Published in final edited form as:

Mult Scler. 2017 November ; 23(13): 1772–1781. doi:10.1177/1352458516685169.

Smokers with MS have greater decrements in quality of life and disability than non-smokers

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Abstract

Background—Tobacco smoke plays a pathogenic role in MS, and may accelerate disease progression, yet some people with MS continue to smoke after disease onset. The average smoker reports diminished health-related quality of life (HRQOL) across many populations.

Objectives—To describe the relationships between smoking status and HRQOL, disease activity, and global disability in a US population with MS.

Methods—We compared smokers to non-smokers in 950 responders to the Spring 2014 update-survey completed by North American Research Committee on MS (NARCOMS) registry participants. HRQOL was assessed using SF-12v2, disease activity was investigated using eight Performance Scales (PS) and three Functionality Scales (FS). Global disability was evaluated using Patient Determined Disease Steps (PDSS) and an Item Response Theory summed score (IRT) based on the PS and FS.

Results—Smokers had lower HRQOL ($p < 0.0001$), reported more disease activity ($p < 0.05$), and greater deficits in all PS and FS ($p: 6 \times 10^{-7}$ to 0.05), except mobility. Smokers and non-smokers did not differ by PDSS, but had substantially greater IRT global disability ($p = 2 \times 10^{-7}$).

Conclusion—Active smoking is meaningfully associated with deficits across multiple domains in people with MS, and adds to the growing literature of the need for MS-tailored smoking cessation programs.

Keywords

multiple sclerosis; smoking; item response theory; disability; quality of life

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Introduction

MS is the leading cause of neurological disability in young adults¹, and affected individuals experience unpredictable symptomatology and disease course, despite therapeutic advances². Consequently, MS negatively impacts well-being, and health related quality of life (HRQOL) is substantially diminished, with possible differences by gender^{3, 4}.

A history of smoking is consistently associated with diminished HRQOL, across many diverse populations⁵. Tobacco smoke plays a pathogenic role in MS⁶, and may accelerate disease progression⁷. Despite the chronicity of MS, affected individuals continue to engage in adverse health behaviors (i.e. smoking) after onset⁸; and for many, these behaviors reflect their MS coping mechanisms⁹.

The relationship between smoking and HRQOL in MS has been assessed in : 57 Italian patients¹⁰; 2,457 international respondents to a web-based survey¹¹; and 251 US postmenopausal women¹². Smoking was associated with lower HRQOL in the Italian study and the international survey, but not among US postmenopausal women. Generalizability of findings to the general US MS population is limited. Therefore, to develop tailored cessation interventions in the US, it is important to characterize active smokers and non-smokers specifically among US individuals with MS.

The present study describes the relationships between smoking status and HRQOL, disease activity, and disability in a diverse sample of US adults with MS. HRQOL was evaluated using the 'Medical Outcomes Study 12-Item Short Form Survey Instrument (SF-12v2)'¹³. Disease activity was measured using Performance Scales © (PS) across eight functional domains and Functionality Scales (FS) that cover three additional domains^{14, 15}. MS global disability was assessed using a valid multifaceted construct based on the PS and FS¹⁵, and using Patient Determined Disease Steps (PDDS), a single item measure of perceived disability with high correlation with Expanded Disability Status Scale (EDSS; $\rho=0.78$)¹⁶. We also conducted gender-stratified and subtype-specific analyses, which have not been previously reported.

Materials and Methods

These analyses were approved by the Institutional Review Board of Case Western Reserve University. North American Research Committee on Multiple Sclerosis (NARCOMS) registry data collection is approved by the Institutional Review Board of University of Alabama at Birmingham.

Study Population

This is a cross-sectional investigation of a random subset of 1,000 NARCOMS registry participants, who self-report having MS and completed the Spring 2014 semiannual update-survey. The NARCOMS registry is voluntary with 38,000 participants, which based on size alone, represents approximately 10% of the US MS population¹. The Spring 2014 survey included questions on demographics, clinical characteristics, HRQOL, and disability measures. Multiple key aspects of this survey, including diagnosis, have been validated with

minimal response shift^{17–21}. The current study was restricted to participants who reported having a MS diagnosis by a physician and who reported their smoking status (N=950). Participants were considered active smokers if they reported smoking “some days” or “every day”. Active smokers also reported the number of cigarettes and/or cigars smoked per day. Self-reported height and current weight were used to calculate body mass index (BMI; kg/m²). Information on age of symptom onset, duration since diagnosis, age at survey completion were available, immunologic therapy in the previous six months, alcohol consumption in the previous six months, and source of MS care. Participants listed their MS subtype as reported to them by a physician (see Table 1).

