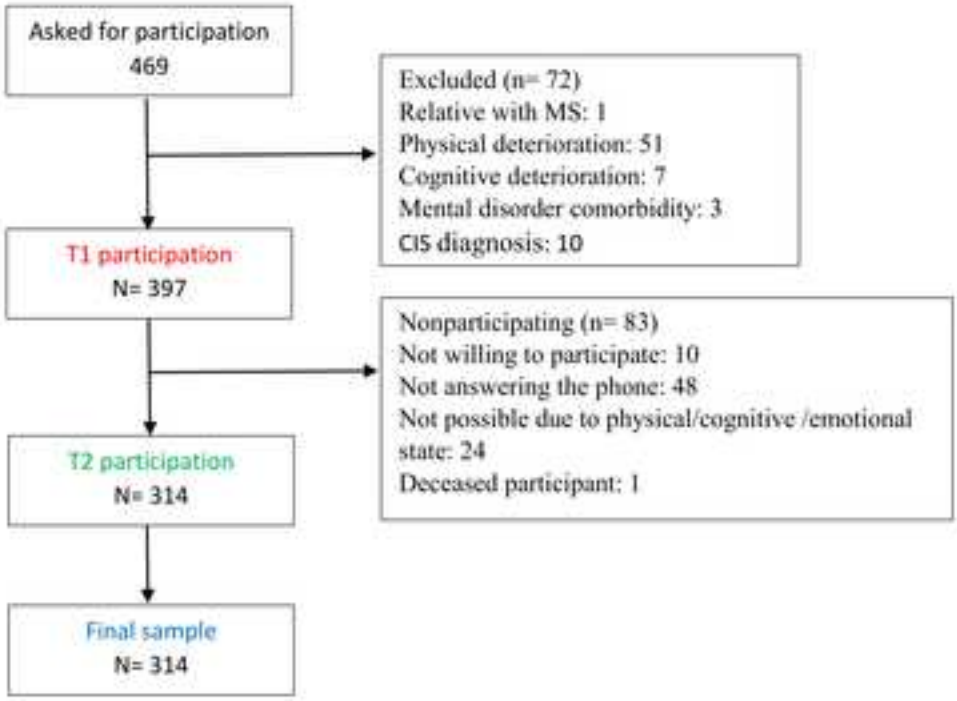

Figure 1. Study flow-chart.

Figure 2

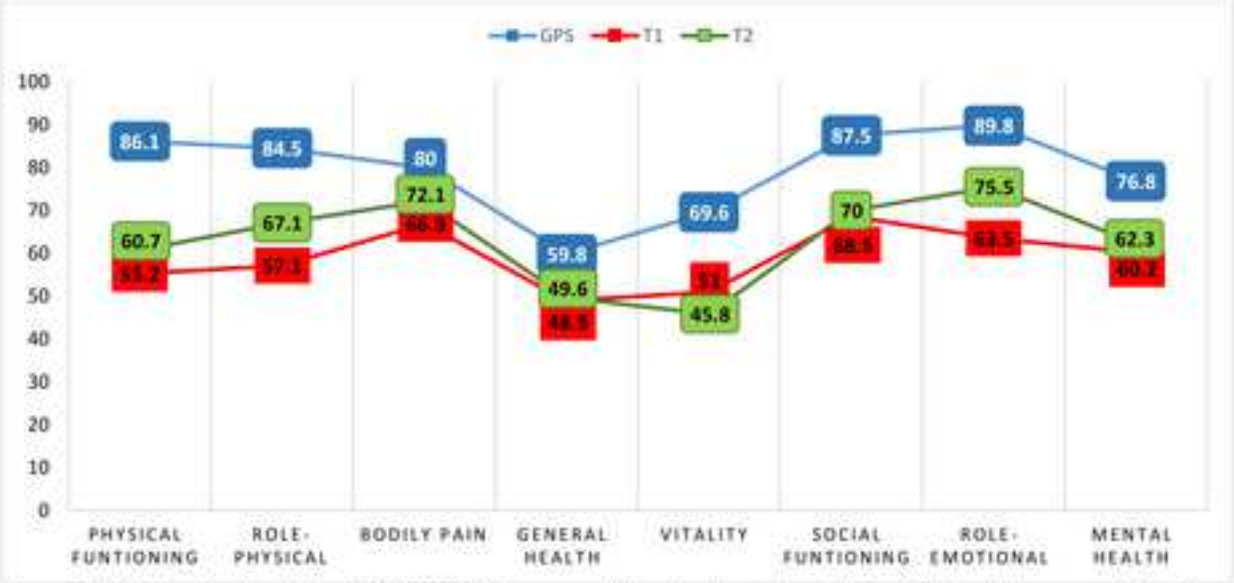

Figure 2. Health-related quality of life (HRQOL) across all domains in patients (T1 and T2) and the general Spanish population.

