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Quality of Life and Depressive Symptomatology in Multiple Sclerosis: A Cross-Sectional Study Between the USA and Spain

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Abstract

Background: For multinational clinical trials in multiple sclerosis (MS), identifying cross-country differences on quality of life (QoL) is important for understanding patients' response variability. No study has compared QoL between Spanish and American MS samples. This study aims to: 1) compare QoL and depressive symptomatology between Spanish and American patients, and against normative data; 2) compare the interrelationship between such constructs between countries; and 3) compare sociodemographic and clinical predictors on these outcomes. **Method:** 114 participants with MS were included and matched for gender, disability and education. The SF-36 Health Survey and BDI-FastScreen (BDI-FS) were the outcomes. ANCOVA, partial-correlations and multiple regression analyses were compared between countries. **Results:** Spaniards reported worse depressive symptomatology and QoL, and clinically significant impairment in all QoL dimensions, while Americans showed clinically significant impairment only in physical domains. Among Spaniards, more Bodily pain was more related to worse Social functioning and Vitality, and worse Vitality was more related to worse Social functioning than among Americans. From the regression models, Physical functioning predicted BDI-FS greater among Americans. Conversely, disability and Role-emotional predicted BDI-FS and Mental health, respectively, significantly stronger in Spain. **Conclusions:** Spaniards show worse QoL and depressive symptomatology and greater clinically significant impairment than the Americans.

Keywords: Multiple sclerosis, quality of life, depression, cross-cultural study, Spain, USA.

Resumen

Calidad de Vida y Sintomatología Depresiva en Esclerosis Múltiple: un Estudio Transversal Entre EE.UU. y España. **Antecedentes:** en los ensayos clínicos multinacionales en esclerosis múltiple (EM) es fundamental identificar diferencias entre países en calidad de vida (CV) para comprender la variabilidad de respuesta entre pacientes. Ningún estudio comparó la CV en EM entre España y EE. UU. Los objetivos de este estudio son: 1) comparar la CV y sintomatología depresiva entre pacientes españoles y estadounidenses, frente a datos normativos; 2) comparar la interrelación de tales constructos entre países; y 3) comparar predictores sociodemográficos y clínicos. **Método:** 114 participantes con EM fueron emparejados por género, discapacidad y educación. SF-36 y BDI-FastScreen (BDI-FS) fueron las variables criterio. ANCOVA, correlaciones parciales y análisis de regresión múltiple fueron comparados entre países. **Resultados:** los españoles muestran peor sintomatología depresiva, CV y deterioro clínicamente significativo en todas las dimensiones, mientras que los estadounidenses presentan deterioro clínicamente significativo en dominios físicos. En España, más Dolor corporal se asoció con peor Funcionamiento social y Vitalidad; y peor Vitalidad se relacionó con peor Funcionamiento social. Además, Funcionamiento físico predijo BDI-FS mucho más entre los estadounidenses; pero en España, la discapacidad y Rol emocional predijeron mucho más BDI-FS y Salud mental, respectivamente. **Conclusiones:** los españoles muestran peor CV y sintomatología depresiva con mayor deterioro clínicamente significativo.

Palabras clave: esclerosis múltiple, calidad de vida, depresión, estudio transcultural, España, EE. UU.

Patient-reported quality of life (QoL) is an important end-point in multinational clinical trials in multiple sclerosis (MS) (Arroyo et al., 2020; Miller et al., 2010; Williams, 2012). Even in some studies, this self-perceived measure shows the most powerful predictive value in comparison to the standardized clinical outcome measures (Pellegrini et al., 2019). Moreover, this unpredictable chronic immune-mediated inflammatory disease of the central nervous system is one of the major causes of disability among middle-aged adults. Consequently, affective disorders such as depression and anxiety are very frequent comorbid conditions among patients with MS (Hanna & Strober, 2020), and both impact the disease course predicting future relapses (Salter et al., 2020). QoL and depression among people living with MS can be affected by various factors that may be socially/culturally related, and therefore may vary in different parts of the world. Because multinational treatment-effectiveness studies require internal validity, identifying cross-country differences is important for understanding patients' response variability, which may be attributed to factors other than effects of MS disease-modifying-therapy (DMT) (Pfennings et al., 1999; Pluta-Fuerst et al., 2011). The few studies that have compared QoL in MS across nations have found cross-country

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differences between MS samples but the causes of these disparities remain unclear and may be due to the limited control of socio-demographic or clinical variables between samples (Murphy et al., 1998; Pakpour et al., 2009; Pfennings et al., 1999; Pluta-Fuerst et al., 2011). Furthermore, to the best of our knowledge, none have contrasted MS samples from Spain and the USA.

Given these existing limitations, recent studies have encouraged further cross-country research on QoL in MS (Pluta-Fuerst et al., 2011; Pugliatti et al., 2012). The current study seeks to extend our knowledge by addressing three primary objectives: a) to compare QoL and depressive symptomatology in individuals with MS between Spain and the USA, after matching both samples (on gender, educational level and disability status) and statistically controlling for key sociodemographic and MS-related variables (age, years of education, the Expanded Disability Status Scale [EDSS] score, and time since MS diagnosis); as well as to analyze the clinical significance of these results in comparison to the general population; b) to examine the relationship between QoL and depressive symptomatology across both countries, after having statistically controlled for the aforementioned variables; and c) to identify sociodemographic and clinical predictors on QoL and depressive symptomatology in each country.

Method

Participants

A total of 297 outpatients with MS (231 Spanish and 66 American participants) were recruited during their routine medical checkup at the University Hospital Virgen Macarena in Seville (Spain) from their staff; or participated in a research study at Drexel University (Philadelphia, PA, USA), being recruited from the staff at the MS center at Thomas Jefferson University Hospital of the city or via website, newsletters and MS groups. All individuals had the local language as the native language and met MS diagnosis criteria. A non-probability sampling technique type purposive was used in both sites and the following exclusion criteria were applied: presence of neurological comorbidity; major psychopathological disorders (e.g., psychosis); and other conditions (e.g., pregnancy). Following this, 114 participants aged 23-61 years were selected and matched (57 participants from each country) according to the following categorical variables: gender, educational level, and disability status. Sociodemographic and clinical data were collected via interview or clinical-facility registers (Table 1).

All participants were evaluated during a single session. Institutional IRB and ethics committees in each participating institution approved the study. All participants provided written informed consent.