Health related quality of life

Participants completed the SF-12v2, which assesses HRQOL, a generic measure of functional health that encompasses 8 psychometric subscales¹³. The SF-12v2 is an abbreviated version of the RAND 36-item health survey (SF-36; which has been validated in MS individuals²²), and captures information on physical functioning (PF), role limitations due to physical health (role-physical; RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role limitations due to emotional health (role-emotion, RE), and mental health (MH), which are linearly transformed into norm based scores¹³. The subscales subsequently comprise a ‘physical component summary’ (PCS; composite of PF, RP, BP and GH) and a ‘mental component summary’ (MCS; composite of VT, SF, RE and MH). The subscales, PCS and MCS scores have a mean of 50 and standard deviation of 10 in the US population, with higher scores reflecting better HRQOL. Individual PCS and MCS scores can be classified according the US age and gender population norms: far below average (<40), below average (<45), or at/above average (≥45). Dichotomous variables for PCS and MCS were created (1=below/far below average, 0=at/above average).

Disease activity and symptom change

Patient-reported outcome measures captured disease activity and disability progression. Disease activity was measured by participants’ response to the occurrence of a relapse in the previous 6 months (1=yes, 0=no/unsure). Disease progression was measured by responses to several questions: 1) progressive worsening of symptoms in the previous 6 months (1=yes, 0=no/unsure); 2) comparison of current symptom severity with symptom severity 6 months ago (categorical variable: 1=much better, 7=much worse); and 3) the eight PS for the following functional domains: mobility, dexterity, vision, fatigue, cognition, bladder/bowel, sensory, spasticity, and 4) three FS for depression, tremor/coordination, and pain. Each scale assesses perceived disability within a functional domain for adults with MS, comparing their current condition to their condition before onset¹⁴. All scales have shown construct validity^{15, 18}.

The PS and FS are recorded on a 6-point ordinal scale (0=normal, 1=minimal disability, 2=mild disability, 3=moderate disability, 4=severe disability, and 5=total disability), except for mobility recorded on a 7-point scale. For this investigation, the PS and FS scoring for specific domains were modified, as done for a previous study of 7,851 NARCOMS participants¹⁵. A pair of adjacent response options for each scale, except fatigue and sensory, were collapsed. For mobility PS, “frequent use of cane” and “severe gait disability” were

collapsed. For vision PS and depression FS, “severe” and “total” were collapsed. The scales for cognition, bladder/bowel, spasticity, tremor/coordination, and pain had “mild” and “moderate” combined. These adjustments were employed as this investigation utilizes an Item Response Theory (IRT) summed score of global MS disability, as done in a previous NARCOMS sample. Chamot *et al.* observed NARCOMS respondents with similar perceived disability selected one of these adjacent response categories with near equal probability¹⁵. Therefore, all subsequent analyses were conducted with these considerations for this current NARCOMS sample.

Global disability

First, we employed a single global disability score based on IRT calibration of the eight PS and three FS, which has robust construct validity with high reliability (89%)¹⁵. The IRT summed score of global disability (henceforth referred to as IRT disability) was developed using a suite of psychometric techniques recommended by the Patient-Reported Outcomes Measurement Information System network in 7,851 NARCOMS subjects^{15, 23}. The IRT framework builds on prior research using categorical factor analysis and bifactor analysis to investigate MS disability²⁴. The IRT disability can be assigned using a conversion table of the Performance Scale Sum (PSS-11), which is a single summed score of the 11 PS and FS¹⁵. To determine whether the 11 scales in our sample had a similar factor structure to the previous study, we performed the same confirmatory factor analyses. Very similar parameter estimates, model fit statistics and indices for both the unidimensional model of global disability and the bifactor model (with a global disability factor and specific factors for physical and mental disability) were obtained in this sample of 950 subjects as compared to the prior study of 7,851 subjects (data not shown)¹⁵. Therefore, we proceeded with applying the IRT weights derived by Chamot *et al.* to our PSS-11 to generate the IRT disability values. Second, global disability was captured by the PDDS (0 to 8 scale) – a single item measure of perceived disability.

Data analysis

There were 98% completed responses for all variables in the study sample (N=950). The relationship between smoking status and each outcome were assessed in unadjusted and adjusted models. Adjusted models included gender, age of symptom onset, age at survey completion, duration from diagnosis, BMI, and MS subtype, as these variables are potential confounders. For analyses, MS subtype was re-categorized as follows: relapsing remitting (RR; 54%), secondary progression (SP; 21%), primary progressive/progressive relapsing (PP/PR; 11%), and clinically isolated syndrome/not known/other (14%). Gender-stratified and MS subtype multigroup (RR only, SP/PP/PR (all progressives) only, SP only, and PP/PR only) models were conducted. There were binary (i.e. relapse in the previous 6 months), continuous (i.e. the MCS), and ordinal (i.e. the PS) outcomes and appropriate regression models were used: logistic, linear, and generalized logistic models, respectively, as implemented in STATA v13.1 (StataCorp, TX). Generalized logistic regression (partial proportional odds models) for ordinal dependent variable differs from traditional ordered logistic models, as the latter requires all independent variables to satisfy the proportional odds (parallel lines) assumption, which can be frequently violated. The partial proportional odds model (using STATA function *gologit2*, with *autofit* option) relaxes the parallel lines