Table 1. Clinical and sociodemographic characteristics of study sample and comparison with dropouts

	MS Sample N=314	Dropouts N=83	*p*
Gender n (%)			
Male	101 (32.2)	23 (27.7)	0.436
Female	213 (67.8)	60 (72.3)	
Age (M±SD)	45.31±10.77	46.3±12.5	0.468
Partnership n (%)			
No partner	85 (27.1)		
Partner	229 (72.9)		
Occupation n (%)			
Employed/In education	116 (36.9)		
Unemployed	198 (63.1)		
Educational level n (%)			
Primary education	44 (14)		
Secondary education	102 (32.5)		
University or higher	168 (53.5)		
EDSS (M±SD)	3.17±1.92		
MS subtype n (%)			
Remittent	272 (86.6)		
Progressive	42 (13.4)		
Months since diagnosis (M±SD)	145.68±89.56		
Months since outbreak (M±SD)	186.11±111.18		
Physical QOL (M±SD)	44.1±11.5	40.6±11.8	0.013*
Mental QOL (M±SD)	45.9±10.4	42.5±10.4	0.011*
GHQ-28 (M±SD)	24.6±14.5	29.2±15.6	0.013*

Table note: Significance value, *$p<0.05$

Table 2. Neurological medication

	Baseline (N=314)	Follow-up (N=314)
No medication n (%)	46 (14.6)	41 (13)
Immune modulator interferon n (%)	60 (19.1)	46 (14.6)
Other immune modulator n (%)	28 (8.9)	23 (7.3)
Selective immunosuppressant n (%)	177 (56.4)	203 (64.6)
Non-selective immunosuppressant n (%)	3 (1.0)	1 (0.3)

Table note: The distribution is not significantly different between baseline and follow up. Chi^2=5.41, p=0.248

Table 3. Comparison of health-related quality of life (SF-12) between T1 and T2

	Mean score (*SD*)			
	T1	T2	*p*	Cohen´s *d*
Physical functioning	55.17 (39.60)	60.67 (39.74)	0.008**	-0.15 (n)
Role-physical	57.05 (33.22)	67.09 (32.80)	0.000**	-0.30 (s)
Bodily pain	66.88 (35.94)	72.05 (34.92)	0.015*	-0.14 (n)
General health	48.85 (27.40)	49.55 (29.51)	0.663	-0.15 (n)
Vitality	51.04 (28.63)	45.78 (28.75)	0.002**	0.18 (n)
Social functioning	68.47 (29.86)	69.98 (31.23)	0.418	-0.05 (n)
Role-emotional	63.46 (28.74)	75.49 (29.85)	0.000**	0.60 (M)
Mental health	60.19 (24.01)	62.30 (25.81)	0.173	-0.08 (n)
Physical Composite Score	44.14 (11.54)	45.50 (11.19)	0.016*	0.98 (L)
Mental Composite Score	45.88 (10.39)	47.18 (11.48)	0.048*	1.033 (L)

Table note: L=large effect size, M=medium effect size, s=small effect size, n=null effect size
Significance value, **$p<0.01$, *$p<0.05$

Table 4. Comparison of health-related quality of life (SF-12) with a Spanish population sample (unpaired t-test)

	T1	T2
	p (d)	*p (d)*
Physical functioning	<0.0001 (0.49s)	<0.0001 (0.40s)
Role-physical	<0.0001 (0.47s)	<0.0001 (0.30s)
Bodily pain	<0.0001 (0.18n)	0.0002 (0.11n)
General health	<0.0001 (0.19n)	<0.0001 (0.17n)
Vitality	<0.0001 (0.30s)	<0.0001 (0.39s)
Social functioning	<0.0001 (0.34s)	<0.0001 (0.31s)
Role-emotional	<0.0001 (0.54M)	<0.0001 (0.29s)
Mental health	<0.0001 (0.33s)	<0.0001 (0.28s)
Physical Composite Score	<0.0001 (0.30s)	<0.0001 (0.23s)
Mental Composite Score	<0.0001 (0.20s)	<0.0001 (0.14n)