Instruments

Quality of life. The *SF-36 Health Survey* is a 36-item questionnaire whose most items refer to the previous four weeks and scores range from 0 (the worst health status) to 100 (the best health status in that dimension). A different version was administered in each country: versions 1 (USA) and 2 (Spain) (Ware & Sherbourne, 1992). In the current study, alpha coefficients ranged from .72 (*General health*) to .95 (*Physical functioning*) for the Spanish sample, and from .74 (*Role-emotional*) to .93 (*Physical functioning*) for the American sample, indicating acceptable-excellent reliability.

Depression measure. The *Beck Depression Inventory-FastScreen* (BDI-FS) is a 7-item self-report which assesses depressive symptomatology independent from neurological symptoms and signs, and is valid for MS population (Benedict et al., 2003). It presents a three-point scale and refers to the last two weeks. Scores range from 0 to 21, with higher scores indicating greater depressive symptomatology. In the current study, alpha coefficients and mean inter-item correlations (MICs) were .82 and .39 for Spanish sample, and .69 and .27 for American sample, respectively. Thus, since a range of .20 to .40 is considered optimal for MICs, all these values were adequate except for the alpha coefficient in the American sample, which was slightly below the standard of .70.

All participants were evaluated with the self-reports during a single session by EFJ in Spain or by research and graduate assistants at Drexel University. EDSS score was provided by a physician and the remaining data was obtained from the clinical-facility registers.

Data analysis

Descriptive analyses consisted of ANOVAs and Cohen's *d*s for continuous variables; and chi-square tests, adjusted standardized residuals, and Cohen's *w* for categorical variables (Cohen, 1992).

SF-36 Health Survey 0-100 scores were standardized (*T* scores) to assure comparability between versions. Therefore, means below 50 for both MS samples represent worse QoL than the general population and above 50 indicate better QoL. The USA (n = 6,742) (Ware et al., 1998) and Spanish general population norms (n = 9,151) (Alonso et al., 1998) were used. To compare QoL and depressive symptomatology between Spain and the USA, ANCOVAs were performed taking into account four covariates: age, months since MS diagnosis, years of education, and EDSS score. Special attention was paid to verifying the ANCOVA assumptions.

To examine the relationship between QoL and depressive symptomatology per country, partial-correlation coefficients were computed between SF-36 subscales and BDI-FS total score for each country, controlling for age, years of education, EDSS score and time since MS diagnosis. Subsequently, we compared these partial-correlations between countries, using a *z*-test.

Finally, to identify potential predictors of the outcomes (depressive symptomatology and SF-36 dimensions) where the greatest differences between groups were found (according to effect sizes), hierarchical multiple regression analyses were performed for each sample. Predictor variables included marital and work status, as well as the covariates (years of education and EDSS score) and the SF-36 subscales which emerged as significant during the preceding analyses (ANCOVAs and correlations). Each variable was entered in each step by the *Enter* method. Marital and work status were re-categorized into *k-1* dummy variables, where *single* and *working* were the reference groups, respectively. We focused on the unique contribution of each predictor to the criterion variable once all the remaining predictors were ruled out. Consequently, we used partial-correlations and f^2 as the effect size index. Finally, those predictors which were significant in the multiple regression models were compared between countries using *t*-tests (Weaver & Wuensch, 2013).

Effect size indexes were included for all analyses (Cohen, 1992). Data were analyzed with IBM-SPSS 22.0 statistical software

Table 1
Sociodemographic and clinical variables in Spain and the United States

	Spain	The United States	
	Variables matched % (*n*)		
Gender: Female / male	75.4 (43) / 24.6 (14)		
Educational level: High / secondary [a]	84.2 (48) / 15.8 (9)		
Disability level (EDSS): Mild / moderate [b]	71.9 (41) / 28.1 (16)		
	Mean (SD)	**Mean (SD)**	$F_{(1, 113)}$, *p* **(Cohen's *d*)**
Age	40.1 (8.1)	42.5 (8.2)	2.45, *.121* (-0.29 S)
Years of education	15.7 (2.9)	15.4 (2.1)	0.50, *.482* (0.13 –)
Months since diagnosis	97.0 (62.4)	103.6 (73.1)	0.27, *.606* (-0.10 –)
EDSS	3.1 (1.6)	3.1 (1.6)	0.00, *.952* (-0.01 –)
Months since last relapse	39.5 (34.6)	35.1 (43.3)	[c] 0.34, *.560* (0.11 –)
	% [d] (*n*)	**% (*n*)**	$\chi^2_{(2, 114)}$, *p* **(*w*)**
Marital status:			0.35, *.842* (0.06 –)
Single	14 (8)	17.5 (10)	
With partner	77.2 (44)	75.4 (43)	
Loss of partner	8.8 (5)	7.0 (4)	
Employment status:			9.89, *.007* (0.29 S)
Working	40.4 (23)*	59.6 (34)*	
Unemployed	8.8 (5)	17.5 (10)	
Disabled	50.9 (29)**	22.8 (13)**	
MS subtypes:			9.60, *.008* (0.29 S)
Relapsing-remitting	80.7 (46)	91.2 (52)	
Progressive	19.3 (11)**	3.5 (2)**	
Unknown	0 (0)	5.3 (3)	
MS-DMT [e]: yes / no / unknown	82.5 (47) / 15.8 (9) / 1.8 (1)	82.5 (47) / 17.5 (10)	1.05, *.591* (0.10 –)
Antidepressants: yes / no	21.1 (12) / 78.9 (45)	22.8 (13) / 77.2 (44)	0.05, *.821* (-0.02 –)
Anxiolytics: yes / no	78.9 (45) / 21.1 (12)	87.7 (50) / 12.3 (7)	1.58, *.209* (0.12 S)
Psychopharmacological treatment: Both / one / none	8.8 (5) / 24.6 (14) / 66.7 (38)	5.3 (3) / 24.6 (14) / 70.2 (40)	0.55, *.759* (0.07 –)

[a] High level: university or high-level vocational training program; secondary level: high school or medium level vocational training program. [b] Mild (EDSS: from 1.5 to 3.5); moderate (EDSS: from 4.0 to 6.5). [c] $F_{(1, 105)}$ due to missing data and some participants who did not have relapses due to their MS course (some progressive forms). [d] Percentage of cases per comparison group. *Adjusted residuals > |1.96|, **Adjusted residuals > |2.58|. Effect sizes: –, null; S, small. [e] MS-DMT: multiple sclerosis disease-modifying therapy

package. No missing data was found in either sample. Statistical significance was defined as $p \leq .05$.