constraints for violating variables. Constrained variables (those meeting the assumption) can be interpreted as they are in ordered logistic models. For all unstratified models, smoking status met the proportional odds assumption, with the exception of the vision PS adjusted model; nonetheless, the parallel lines assumption was relaxed to facilitate simplified interpretation. The primary reason for employing the partial proportional odds model was to allow non-proportional lines for violating adjusting variables, allowing for more parsimonious models.

Results

Eleven percent (N=105) of the MS study population were active smokers, and they did not differ from non-smokers by gender ratio, age of symptom onset, duration from diagnosis, immunologic therapy, alcohol consumption, source of MS care, race/ethnicity, or MS subtype (Table 1). However, active smokers were younger at survey completion and had a lower BMI compared to non-smokers (56yrs vs 59yrs, $p=9.0 \times 10^{-3}$; and 25 kg/m^2 vs 27 kg/m^2 , $p=3 \times 10^{-3}$).

HRQOL

As expected, people with MS scored lower on all HRQOL subscales than the average US population (mean=50, S.D.=10) (Table 1). Active smokers scored significantly lower on all subscales, except for PF, and lower on both the MCS ($p=3.9 \times 10^{-5}$) and PCS ($p=1 \times 10^{-4}$) components of the SF-12v2 compared to MS non-smokers (Table 2). In the analyses of the dichotomous variables, MS active smokers had twice the odds of a MCS *below* or *far below* compared to *at* or *above* the US population average than for non-smoker MS individuals ($\text{OR}_{\text{MCS}}=2.0$ (95%CI: 1.3, 3.1), $p=1 \times 10^{-3}$). A similar relationship was observed for the PCS binary variable ($\text{OR}_{\text{PCS}}=2.4$ (95%CI: 1.4, 4.0), $p=2 \times 10^{-3}$). Among smokers, there were no associations between number of cigarettes smoked and HRQOL (data not shown). Collectively, the associations illustrate significant HRQOL decreases in people with MS who are active smokers compared to non-smokers. However, when analyses were stratified by gender, the diminished relationships between HRQOL and smoking were primarily driven by the effect in female MS individuals (Table 2).

Disease activity

MS individuals who were active smokers were 70% ($p=0.02$) more likely to report a relapse in the previous 6 months than non-smokers (Table 2). These active smokers were also 60% ($p=0.03$) more likely to report their overall symptomatology was currently worse than 6 months ago compared to non-smokers. Interestingly, current smokers did not experience an excessive progressive worsening of symptoms (not related to a relapse) in the previous 6 months than non-smoker MS individuals ($p=0.74$). Gender-stratified analyses demonstrated that the significant relationships between disease activity and smoking was restricted to female MS individuals (Table 2). Among smokers, there were no differences by number of cigarettes smoked (data not shown).

Symptom change

Across all PS and FS, with the exception of the mobility PS, active smokers reported greater disability compared to non-smoker MS individuals, when comparing their current disability to their ability prior MS onset (Table 2). Active smokers were approximately 50% more like to report greater disability in bladder/bowel domain, sensory symptoms, and spasticity compared to non-smokers ($p < 0.05$). For dexterity, vision, fatigue, cognitive symptoms, depression, tremor and coordination, and pain, smokers were at least twice as likely to report greater disability across these functional domains compared to non-smokers ($p < 5 \times 10^{-4}$), with the largest magnitude of effect observed for fatigue (OR=2.6 (95%CI=1.8, 3.7), $p = 6 \times 10^{-7}$). These relationships were fairly consistent across genders, with one exception being male smokers reporting greater bladder/bowel disability than male non-smokers (OR=2.2 (95%CI: 1.0, 4.7), $p = 0.04$), while there was no difference in females (Table 2). Furthermore, there were no appreciable differences by number of cigarettes smoked amongst smokers (data not shown).

Global disability

Using the IRT disability measure, which incorporates disability information from all functional domains, active smokers had significantly higher disability scores than non-smoker MS individuals ($\beta = 7.7$ (95%CI: 4.8, 10.7), $p = 2 \times 10^{-7}$). This association was consistent across genders (Table 2). Global disability as captured by the PDDS did not differ between active smokers and non-smokers, though there was evidence for female smokers reporting a higher PDDS score than female non-smokers (OR=1.6 (95%CI: 1.1, 2.4), $p = 0.02$) (Table 2). Last, disability did not vary by numbers of cigarettes smoked amongst smokers (data not shown).