Table note: M=medium effect size, s=small effect size, n=null effect size

Table 5. Differences between T1 and T2 in mental health (GHQ-28) (paired t-test)

	Mean score (*SD*)			
	T1	T2	*p*	Cohen´s *d*
Somatic symptoms	6.99 (4.51)	5.95 (4.58)	0.000**	0.47 (s)
Anxiety and insomnia	6.61 (5.20)	5.62 (5.07)	0.001**	0.26 (s)
Social dysfunction	8.13 (3.55)	8.21 (3.80)	0.732	-0.02 (n)
Severe depression	2.95 (4.50)	2.18 (4.25)	0.001**	-0.45 (s)
GHQ28-total	24.68 (14.50)	21.96 (14.65)	0.000**	0.55 (M)

Table note: M=medium effect size, s=small effect size, n=null effect size
Significance value, **$p<0.01$

Table 6. Quality of life and mental health predictors (binomial logistic regression models)

		B	*E.T.*	*Wald*	*p*	*OR* (95% *C.I*)
Men	PCS	-0.023	0.284	0.007	0.935	0.977 (0.560-1.706)
	MCS	0.503	0.258	3.801	0.051	1.654 (0.997-2.742)
	GHQ-28	-0.896	0.277	10.491	0.001**	0.408 (0.237-0.702)
Age	PCS	-0.033	0.015	4.592	0.032*	0.968 (0.939-0.997)
	MCS	0.014	0.014	1.037	0.308	1.014 (0.987-1.042)
	GHQ-28	0.010	0.015	0.503	0.478	1.010 (0.982-1.040)
Partner	PCS	0.041	0.294	0.019	0.890	1.042 (0.586-1.852)
	MCS	0.208	0.266	0.614	0.433	1.231 (0.732-2.072)
	GHQ-28	-0.224	0.278	0.651	0.420	0.799 (0.464-1.377)
Primary education	PCS	-0.106	0.406	0.068	0.795	0.900 (0.406-1.995)
	MCS	-0.643	0.370	3.019	0.082	0.526 (0.255-1.086)
	GHQ-28	0.992	0.397	6.236	0.013*	2.697 (1.238-5.875)
Secondary education	PCS	-0.582	0.295	3.893	0.048	0.559 (0.313-0.996)
	MCS	-0.381	0.268	2.028	0.154	0.683 (0.404-1.154)
	GHQ-28	0.621	0.282	4.832	0.028*	1.861 (1.070-3.237)
University or higher	PCS			3.980	0.137	
	MCS			3.975	0.137	
	GHQ-28			8.652	0.013*	
Employed/ student	PCS	0.266	0.299	0.796	0.372	1.305 (0.727-2.344)
	MCS	0.172	0.283	0.371	0.542	1.188 (0.682-2.068)
	GHQ-28	-0.196	0.295	0.444	0.505	0.822 (0.461-1.464)
Months since diagnosis	PCS	0.000	0.003	0.030	0.862	1.000 (0.995-1.004)
	MCS	0.000	0.002	0.001	0.979	1.000 (0.995-1.005)
	GHQ-28	0.000	0.003	0.005	0.946	1.000 (0.995-1.005)
Months since outbreak	PCS	0.002	0.002	0.755	0.385	1.002 (0.998-1.006)
	MCS	0.002	0.002	1.236	0.266	1.002 (0.998-1.006)
	GHQ-28	-0.005	0.002	3.919	0.048*	0.995 (0.991-1.000)
EDSS	PCS	-0.498	0.094	28.212	0.000**	0.608 (0.506-0.731)
	MCS	-0.163	0.078	4.317	0.038*	0.850 (0.729-0.991)
	GHQ-28	0.300	0.084	12.728	0.000**	1.349 (1.145-1.591)
Remittent	PCS	0.206	0.502	0.169	0.681	1.229 (0.459-3.290)
	MCS	0.247	0.413	0.357	0.550	1.280 (0.569-2.877)
	GHQ-28	0.247	0.413	0.357	0.550	1.280 (0.569-2.877)
Constant	PCS	2.637	0.953	7.654	0.006	13.969 (0.560-1.706)
	MCS	-0.941	0.832	1.279	0.258	0.390
	GHQ-28	-0.229	0.872	0.069	0.793	0.795

Table note: OR=Odds Ratio; *CI*=Confidence Interval
Significance value,**p<0.01, *p<0.05