Results

Sociodemographic and clinical variables of the samples

The samples from both countries differed in only two domains: *employment status* and *MS subtypes*. Specifically, more American participants reported being employed and more Spanish participants reported not working due to disability, as well as to having been diagnosed with progressive types of MS (see Table 1). No other statistically significant differences were found in sociodemographic and clinical variables between both samples.

Comparison of QoL (SF-36) and depressive symptomatology (BDI-FS) between countries

Prior to final analysis, ANCOVA assumptions were verified in all variables except for homogeneity of regression slopes for one covariate in a model: years of education (in *Physical functioning*), which was not a statistically significant covariate. Therefore, its exclusion as a covariate in the model for *Physical functioning* did not change the main results.

The following covariates were statistically significant in the following SF-36 criteria: EDSS score in *Physical functioning* ($p < .001$), *Role-physical* ($p = .002$), *General health* ($p = .021$), and *Social functioning* ($p = .031$); age in *Role-emotional* ($p = .042$); and years of education in *Role-emotional* ($p = .036$). No statistically significant covariates were observed for the BDI-FS.

After entering these covariates, no statistically significant differences were found as a function of progressive or relapsing-remitting types between countries on QoL or BDI-FS outcomes (interaction effects between MS course and country: $p > .05$ for BDI-FS and SF-36 subscales), except for *General health*, where the interaction effect achieved statistical significance ($p = .019$). Specifically, a progressive MS course in the USA was related to better general perception of health in comparison to Spanish patients with progressive MS type ($p = .004$) and to American patients with a relapsing-remitting type ($p = .007$). Therefore, the different MS-course percentage between countries was globally canceled out.

After having controlled for various clinical and sociodemographic covariates, statistically significant differences were found on all SF-36 subscales and BDI-FS between countries, except for *Role-emotional* ($p = .164$) and *Role-physical* ($p = .123$). More importantly, significant differences between the samples (*p*s < .01), reaching relevant effect sizes, were observed on the SF-36 dimensions of *Bodily pain*, *Vitality*, *Social functioning* (large effect sizes), and *Mental health* (medium effect size). Therefore, these four dimensions were focused on for further analyses and interpretation. Physical functioning, although with medium effect-size difference between countries, was considered a predictor and not a criterion variable in further models.

In comparison to the general population, Spanish participants showed much worse quality of life in all dimensions (medium and large effect sizes), and American participants significantly differed from the norms on only three QoL dimensions: *Physical functioning*, *Role-physical* and *General health*- (medium effect sizes).

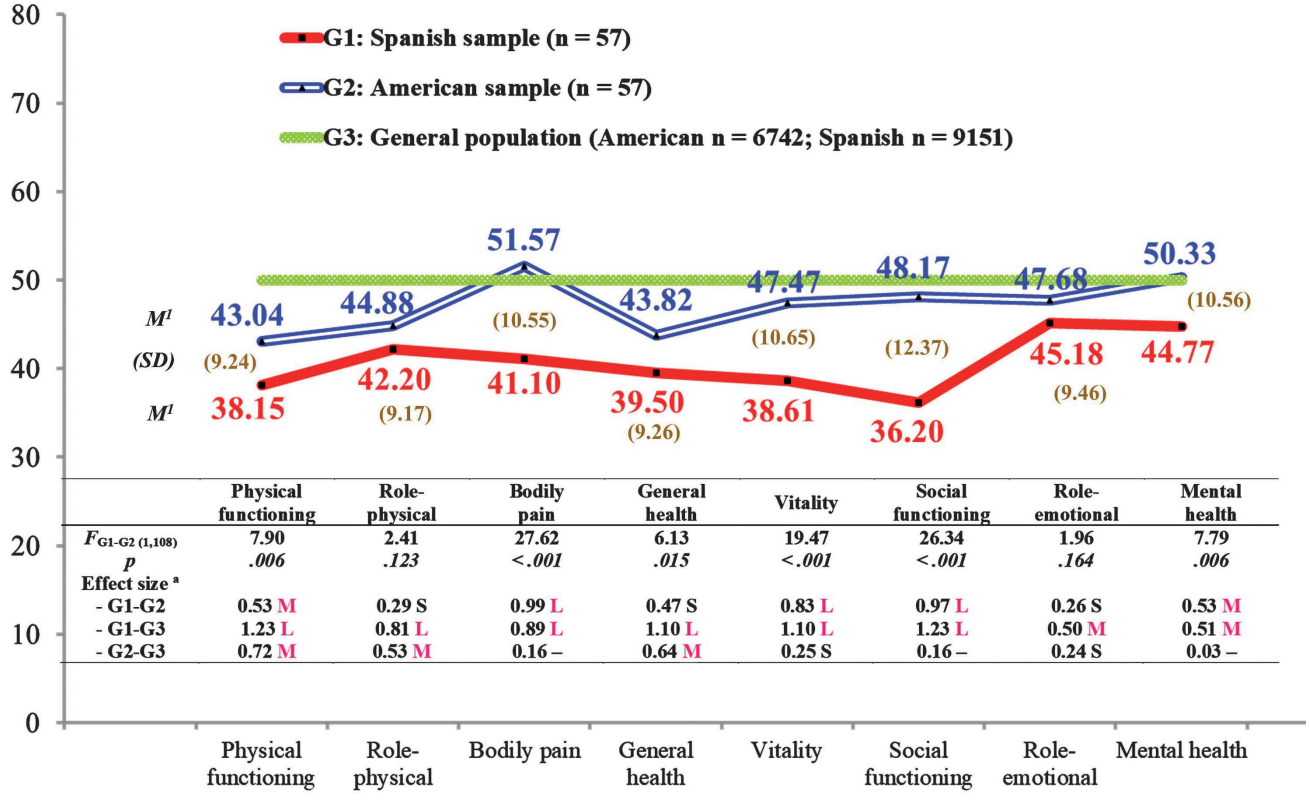
All the SF-36 covariate-adjusted means compared by country and normative values are presented in Figure 1.