MS subtype

In MS subtype multigroup analyses, direction and magnitude of effects trended across the sub-analyses (Table 3), similar to the adjusted models for all MS individuals (Table 2). RR smokers were twice as likely to report a relapse in the previous 6 months compared to non-smokers. There was no evidence of association between smoking status and the dexterity, bladder/bowel, and spasticity PS in SP individuals, while there were trends in RR and PP/PR MS (Table 2). Furthermore, there was no evidence for an association between smoking status and PDDS across MS subtypes. However, the pattern of association between IRT disability and smoking status, though not necessarily significant in all sub-analyses, appeared consistent ($\beta_{RR} = 7.0$ (95%CI: 3.0, 11.0), $p = 6 \times 10^{-4}$; $\beta_{SP/PP/PR} = 7.0$ (95%CI: 1.9, 12.1), $p = 7 \times 10^{-3}$; $\beta_{SP} = 6.0$ (95%CI: -0.4, 12.4), $p = 0.07$; $\beta_{PP/PR} = 7.5$ (95%CI: -1.4, 16.3), $p = 0.10$; Table 3).

Discussion

This is the first US MS study to characterize HRQOL, disease activity and disability, between active smokers to non-smokers in men and women. Results demonstrate that on average, active smokers with MS have significantly lower HRQOL and greater disability than non-smokers. The relationships between smoking and HRQOL were only statistically significant in women, however the non-significant effects in the smaller male sample were of

the same direction. Similar to prior studies, smokers with MS accumulated greater disability across most functional domains than non-smokers, irrespective of gender. We observed no variation between these health outcome measures and number of cigarettes smoked amongst active MS smokers.

The study population appears representative of the general US MS population, by gender distribution, age of symptom onset, and MS subtype²⁵. The prevalence of smoking was lower than in the respective 2014 age and gender US subpopulation²⁶; however this was expected as decreased smoking prevalence has been reported in other US MS populations^{9, 12, 27}, further supporting the external validity of this US MS study population. A key limitation of this study is the generalizability to people with MS who are not non-Hispanic whites (5% of the study population).

Our HRQOL results are consistent with a large international survey of individuals with MS (N=2,469; 31% from the US), that demonstrated HRQOL in smokers were significantly lower than never smokers, and current smokers' HRQOL were appreciably lower than former smokers¹¹. Weiland *et al.* also did not observe HRQOL differences by number of cigarettes currently smoked¹¹. A longitudinal study of postmenopausal women living with MS did not observe any association between smoking and mean change in HRQOL over a three year period¹². The authors did not report baseline or follow-up measures of HRQOL by smoking status, therefore comparisons to the current study population were not possible. Nonetheless, when current analyses were restricted to women of postmenopausal age (≥ 55yrs; N=493), results were fairly unchanged from those in Table 2 (data not shown).

In this study, active smokers with MS were more likely to report having a relapse and worsening of symptoms within the previous 6 months than non-smokers, and appears restricted to women. Our study is not directly comparable to prior studies, which examined relapse rate; those studies did not observe a relationship between smoking and increased relapse rate^{11, 28–30}.

This is the first study to examine the eight PS and three FS by smoking status in a MS population. We demonstrate active smokers report greater disability than non-smokers for the following functional domains: dexterity, vision, fatigue, cognition, bladder/bowel, sensory, spasticity, depression, tremor/coordination, and pain, and relationships were reasonably consistent across men and women with MS (Table 2). We explored the pairwise correlation between the 11 domain scores and no correlation coefficient was 0.6, and 50% of the coefficients were 0.4 (Supplementary Table 1). The correlation pattern, as well as previous categorical factor analyses^{15, 24, 31}, demonstrate the 11 PS and FS have shared and unique properties illustrating the pervasive impact of smoking on multiple functional domains. The one domain not affected by smoking was mobility, and this was consistent across MS subtypes.

Using a validated construct of MS global disability (IRT disability), active MS smokers had significantly greater disability than non-smokers ($p=2 \times 10^{-7}$), and the relationships had similar trends across MS subtypes. We specifically sought to examine MS global disability using a measure that incorporated information from multiple functional domains¹⁵, unlike

EDSS and related derivatives, which predominantly measure ambulation and inadequately captures impairment in other functional systems³². When we investigated PDDS, which approximates EDSS, there were no differences by smoking status, consistent with our findings for the HRQOL PF subscale and the mobility PS, and with other studies investigating EDSS and Multiple Sclerosis Severity Score (disability measure based on EDSS)^{28, 33–35}. The relationships between smoking status and IRT disability and PDDS demonstrated similar patterns across MS subtypes.

The results, including those for the individual measures of PS, FS, MCS, PCS, and IRT disability, clearly show active smoking is meaningfully associated with greater decrements in functional domains not commonly evaluated in people with MS. Although most adults with MS understand the detrimental effects of smoking on health, many smokers continue to engage in smoking as a coping strategy for stress, including 80% of MS smokers⁹. Furthermore, there is evidence of a substantial unmet need for smoking cessation services (59% of current smokers)²⁷. This study adds to the growing literature of the need for MS-tailored smoking cessation programs. This study also provides useful information for clinicians by showing that MS individuals who are actively smoking are likely experiencing a more severe clinical course (with greater deficits in all domains), which goes beyond the notion that these individuals who smoke are merely at risk for severe disease at an unknown future time point.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

DO and DG are supported by National Institutes of Health (Clinical and Translational Science Collaborative of Cleveland (KL2TR000440)) KL2 Awards. The funding agreement ensured the authors' independence in designing the study, interpreting the data, writing, and publishing the report. The NARCOMS registry is supported in part by the Consortium of Multiple Sclerosis Centers. The authors are grateful for the data access provided at no cost. Performance Scales, Copyright Registration Number/ Date: TXu000743629 / 1996-04-04; assigned to DeltaQuest Foundation, Inc., effective October 1, 2005. US Copyright law governs terms of use.

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Table 1

Subjects characteristics by current smoking status, at interview in 2014.

Variable	Study population	Non-smoker	Current Smoker	P (NS vs CS) ^a
N	950	845	105	
Sex (% Male)	23.5	23.1	26.7	0.41
Age symptom onset (mean, S.D.)	31.2 (9.7)	31.4 (9.8)	29.6 (8.8)	0.07
Age diagnosis (mean, S.D.)	38.2 (9.4)	38.4 (9.5)	37.1 (8.6)	0.18
Age at interview (mean, S.D.)	58.7 (10.2)	59.0 (10.3)	56.3 (9.2)	9.3x10⁻³
Duration from diagnosis (mean, S.D.)	20.0 (9.8)	20.1 (9.9)	18.7 (8.9)	0.16
BMI (kg/m ² ; mean, S.D.)	27.1 (6.6)	27.3 (6.6)	25.3 (6.3)	2.9x10⁻³
Immunologic therapy in the past 6 months (%)	64.1	63.9	66.0	0.67
No alcohol consumption in the past 6 months (%)	35.4	35.0	37.5	0.61
MS care (%)	Specialized MS center	28.3	26.0	0.85
	Private neurologist	55.3	53.9	
	General Practitioner	6.8	7.7	
	Other	4.5	5.8	
	No MS care	5.2	6.7	
Ethnicity (% Hispanic)	2.0	2.0	1.9	0.94
Race (%)	White	95.0	93.3	0.09
	Black	2.2	2.9	
	Other	2.4	1.9	
	Multiracial	0.4	1.9	
	CIS	0.7	0.0	
MS subtype (%)	RR	53.9	55.2	0.54
	SP	21.0	17.1	
	PP	8.4	6.7	
	PR	3.0	4.8	
	DK/Unsure	11.5	13.3	
	Other	1.6	2.9	

Variable	Study population	Non-smoker	Current Smoker	P (NS vs CS) ^a
HRQOL subscale (mean, S.D.)	PF	35.0 (10.3)	37.2 (11.8)	0.06
	RP	36.1 (9.7)	39.1 (10.6)	5.9x10⁻³
	BP	41.7 (11.1)	45.7 (10.6)	2.7x10⁻⁴
	GH	42.7 (9.8)	46.2 (10.4)	1.2x10⁻³
	VT	41.4 (9.4)	44.5 (10.3)	4.7x10⁻³
	SF	40.7 (11.1)	44.5 (10.7)	2.6x10⁻⁴
	RE	37.1 (13.2)	44.6 (11.7)	8.7x10⁻⁶
	MH	45.0 (10.7)	49.1 (9.7)	6.4x10⁻⁵
Number of cigarettes smoked a day			13.4 (8.6) ^β	

BMI: body mass index; BP: bodily pain; CIS: clinically isolated syndrome; CS: current smoker; DK: don't know; GH: general health; MH: mental health; NS: non-smoker; PF: physical functioning; PP: primary progressive; RP: progressive relapsing; RE: role-emotion; RR: relapsing remitting; RP: role-physical; SF: social functioning; SP: secondary progressive; VT: vitality.

^a Bivariate associations between smoking status and individual variables were conducted using Chi-Squared tests and Student's T-tests for categorical and continuous variables, respectively.

^β N=90

Table 2

The associations between current smoking status and HRQOL, disease activity, symptom change, and global disability in MS participants.