Analysis of BDI-FS scores revealed another significant difference between both samples ($F_{(1, 108)} = 11.60, p = .001$, Cohen's $d = 0.64$), with American participants endorsing lower levels of depressive symptomatology ($M = 2.2$, $SD = 3.0$) compared to their Spanish counterparts ($M = 4.1$, $SD = 3.0$). According to the cut-off criteria for screening depression (≥ 4) previously reported in MS population, a significantly higher percentage of Spanish participants exceeded that clinical threshold [52.6% vs. 22.8%, $\chi^2(2, 114) = 10.79, p = .001, w = 0.31$], indicating greater level of depressive symptomatology.

Relationship between SF-36 and BDI-FS in each country controlling for age, years of education, EDSS score and time since MS diagnosis

All the partial-correlations were positive between QoL subscales except for the relationship between these and the BDI-FS score, which all were negative.

Analysis of partial-correlation comparisons between countries further revealed a pattern of significant differences in interrelationships depicted in the correlation matrix. More



	Physical functioning	Role-physical	Bodily pain	General health	Vitality	Social functioning	Role-emotional	Mental health
$F_{G1\text{-}G2\ (1,108)}$	7.90	2.41	27.62	6.13	19.47	26.34	1.96	7.79
p	*.006*	*.123*	*<.001*	*.015*	*<.001*	*<.001*	*.164*	*.006*
Effect size [a]								
- G1-G2	0.53 M	0.29 S	0.99 L	0.47 S	0.83 L	0.97 L	0.26 S	0.53 M
- G1-G3	1.23 L	0.81 L	0.89 L	1.10 L	1.10 L	1.23 L	0.50 M	0.51 M
- G2-G3	0.72 M	0.53 M	0.16 –	0.64 M	0.25 S	0.16 –	0.24 S	0.03 –

Figure 1. Comparison between Spanish and American MS samples against normative data
Note:
[1] T scores adjusted for covariates (age, months since MS diagnosis, years of education and EDSS score): means below 50 represent worse QoL than the general population and above 50 indicate better QoL.
[a] Effect sizes (Cohen's *d*): – , null; S, small; M, medium; L, large

specifically, correlations between *Bodily pain* and *Vitality*, *Bodily pain* and *Social functioning*, *Vitality* and *Social functioning*, as well as *Role-emotional* and *Mental health* were statistically different between the countries, with MS participants from Spain obtaining significantly greater *r*-values (see Table 2). Conversely, MS participants from the USA obtained significantly higher correlation coefficient on *Physical functioning* and BDI-FS. This pattern of results suggests a stronger relationship between lower levels of subjective physical functioning and higher level of depressive symptomatology perceived in the American sample, while in Spain higher bodily pain was related to worse levels of energy/fatigue and social functioning; worse levels of energy was associated with worse social functioning; and more role limitations due to emotional functioning was stronger related to much poorer mental well-being.

Predictors of QoL and depressive symptomatology in each country

Five hierarchical multiple regression models (on the four QoL dimensions with the greatest differences between countries and on the BDI-FS) revealed significant predictors in each sample (see Table 3).

However, the focus of the analyses here was to identify significant differences (*t*-tests) regarding the predictors included between countries (see Table 4). Regarding the BDI-FS, disability status predicted depressive severity more in Spain than in the USA (p = .002). On the contrary, *Physical functioning* predicted depressive severity in the USA but not in Spain (p = .011). Regarding the *Mental health* outcome, *Role-emotional* predicted it more in Spain than in the USA (p = < .001), while disability

Table 2
Partial-correlation comparisons for BDI-FS and SF-36 subscales between Spain and USA

Variables	r_1 Spain	r_2 USA	r_1,[a]	r_2,[b]	r_{diff} [c]	SE_{diff} [d]	*p*
PF, BDI-FS	-.07	-.43**	-0.074	-0.459	0.385	0.19	.046
RP, BDI-FS	-.39**	-.44**	-0.412	-0.466	0.054	0.19	.778
BP, BDI-FS	-.32*	-.39**	-0.329	-0.408	0.079	0.19	.682
GH, BDI-FS	-.35*	-.38**	-0.365	-0.401	0.036	0.19	.852
VT, BDI-FS	-.45**	-.54***	-0.487	-0.597	0.11	0.19	.568
SF, BDI-FS	-.64***	-.50***	-0.762	-0.545	-0.216	0.19	.261
RE, BDI-FS	-.66***	-.55***	-0.793	-0.617	-0.176	0.19	.361
MH, BDI-FS	-.76***	-.79***	-1.001	-1.058	0.057	0.19	.766
PF, RP	.59***	.44**	0.681	0.472	0.209	0.19	.279
PF, BP	.47***	.48***	0.504	0.519	-0.015	0.19	.936
PF, GH	.51***	.57***	0.559	0.652	-0.093	0.19	.628
PF, VT	.47***	.41**	0.513	0.44	0.072	0.19	.707
PF, SF	.43**	.27	0.464	0.276	0.188	0.19	.329
PF, RE	.18	.32*	0.182	0.328	-0.146	0.19	.447
PF, MH	.17	.29*	0.17	0.293	-0.124	0.19	.521
RP, BP	.49***	.24	0.541	0.239	0.302	0.19	.117
RP, GH	.46**	.32*	0.492	0.326	0.166	0.19	.388
RP, VT	.62***	.47***	0.723	0.506	0.217	0.19	.259
RP, SF	.57***	.54***	0.652	0.6	0.052	0.19	.787
RP, RE	.46**	.47***	0.497	0.504	-0.006	0.19	.974
RP, MH	.47***	.41**	0.51	0.432	0.078	0.19	.685
BP, GH	.42**	.50***	0.451	0.551	-0.099	0.19	.606
BP, VT	.68***	.24	0.827	0.244	0.584	0.19	.002
BP, SF	.63***	.20	0.746	0.204	0.543	0.19	.005
BP, RE	.47***	.24	0.513	0.247	0.266	0.19	.167
BP, MH	.43**	.33*	0.46	0.342	0.118	0.19	.539
GH, VT	.63***	.45**	0.735	0.487	0.248	0.19	.198
GH, SF	.51***	.31*	0.559	0.319	0.239	0.19	.214
GH, RE	.35*	.21	0.365	0.216	0.149	0.19	.438
GH, MH	.41**	.31*	0.434	0.322	0.113	0.19	.558
VT, SF	.71***	.47***	0.889	0.506	0.383	0.19	.047
VT, RE	.50***	.44**	0.551	0.467	0.083	0.19	.665
VT, MH	.57***	.59***	0.648	0.676	-0.029	0.19	.882
SF, RE	.56***	.40**	0.631	0.428	0.203	0.19	.292
SF, MH	.71***	.52***	0.881	0.576	0.305	0.19	.113
RE, MH	.77***	.35*	1.020	0.362	0.658	0.19	.001