Variable (mean and S.D. or percentage)	Current Smoker (N=105)	Non- smoker (N=845)	Unadjusted β /OR (95% CI) (N=950)	P	Adjusted δ β /OR (95% CI) (N=945)	P	Males Adjusted β /OR (95% CI) (N=223)	P	Females Adjusted β /OR (95% CI) (N=722)	P
HRQOL										
PCS $\bar{x}$	37.3 (10.3)	39.6 (10.8)	-2.24 (-4.43, -0.06)	0.044	-3.81 (-5.73, -1.89)	1 x10⁻⁴	-2.00 (-5.58, 1.59)	0.27	-4.23 (-6.50, -1.95)	2.9x10⁻⁴
PCS binary (1=Below/Far Below average; 0=At/Above average)	78.1%	69.4%	1.58 (0.97, 2.57)	0.07	2.35 (1.36, 4.04)	2.1x10⁻³	1.86 (0.59, 5.84)	0.29	2.54 (1.37, 4.71)	3.2x10⁻³
MCS $\bar{x}$	44.3 (11.6)	49.2 (10.5)	-4.84 (-7.01, -2.68)	1.2x10⁻⁵	-4.58 (-6.76, -2.41)	3.9x10⁻⁵	-2.10 (-6.50, 2.31)	0.35	-5.40 (-7.94, -2.97)	3.2x10⁻⁵
MCS binary (1=Below/Far Below average; 0=At/Above average)	48.6%	31.7%	2.03 (1.35, 3.06)	6.7x10⁻⁴	2.03 (1.33, 3.11)	1.0x10⁻³	1.33 (0.57, 3.11)	0.51	2.36 (1.44, 3.87)	7.0x10⁻⁴
Disease activity										
Relapse in the previous 6 months (1=Yes; 0=No/Don't Know)	25.7%	16.7%	1.73 (1.07, 2.77)	0.024	1.66 (1.03, 2.71)	0.039	1.08 (0.39, 3.00)	0.89	1.95 (1.11, 3.43)	0.020
Progressive worsening of symptoms in previous 6 months (1=Yes; 0=No)	32.7%	34.0%	0.94 (0.61, 1.46)	0.796	1.08 (0.68, 1.73)	0.74	1.16 (0.49, 2.73)	0.74	1.06 (0.60, 1.88)	0.83
Compare MS symptoms to 6 months ago? (1=Much better; 7=Much Worse)	4.6 (1.0)	4.4 (0.8)	1.41 (0.95, 2.09)	0.086	1.58 (1.06, 2.38) β	0.026	1.28 (0.58, 2.82) β	0.55	1.70 (1.06, 2.74) β	0.029
Performance Scales (0=normal)										
Mobility (0 to 5)	3.0 (2.0)	2.9 (2.1)	1.06 (0.75, 1.50)	0.739	1.39 (0.96, 2.01)	0.08	1.00 (0.49, 2.02) β	0.99	1.49 (0.97, 2.29) β	0.07
Dexterity (0 to 4)	2.1 (1.3)	1.6 (1.3)	1.84 (1.29, 2.61)	7.6x10⁻⁴	2.36 (1.62, 3.43)	7.5x10⁻⁶	1.63 (0.78, 3.43)	0.20	2.75 (1.78, 4.26)	5.6x10⁻⁶
Vision (0 to 4)	1.6 (1.2)	1.2 (1.1)	1.82 (1.27, 2.62) α	1.0x10⁻³	2.08 (1.43, 3.02) α	1.2x10⁻⁴	2.94 (1.37, 6.33)	5.8x10⁻³	1.75 (1.14, 2.68) α	0.010
Fatigue (0 to 5)	3.3 (1.2)	2.5 (1.4)	2.17 (1.51, 3.12)	2.5x10⁻⁵	2.58 (1.78, 3.74)	6.2x10⁻⁷	2.69 (1.26, 5.72) β	0.010	2.53 (1.63, 3.92)	2.9x10⁻⁵
Cognitive Symptoms (0 to 4)	1.9 (1.3)	1.5 (1.2)	1.76 (1.22, 2.53)	2.5x10⁻³	1.91 (1.30, 2.81)	9.5x10⁻⁴	2.51 (1.14, 5.52) β	0.022	1.77 (1.14, 2.76)	0.011
Bladder/Bowel (0 to 4)	2.0 (1.3)	1.8 (1.3)	1.18 (0.83, 1.69)	0.351	1.60 (1.08, 2.37)	0.019	2.20 (1.04, 4.69)	0.040	1.34 (0.85, 2.12)	0.21
Sensory Symptoms (0 to 5)	1.9 (1.3)	1.7 (1.3)	1.29 (0.90, 1.86)	0.166	1.46 (1.01, 2.12)	0.047	1.30 (0.64, 2.67)	0.47	1.50 (0.96, 2.33)	0.07
Spasticity Symptoms (0 to 4)	1.9 (1.3)	1.7 (1.4)	1.35 (0.95, 1.92)	0.092	1.59 (1.09, 2.31)	0.016	1.60 (0.77, 3.33) α	0.21	1.61 (1.03, 2.52)	0.036
Functional Scales (0=normal)										