Note: PF: SF-36 Physical functioning; RP: SF-36 Role-physical; BP: SF-36 Bodily pain; GH: SF-36 General health; VT: SF-36 Vitality; SF: SF-36 Social functioning; RE: SF-36 Role-emotional; MH: SF-36 Mental health; BDI-FS: Beck Depression Inventory-FastScreen. Statistically significant at *p < .05; **p < .01; ***p < .001. [a] Prime correlation for r_1. [b] Prime correlation for r_2. [c] r_1-r_2 difference. [d] Standard error of r_1-r_2 difference

Table 3
Hierarchical multiple regression analyses for each country

		Unstandardized coefficients		Standardized coefficients			
SF-36 Bodily pain		**B**	**SE** [a]	**Beta**	***t***	***p***	***f*** [2 b]
Spain	(Constant)	12.04	8.57		1.40	.167	
	Vitality	0.44	0.15	.45	2.99	.004	0.18 M
	Social functioning	0.25	0.12	.32	2.12	.039	0.09 S
	Education (years)	0.19	0.42	.05	0.47	.644	0.00 –
	Partner vs. single	-0.11	3.31	-.00	-0.03	.975	
	Loss of partner vs. single	-2.19	5.07	-.06	-0.43	.668	
	Disability vs. active	0.97	2.47	.04	0.39	.695	
	Unemployment vs. active	-3.11	4.43	-.08	-0.70	.487	
USA	(Constant)	9.60	11.19		0.86	.395	
	Vitality	0.21	0.14	.21	1.47	.148	0.04 S
	Social functioning	0.10	0.14	.11	0.73	.467	0.01 –
	Education (years)	1.80	0.61	.39	2.96	.005	0.18 M
	Partner vs. single	-2.95	3.26	-.13	-0.90	.371	
	Loss of partner vs. single	0.43	5.56	.01	0.08	.939	
	Disability vs. active	4.50	3.20	.20	1.41	.166	
	Unemployment vs. active	3.19	3.30	.13	0.97	.339	
SF-36 Vitality							
Spain	(Constant)	9.99	5.16		1.94		.059
	Bodily pain	0.36	0.12	.36	3.17	.003	0.20 M
	Social functioning	0.37	0.10	.47	3.93	< .001	0.32 M-L
	EDSS	-1.03	0.71	-.14	-1.45	.152	
	Partner vs. single	1.88	2.91	.07	0.65	.520	
	Loss of partner vs. single	2.60	4.46	.07	0.58	.563	
	Disability vs. active	2.45	2.26	.11	1.08	.284	
	Unemployment vs. active	5.20	3.72	.13	1.40	.169	
USA	(Constant)	17.99	9.08		1.98	.053	
	Bodily pain	0.21	0.13	.21	1.65	.105	0.06 S
	Social functioning	0.39	0.13	.40	3.04	.004	0.19 M
	EDSS	-0.28	0.87	-.05	-0.33	.746	
	Partner vs. single	1.96	3.19	.09	0.61	.543	
	Loss of partner vs. single	-0.99	5.57	-.03	-0.18	.860	
	Disability vs. active	-0.28	3.33	-.01	-0.08	.934	
	Unemployment vs. active	-3.88	3.24	-.15	-1.20	.236	
SF-36 Social functioning							
Spain	(Constant)	1.13		7.03	0.16	.873	
	Bodily pain	0.33	0.16	.26	2.06	.045	0.09 S
	Vitality	0.64	0.16	.51	3.93	< .001	0.32 M-L
	EDSS	0.01	0.95	.00	0.01	.989	
	Partner vs. single	-0.69	3.83	-.02	-0.18	.857	
	Loss of partner vs. single	-6.74	5.80	-.13	-1.16	.251	
	Disability vs. active	-4.58	2.94	-.16	-1.56	.125	
	Unemployment vs. active	0.20	4.99	.00	0.04	.968	
USA	(Constant)	26.36	8.83		2.99	.004	
	Bodily pain	0.11	0.13	.11	0.83	.409	0.01 –
	Vitality	0.41	0.13	.40	3.04	.004	0.19 M
	EDSS	-1.29	0.87	-.20	-1.49	.143	
	Partner vs. single	1.92	3.25	.08	0.59	.557	
	Loss of partner vs. single	0.53	5.67	.01	0.09	.926	
	Disability vs. active	-1.21	3.39	-.05	-0.36	.724	
	Unemployment vs. active	-0.80	3.34	-.03	-0.24	.812	

Table 3 (continuated)
Hierarchical multiple regression analyses for each country

		Unstandardized coefficients		Standardized coefficients			
SF-36 Mental health		**B**	**SE** [a]	**Beta**	*t*	*p*	f^{2} [b]
Spain	(Constant)	4.90	8.06		0.61	.546	
	Role-emotional	1.01	0.13	.75	7.82	< .001	1.23 L
	Education (years)	-0.25	0.35	-.06	-0.71	.479	
	Partner vs. single	0.34	2.75	.01	0.13	.901	
	Loss of partner vs. single	-5.08	4.22	-.13	-1.20	.234	
	Disability vs. active	-1.98	2.08	-.09	-0.95	.347	0.02 S
	Unemployment vs. active	-4.48	3.64	-.11	-1.23	.225	
USA	(Constant)	19.72	10.63		1.86	.069	
	Role-emotional	0.33	0.12	.36	2.66	.010	0.14 S-M
	Education (years)	0.94	0.63	.20	1.50	.141	
	Partner vs. single	-1.20	3.43	-.05	-0.35	.728	
	Loss of partner vs. single	-5.19	5.71	-.14	-0.91	.367	
	Disability vs. active	6.42	3.30	.28	1.95	.057	0.08 S
	Unemployment vs. active	1.92	3.36	.07	0.57	.571	
BDI FastScreen							
Spain	(Constant)	2.16	2.13		1.02	.313	
	Physical functioning	0.02	0.04	.08	0.57	.571	0.01 –
	Partner vs. single	-0.49	1.35	-.06	-0.36	.717	
	Loss of partner vs. single	2.27		2.00	.18	1.13	.263
	Disability vs. active	2.54	1.04	.35	2.45	.018	0.12 S-M
	Unemployment vs. active	-0.07	1.74	-.01	-0.04	.970	
USA	(Constant)	7.53	1.33		5.66	< .001	
	Physical functioning	-0.10	0.03	-.53	-3.86	< .001	0.29 M
	Partner vs. single	-0.94	0.70	-.19	-1.34	.185	
	Loss of partner vs. single	0.39	1.20	.05	0.32	.749	
	Disability vs. active	-1.58	0.76	-.31	-2.08	.043	0.09 S
	Unemployment vs. active	0.22	0.71	.04	0.32	.753	

[a] SE: standard error; [b] Effect sizes: –. null; S. small; M. medium; L. large

status predicted it more in the USA than in Spain (p = .030), although the regression coefficient of this predictor in the USA was only marginally significant (p = .057). Finally, years of education predicted *Bodily pain* in the USA but not in Spain (p = .030). However, this one was a covariate ruled out in the ANCOVA models and partial-correlations analyses, so it is not relevant to explain the aforementioned between-country differences.

No other statistically significant differences between predictors included for each country were found.

Discussion

The current study is the first to report differences in depressive symptomatology and quality of life between MS patients from Spain and the USA while utilizing careful methodology to match the samples and control for key demographic and disease variables. Spanish participants showed higher levels of depressive symptomatology and worse QoL on five of the eight dimensions of the SF-36 than the Americans. Further, stronger interrelationship between these QoL constructs was found among the Spanish MS patients in comparison to the American participants, such that more *Bodily pain* was more related to worse *Social functioning* and *Vitality*, and worse *Vitality* was more related to worse *Social functioning* in Spain.

Those from the USA revealed a stronger relationship between higher levels of depressive symptomatology and worse physical functioning, which also emerged as a unique and relevant (medium effect size) predictor of depressive symptomatology. Among the Spanish participants, depressive symptomatology was uniquely predicted by disability. General mental health was also found to be differentially predicted between countries, with more role limitations due to emotional problems emerging as the unique and powerful predictor of worse general mental health in Spain. Therefore, these preliminary results show that the emotional suffering is more related with physical impairment among Americans, while this emotional suffering is more associated with its own consequential functional limitations in Spanish patients.

Given the lack of published clinical literature which directly contrasts QoL and depressive symptomatology of MS patients from Spain and the USA, it may be helpful to interpret the current results in the cultural and economic contexts. Both the USA and Spain belong to the broad category of developed, high income countries, with largely comparable Western standards of living, quality of life, and personality characteristics (Kochhar, 2017;

Table 4
Results of t-tests between countries on significant predictor variables (unstandardized coefficients) for each multiple regression model

Criterion/predictors	B_1 Spain	B_2 USA	B diff	SE diff	*t*	df	*p*
Bodily Pain							
VT	0.44	0.21	0.23	0.21	1.13	98	.263
SF	0.25	0.10	0.15	0.18	0.83	98	.410
Education	0.19	1.80	-1.61	0.73	-2.21	98	.030
Vitality							
BP	0.36	0.21	0.16	0.17	0.91	98	.366
SF	0.37	0.39	-0.02	0.16	-0.11	98	.910
Social functioning							
BP	0.33	0.11	0.22	0.21	1.07	98	.288
VT	0.64	0.41	0.24	0.21	1.13	98	.260
Mental health							
RE	1.01	0.33	0.68	0.19	3.64	100	< .001
Disability	-1.98	6.42	-8.40	3.81	-2.20	100	.030
BDI-FS							
PF	0.02	-0.10	0.13	0.05	2.61	89	.011
Disability	2.54	-1.58	4.12	1.29	3.20	93	.002

Note: PF: SF-36 Physical functioning; BP: SF-36 Bodily pain; VT: SF-36 Vitality; SF: SF-36 Social functioning; RE: SF-36 Role-emotional

McCrae & Terracciano, 2005; Vilagut et al., 2008). In the general population, various metrics of depression (e.g., prevalence, age of onset, etc.) reported for both countries indicate that individuals from the USA may experience this mental health issue up to twice as much as those in Spain (Kessler & Bromet, 2013). Therefore, the finding of higher rates of depression and worse QoL in the Spanish sample is novel and not entirely consistent with those previously published, such as reports of a higher QoL in Spanish MS patients compared to those from England, a developed, Western, Anglophile nation (Cella et al., 1996; Chang et al., 2002). However, these differences are likely due to different methodology and sample characteristics, as the English sample was older and had higher median EDSS scores, and both factors are related to worse QoL levels (Fernández-Jiménez & Arnett, 2015). In this sense, the worse QoL and depressive symptomatology observed among Spaniards compared with the Americans may also be attributed to higher unemployment due to disability status among the Spanish patients of this study (Contentti et al., 2018; Maurino et al., 2020). On the other hand, the results which show a connection between depression and physical functioning (in the USA sample), and pain, social functioning and vitality (in the Spanish MS patients) are comparable to the published reports of the relationship between these constructs in each country (Fernández-Muñoz et al., 2018; McPheters & Sandberg, 2010; Motl et al., 2009).

There are several limitations to this study, which should be considered when interpreting the results and which may be addressed in future studies. The cross-sectional design of the study makes it impossible to draw firm conclusions about causal relationships between variables. Therefore, prospective studies are needed to address causality. Other potentially important and confounding variables (e.g., coping styles, cognitive impairment, perceived social support) were not included in the current study (Gil Moreno et al., 2013; Henry et al., 2019; Keramat-Kar et al., 2019). A generic, instead of a MS-specific, self-reported health status instrument was used to measure QoL, since it is the most widely validated and used questionnaire across countries and clinical populations, as well as, it allows to compare results against the general population. Although the *SF-36 Health Survey* has been criticized due to ceiling and floor effects, MS-specific instruments also show some of these shortcomings (Bandari et al., 2010) and the norm based scores, as were used in the current study, are more robust against these psychometric limitations. Additionally, while the between-sample imbalance regarding MS course was globally corrected after having controlled for covariates, the SF-36 *General health* subscale score was statistically different between MS subtypes and countries. However, previous studies did not find relationship between global QoL or specific domains and MS subtypes when several predictors were included in the same model (Fernández et al., 2011). Future studies with larger samples should replicate this work and examine the differences in QoL between countries as a function of the MS subtypes.