Variable (mean and S.D. or percentage)	Current Smoker (N=105)	Non- smoker (N=845)	Unadjusted β /OR (95% CI) (N=950)	P	Adjusted δ β /OR (95% CI) (N=945)	P	Males Adjusted β /OR (95% CI) (N=223)	P	Females Adjusted β /OR (95% CI) (N=722)	P
Depression (0 to 4)	1.6 (1.3)	1.2 (1.1)	2.01 (1.39, 2.91)	2.3x10⁻⁴	2.01 (1.38, 2.95)	3.0x10⁻⁴	2.47 (1.20, 5.07)	0.014	1.84 (1.18, 2.89)	7.4x10⁻³
Tremor and Coordination (0 to 4)	2.0 (1.4)	1.3 (1.3)	2.29 (1.60, 3.27)	6.0x10⁻⁶	2.83 (1.94, 4.14)	7.6x10⁻⁸	1.80 (0.85, 3.83)	0.13	3.41 (2.18, 5.34)	8.2x10⁻⁸
Pain (0 to 4)	2.2 (1.4)	1.6 (1.4)	2.15 (1.50, 3.07)	3.0x10⁻⁵	2.65 (1.80, 3.89)	6.6x10⁻⁷	2.64 (1.27, 5.49) γ	9.6x10⁻³	2.64 (1.68, 4.15)	2.5x10⁻⁵
Global Disability										
IRT disability $\ddagger$	56.8 (14.9)	50.5 (16.0)	6.29 (3.02, 9.55)	1.7x10⁻⁴	7.74 (4.83, 10.65)	2.2x10⁻⁷	7.40 (1.19, 13.60)	0.020	7.57 (4.24, 10.89)	9.4x10⁻⁶
PDDS (0=normal; 8=Bedridden)	3.7 (2.2)	3.6 (2.4)	1.08 (0.76, 1.51)	0.678	1.43 (1.00, 2.04) β	0.051	0.84 (0.42, 1.69) β	0.62	1.61 (1.06, 2.44) β	0.024

BMI: body mass index; IRT disability: Item Response Theory summed score of global MS disability; MCS: mental component summary; OR: odds ratio; PCS: physical component summary; PDDS: patient derived disease steps.

$\ddagger$ The measures of association reported for these outcomes are betas from linear regression models. The remaining measures of association are odds ratios.

δ Models were adjusted for gender, BMI, MS subtype, age of symptom onset, duration from diagnosis, and age at interview.

α Smoking status violated the parallel lines assumption, but constrained to the assumption.

β MS subtype violated the parallel lines assumption, unfortunately when MS subtype was treated as non-proportional the model did not converge; therefore it was constrained to the assumption.

γ The partial proportional odds model did not converge, however smoking status met the parallel lines assumption in the unadjusted model, therefore all other predictors were constrained to the assumption.

Table 3

The associations between current smoking status and HRQOL, disease activity, symptom change, and global disability by MS subtype.