The current study highlights important differences in variables which contribute to physical and mental health of MS patients in Spain and the USA. By uncovering such cross-country factors, researchers and clinicians can better understand the influence of potentially hidden symptoms (e.g., depression, fatigue) and underlying processes which effect and maintain them, which has received relatively little attention in the literature and continues to be unmet needs in MS (Rooney et al., 2019). Finally, it is likely that wider culture-driven variables need to be accounted for and included in designing comprehensive treatment approaches in MS.

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References

Alonso, J., Regidor, E., Barrio, G., Prieto, L., Rodríguez, C., & de la Fuente, L. (1998). Valores poblacionales de referencia de la versión española del Cuestionario de Salud SF-36 [Population reference values of the Spanish version of the Health Questionnaire SF-36]. *Medicina Clínica*, *111*(11), 410-416.

Arroyo, R., Bury, D. P., Guo, J. D., Margolin, D. H., Melanson, M., Daizadeh, N., & Cella, D. (2020). Impact of alemtuzumab on health-related quality of life over 6 years in CARE-MS II trial extension patients with relapsing-remitting multiple sclerosis. *Multiple Sclerosis Journal*, *26*(8), 955-963. https://doi.org/10.1177/1352458519849796

Bandari, D. S., Vollmer, T. L., Khatri, B. O., & Tyry, T. (2010). Assessing quality of life in patients with multiple sclerosis. *International Journal of MS Care*, *12*(1), 34-41. https://doi.org/10.7224/1537-2073-12.1.34

Benedict, R. H. B., Fishman, I., McClellan, M. M., Bakshi, R., & Weinstock-Guttman, B. (2003). Validity of the Beck Depression Inventory-Fast Screen in multiple sclerosis. *Multiple Sclerosis*, *9*(4), 393-396. https://doi.org/10.1191/1352458503ms902oa

Cella, D. F., Dineen, K., Arnason, B., Reder, A., Webster, K. A., Karabatsos, G., Chang, C., Lloyd, S., Steward, J., & Stefoski, D. (1996). Validation of the functional assessment of multiple sclerosis quality of life instrument. *Neurology*, *47*(1), 129-139. https://doi.org/10.1212/wnl.47.1.129

Chang, C. H., Cella, D., Fernández, O., Luque, G., de Castro, P., de Andrés, C., Casanova, B., Hernández, M. A., Prieto, J. M., Fernández, V. E., de Ramón, E., & Grupo Español de Calidad de Vida en Esclerosis Múltiple (2002). Quality of life in multiple sclerosis patients in Spain. *Multiple Sclerosis*, *8*(6), 527-531. https://doi.org/10.1191/1352458502ms851oa

Cohen, J. (1992). A power primer. *Psychological Bulletin*, *112*(1), 155-159.

Contentti, E. C., López, P., Balbuena, M. E., & Tkachuk, V. (2018). Impact of multiple sclerosis on employment and its association with anxiety, depression, fatigue and sleep disorders. *Neurology*, *90*(15, Suppl.), P2.424.

Fernández, O., Baumstarck-Barrau, K., Simeoni, M. C., Auquier, P., & MusiQoL study group (2011). Patient characteristics and determinants of quality of life in an international population with multiple sclerosis: Assessment using the MusiQoL and SF-36 questionnaires. *Multiple Sclerosis*, *17*(10), 1238-1249. https://doi.org/10.1177/1352458511407951

Fernández-Jiménez, E., & Arnett, P. A. (2015). Impact of neurological impairment, depression, cognitive function and coping on quality of life of people with multiple sclerosis: A relative importance analysis. *Multiple Sclerosis*, *21*(11), 1468-1472. https://doi.org/10.1177/1352458514562439

Fernández-Muñoz, J. J., Cigarán-Méndez, M., Navarro-Pardo, E., Pérez-de-Heredia-Torres, M., Parás-Bravo, P., & Fernández-de-Las-Peñas, C. (2018). Is the association between health-related quality of life and fatigue mediated by depression in patients with multiple sclerosis? A Spanish cross-sectional study. *BMJ Open*, *8*(1), Article e016297. https://doi.org/10.1136/bmjopen-2017-016297

Gil-Moreno, M. J., Cerezo-García, M., Marasescu, R., Pinel-González, A., López-Álvarez, L., & Aladro-Benito, Y. (2013). Neuropsychological syndromes in multiple sclerosis. *Psicothema*, *25*(4), 452-460. https://doi.org/10.7334/psicothema2012.308

Hanna, M., & Strober, L. B. (2020). Anxiety and depression in Multiple Sclerosis (MS): Antecedents, consequences, and differential impact on well-being and quality of life. *Multiple Sclerosis and Related Disorders*. Advance online publication. https://doi.org/10.1016/j.msard.2020.102261

Henry, A., Tourbah, A., Camus, G., Deschamps, R., Mailhan, L., Castex, C., Gout, O., & Montreuil, M. (2019). Anxiety and depression in patients with multiple sclerosis: The mediating effects of perceived social support. *Multiple Sclerosis and Related Disorders*, *27*, 46-51. https://doi.org/10.1016/j.msard.2018.09.039

Keramat-Kar, M., Whitehead, L., & Smith, C. M. (2019). Characteristics and correlates of coping with multiple sclerosis: A systematic review. *Disability and Rehabilitation*, *41*(3), 250-264. https://doi.org/10.1080/09638288.2017.1387295

Kessler, R. C., & Bromet, E. J. (2013). The epidemiology of depression across cultures. *Annual Review of Public Health*, *34*, 119-138. https://doi.org/10.1146/annurev-publhealth-031912-114409

Kochhar, R. (2017). Middle Class Fortunes in Western Europe. Pew Research Center. https://www.pewresearch.org/global/wp-content/uploads/sites/2/2017/04/ST_2017.04.24_Western-Europe-Middle-Class_FINAL.pdf

Maurino, J., Martínez-Ginés, M. L., García-Domínguez, J. M., Solar, M. D., Carcelén-Gadea, M., Ares-Luque, A., Ballabriga, J., Navarro-Cantó, L., Medrano, N., & Honan, C. A. (2020). Workplace difficulties, health-related quality of life, and perception of stigma from the perspective of patients with Multiple Sclerosis. *Multiple Sclerosis and Related Disorders*. Advance online publication. https://doi.org/10.1016/j.msard.2020.102046

McCrae, R. R., & Terracciano, A. (2005). Personality profiles of cultures: Aggregate personality traits. *Journal of Personality and Social Psychology*, *89*(3), 407-425. https://doi.org/10.1037/0022-3514.89.3.407

McPheters, J. K., & Sandberg, J. G. (2010). The relationship among couple relationship quality, physical functioning, and depression in multiple sclerosis patients and partners. *Families, Systems & Health: The Journal of Collaborative Family Healthcare*, *28*(1), 48-68. https://doi.org/10.1037/a0018818

Miller, D., Rudick, R. A., & Hutchinson, M. (2010). Patient-centered outcomes: Translating clinical efficacy into benefits on health-related quality of life. *Neurology*, *74*(17.3, Suppl.), S24-S35. https://doi.org/10.1212/WNL.0b013e3181dbb884

Motl, R. W., McAuley, E., Snook, E. M., & Gliottoni, R. C. (2009). Physical activity and quality of life in multiple sclerosis: Intermediary roles of disability, fatigue, mood, pain, self-efficacy and social support. *Psychology, Health & Medicine*, *14*(1), 111-124. https://doi.org/10.1080/13548500802241902

Murphy, N., Confavreux, C., Haas, J., König, N., Roullet, E., Sailer, M., Swash, M., Young, C., & Mérot, J. L. (1998). Quality of life in multiple sclerosis in France, Germany, and the United Kingdom. Cost of Multiple Sclerosis Study Group. *Journal of Neurology, Neurosurgery, and Psychiatry*, *65*(4), 460-466. https://doi.org/10.1136/jnnp.65.4.460

Pakpour, A. H., Yekaninejad, M. S., Mohammadi, N. K., Molsted, S., Zarei, F., Patti, F., & Harrison, A. (2009). Health-related quality of life in Iranian patients with multiple sclerosis: A cross-cultural study. *Neurologia I Neurochirurgia Polska*, *43*(6), 517-526.

Pellegrini, F., Copetti, M., Bovis, F., Cheng, D., Hyde, R., de Moor, C., Kieseier, B. C., & Sormani, M. P. (2020). A proof-of-concept application of a novel scoring approach for personalized medicine in multiple sclerosis. *Multiple Sclerosis*, *26*(9), 1064-1073. https://doi.org/10.1177/1352458519849513

Pfennings, L., Cohen, L., Miller, D., Gerbaud, L., Vleugels, L., Freeman, J., Vernay, D., Biolay, S., Ketelaer, P., Thompson, A., Polman, C., & van der Ploeg, H. (1999). Using the Short Form-36 with multiple sclerosis patients in five countries: A cross-cultural comparison. *Psychological Reports*, *85*(1), 19-31. https://doi.org/10.2466/pr0.1999.85.1.19

Pluta-Fuerst, A., Petrovic, K., Berger, T., Fryze, W., Fuchs, S., Gold, R., Kozubski, W., Ladurner, G., Petereit, H., Potemkowski, A., Rieckmann, P., Sailer, M., Szczudlik, A., Vass, K., Weber, T., Zakrzewska-Pniewska, B., & Fazekas, F. (2011). Patient-reported quality of life in multiple sclerosis differs between cultures and countries: A cross-sectional Austrian-German-Polish study. *Multiple Sclerosis*, *17*(4), 478-486. https://doi.org/10.1177/1352458510391341

Pugliatti, M., Eskic, D., Mikolcić, T., Pitschnau-Michel, D., Myhr, K. M., Sastre-Garriga, J., Otero, S., Wieczynska, L., Torje, C., Holloway, E., Rienhoff, O., Friede, T., Buckow, K., Ellenberger, D., Hillert, J., Glaser, A., Flachenecker, P., Fuge, J., Schyns-Liharska, T., … EUReMS Consortium (2012). Assess, compare and enhance the status of Persons with Multiple Sclerosis (MS) in Europe: A European Register for MS. *Acta Neurologica Scandinavica*, *126* (Suppl. 195), 24-30. https://doi.org/10.1111/ane.12024

Rooney, S., Wood, L., Moffat, F., & Paul, L. (2019). Prevalence of fatigue and its association with clinical features in progressive and non-progressive forms of Multiple Sclerosis. *Multiple Sclerosis and Related Disorders*, *28*, 276-282. https://doi.org/10.1016/j.msard.2019.01.011

Salter, A., Kowalec, K., Fitzgerald, K. C., Cutter, G., & Marrie, R. A. (2020). Comorbidity is associated with disease activity in MS: Findings from the CombiRx trial. *Neurology*, *95*(5), e446-e456. https://doi.org/10.1212/WNL.0000000000010024

Vilagut, G., Valderas, J. M., Ferrer, M., Garin, O., López-García, E., & Alonso, J. (2008). Interpretación de los cuestionarios de salud SF-36 y SF-12 en España: componentes físico y mental [Interpretation of SF-36 and SF-12 questionnaires in Spain: Physical and mental components]. *Medicina Clínica*, *130*(19), 726-735. https://doi.org/10.1157/13121076

Ware, J. E., Gandek, B., Kosinski, M., Aaronson, N. K., Apolone, G., Brazier, J., Bullinger, M., Kaasa, S., Leplège, A., Prieto, L., Sullivan, M., & Thunedborg, K. (1998). The equivalence of SF-36 summary health scores estimated using standard and country-specific algorithms in 10 countries: Results from the IQOLA Project. International Quality of Life Assessment. *Journal of Clinical Epidemiology*, *51*(11), 1167-1170. https://doi.org/10.1016/s0895-4356(98)00108-5

Ware, J. E., & Sherbourne, C. D. (1992). The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Medical Care*, *30*(6), 473-483.

Weaver, B., & Wuensch, K. L. (2013). SPSS and SAS programs for comparing Pearson correlations and OLS regression coefficients. *Behavior Research Methods*, *45*(3), 880-895. https://doi.org/10.3758/s13428-012-0289-7

Williams, L. S. (2012). Patient-reported outcomes: Progress toward speaking the patient's language. *Neurology*, *78*(23), 1813-1814. https://doi.org/10.1212/WNL.0b013e318258f878