Variable (mean and S.D. or percentage)	RR Adjusted β /OR (95% CI) (N=512)	P	SP/PP/PR Adjusted β /OR (95% CI) (N=307)	P	SP Adjusted β /OR (95% CI) (N=199)	P	PP/PR Adjusted β /OR (95% CI) (N=108)	P
HRQOL								
PCS [‡]	-3.43 (-6.24, -0.62)	0.017	-3.54 (-6.39, -0.69)	0.015	-2.57 (-6.36, 1.21)	0.18	-4.51 (-9.09, 0.07)	0.054
PCS binary (1=Below/Far Below average; 0=At/Above average)	2.40 (1.28, 4.49)	6.4x10⁻³	2.65 (0.32, 21.99)	0.37	2.30 (0.25, 21.20)	0.46	–	–
MCS [‡]	-4.33 (-7.10, -1.56)	2.2x10⁻³	-2.82 (-7.01, 1.37)	0.19	-2.81 (-8.19, 2.57)	0.30	-0.93 (-8.03, 6.17)	0.80
MCS binary (1=Below/Far Below average; 0=At/Above average)	2.40 (1.34, 4.28)	3.1x10⁻³	1.19 (0.53, 2.64)	0.68	1.12 (0.38, 3.26)	0.84	0.88 (0.25, 3.13)	0.84
Disease activity								
Relapse in the previous 6 months (1=Yes; 0=No/Don't Know)	2.26 (1.21, 4.23)	0.011	1.32 (0.49, 3.55)	0.59	1.69 (0.48, 5.94)	0.42	1.05 (0.18, 5.96)	0.96
Progressive worsening of symptoms in previous 6 months (1=Yes; 0=No)	1.57 (0.81, 3.04)	0.18	1.06 (0.48, 2.33)	0.89	1.00 (0.35, 2.86)	1.00	1.39 (0.38, 5.04)	0.62
Compare MS symptoms to 6 months ago? (1=Much better; 7=Much Worse)	2.19 (1.23, 3.89)	7.4x10⁻³	1.40 (0.65, 2.95) [‡]	0.39	1.09 (0.41, 2.90) [‡]	0.87	1.99 (0.59, 6.73)	0.27
Performance Scales (0=normal)								
Mobility (0 to 5)	1.51 (0.92, 2.47)	0.10	1.07 (0.53, 2.16) [‡]	0.86	0.96 (0.39, 2.39) [‡]	0.93	1.09 (0.34, 3.47) [‡]	0.88
Dexterity (0 to 4)	2.79 (1.69, 4.59)	5.8x10⁻⁵	1.55 (0.75, 3.21)	0.24	1.00 (0.41, 2.49)	0.99	2.90 (0.83, 10.15)	0.095
Vision (0 to 4)	1.85 (1.12, 3.07)	0.017	2.70 (1.33, 5.48) [‡]	5.9x10⁻³	2.21 (0.88, 5.52) [‡]	0.09	3.20 (1.00, 10.22)	0.049
Fatigue (0 to 5)	2.30 (1.39, 3.81)	1.3x10⁻³	3.01 (1.52, 5.98) [‡]	1.6x10⁻³	2.03 (0.87, 4.77)	0.10	4.74 (1.47, 15.32) [‡]	9.2x10⁻³
Cognitive Symptoms (0 to 4)	1.89 (1.12, 3.21) [‡]	0.017	1.91 (0.92, 3.97)	0.08	1.63 (0.64, 4.17) [‡]	0.31	2.03 (0.61, 6.81)	0.25
Bladder/Bowel (0 to 4)	1.67 (0.99, 2.85)	0.057	1.09 (0.52, 2.28)	0.82	0.81 (0.29, 2.24)	0.68	1.44 (0.44, 4.64)	0.55
Sensory Symptoms (0 to 5)	1.42 (0.85, 2.36) [‡]	0.18	1.48 (0.73, 2.99)	0.27	1.45 (0.56, 3.73)	0.44	1.42 (0.47, 4.35) [‡]	0.54
Spasticity Symptoms (0 to 4)	1.99 (1.19, 3.32)	8.3x10⁻³	1.07 (0.52, 2.20)	0.85	0.79 (0.31, 2.01)	0.63	1.54 (0.49, 4.82)	0.46
Functional Scales (0=normal)								
Depression (0 to 4)	1.81 (1.06, 3.08)	0.027	1.96 (0.97, 3.94)	0.059	2.76 (1.11, 6.87)	0.03	1.21 (0.40, 3.69)	0.74
Tremor and Coordination (0 to 4)	2.39 (1.43, 4.01) [‡]	9.0x10⁻⁴	3.04 (1.48, 6.22)	2.4x10⁻³	3.47 (1.39, 8.071)	7.9x10⁻³	2.16 (0.67, 7.01)	0.20
Pain (0 to 4)	2.09 (1.24, 3.52)	5.9x10⁻³	3.04 (1.51, 6.12)	1.8x10⁻³	2.15 (0.84, 5.47)	0.11	4.94 (1.62, 14.99) [‡]	4.8x10⁻³

Variable (mean and S.D. or percentage)	RR Adjusted ^δ β/OR (95% CI) (N=512)	P	SP/PP/PR Adjusted β/OR (95% CI) (N=307)	P	SP Adjusted β/OR (95% CI) (N=199)	P	PP/PR Adjusted β/OR (95% CI) (N=108)	P
Global Disability								
IRT disability ^γ	6.99 (3.01, 10.98)	6.2x10⁻⁴	6.99 (1.89, 12.09)	7.4x10⁻³	6.02 (-0.40, 12.44)	0.07	7.45 (-1.42, 16.33)	0.10
PDDS (0=normal; 8=Bedridden)	1.55 (0.96, 2.50)	0.075	1.12 (0.57, 2.22) ^γ	0.74	1.03 (0.43, 2.44) ^γ	0.95	1.00 (0.32, 3.15) ^γ	1.00

BMI: body mass index; IRT disability: Item Response Theory summed score of global MS disability; MCS: mental component summary; OR: odds ratio; PCS: physical component summary; PDDS: patient derived disease steps. PP: primary progressive; PR: progressive relapsing; RR: relapsing remitting; SP: secondary progressive.

^γThe measures of association reported for these outcomes are betas from linear regression models. The remaining measures of association are odds ratios.

^δModels were adjusted for gender, BMI, age of symptom onset, duration from diagnosis, and age at interview.

^αSmoking status violated the parallel lines assumption, but constrained to the assumption.

^γThe partial proportional odds model did not converge, however smoking status met the parallel lines assumption in the unadjusted model, therefore all other predictors were constrained to the assumption.