Title:

Smoking cessation and the reduction of disability progression in Multiple Sclerosis: a cohort study

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ABSTRACT

Background: Smoking is associated with a more severe disease course in people with multiple sclerosis (MS). The magnitude of effect of smoking cessation on MS progression is unknown. The aim of this study was to quantify the impact of smoking cessation on reaching MS disability milestones.

Methods: This is a cross-sectional study with retrospective reports. A comprehensive smoking questionnaire was sent to 1270 patients with MS registered between 1994 and 2013 in the Nottingham University Hospital MS Clinics database. Demographic and clinical data were extracted from the clinical database. Cox proportional hazard regression was used to estimate effects of smoke-free years on the time to Expanded Disability Status Scale (EDSS) scores 4.0 and 6.0. MS Impact Scale 29 (MSIS-29) and Patient Determined Disease Steps (PDDS) were used to assess the physical and psychological impact of smoking.

Results: Each 'smoke-free year' was associated with 0.96 (95% CI: 0.95 to 0.97) times decreased risk of reaching EDSS 4.0 and 0.97 (95%CI: 0.95 to 0.98) times decreased risk of reaching EDSS 6.0. Non-smokers showed a significantly lower level of disability in all the self-reported outcomes compared with current smokers.

Conclusion: The reduction in the risk of disability progression after smoking cessation is significant and time-dependent. The earlier the patients quit, the stronger the reduction in the risk of reaching disability milestones. The quantitative estimates of the

impact of smoking cessation on reaching disability milestones in MS can be used in interventional trials.

IMPLICATIONS

This study provides for the first time quantitative estimates of the effects of smoking cessation in MS, essential for informing smoking cessation trials.

The clear effect of smoking cessation on MS progression suggests the need to consider adjusting for smoking cessation when assessing for treatment effects in clinical trials of treatments for MS.

Smoking cessation should be an early intervention in people with MS.

INTRODUCTION

Multiple Sclerosis (MS) is a chronic, disabling neurological condition with a 50% higher risk to occur in tobacco smokers[1,2]. This increased susceptibility to MS in smokers declines after smoking cessation[3]. Continuing smoking after the onset of MS worsens the clinical course[4]. Smokers with MS have more severe disease[5,6] and increased risk of reaching higher disability scores in a shorter time than non-smokers[7,8]. Smoking cessation is beneficial in MS[4,8], but the impact on reaching disability milestones has not yet been quantified. There is typically a delay between the time a preventive measure is instituted and the time positive changes become discernible[9]. How the number of smoke-free years relates to MS progression (the degree of reduction in the risk of progression in those who quit) is unknown. In this study we address this point.

We previously reported that patients who stopped smoking, whether before or after MS onset, have significantly lower risk of disability progression compared with those who continued to smoke[4]. A recent Swedish study showed a reduction in the time to secondary progressive MS in those who continued to smoke compared to those who quit smoking shortly after the diagnosis of MS[8]. However, those studies do not quantify the effect of smoking cessation on reaching MS relevant disability scores. Here we quantify this impact and aim to provide numbers for sample size calculations in smoking cessation trials.

Patient-based outcomes are increasingly used in the assessment of treatment interventions in MS. D'Hooghe et al.[10] used a self-reported assessment of disability

based on Expanded Disability Status Scale (EDSS) and on the Disease Steps scale and showed that smoking was associated with higher risk of reaching EDSS 6.0 (i.e. requiring a walking aid to walk about 100m with or without resting) in relapsing-remitting MS (RRMS)[10]. There are no data on the impact of smoking in current, ex- and non-smokers with MS and the effects of smoking on the physical and psychological MS dimensions, from the perspective of patients.

Here, we study the effect of smoke-free years on MS disability milestones and we assess the impact of smoking on physical and psychological patient-reported outcomes in a large clinic-based MS population. In particular, we examine the impact of smoking cessation after disease onset on disability progression.

METHODS

We performed a questionnaire-based, cross-sectional study with retrospective reports, assessing the status and history of smoking; and the impact of smoking on physical and psychological dimensions of self-reported outcomes in a specialist clinic-based MS patient population

Setting:

We used demographic and clinical data from patients registered in the Nottingham University Hospital MS Clinics database between 1994 and 2013. These clinics cover over 3000 patients and are major catchment and referral centres in East Midlands UK. The centre and patient population have been described in more detail elsewhere[4,11]. Data regarding sex, age at last disability assessment, age at MS onset, clinical course

(relapsing-remitting-RRMS; secondary progressive-SPMS; and primary progressive-PPMS),duration of exposure to disease modifying treatments (DMTs), and disability as measured by EDSS[12] were obtained from the clinical database. EDSS is a disability scale, described below. This database includes on average four EDSS scores per patient. These were estimated by a neurologist during clinic visits.

Exposure and Outcomes:

Smoking: In 2013, a comprehensive smoking questionnaire with questions obtained from the Health Survey for England 2010, Respiratory Health (NS)[13] and European Community Respiratory Health Survey II (ECRHS)[14] was sent to 1270 patients with MS fulfilling the McDonald and/or Poser criteria[15,16]. Patients were eligible to participate if they were ≥18 years old at the time of study, had clinically definite MS and their residence details were available. Detailed data regarding individual smoking status and history were obtained. Patients were asked about the age when they started smoking regularly, the age when they cut down or stopped smoking, and the intensity of smoking (average number of cigarettes smoked per day). Regular smoking was defined by the European Community Respiratory Health Survey II criteria [14] as ≥20 packs of cigarettes or 12 oz (360 g) of tobacco in a lifetime, or ≥1 cigarette per day or 1 cigar per week for 1 year, and confirmation of smoking within the past month. 411 patients had been included in our previous work[4]. Patients were grouped as non-smokers, ex-smokers or current smokers.

Outcome Measures

Data needed to calculate the time to disability milestones EDSS 4.0 (can walk without aid or rest for 500 m) and 6.0 (requires aid to walk about 100 m with or without resting) [12] were extracted from the clinical database. The EDSS scale ranges from 0 to 10 in increments of 0.5 units that mean higher levels of disability [12]. The EDSS steps 1.0 to 4.5 refer to people with MS who can walk without any aid, while steps 5.0 to 9.5 are defined by the impairment to walking [12]. The EDSS steps 4 and 6 are established milestones in clinical studies.

The physical and psychological impact of MS from patients' perspective were assessed using Multiple Sclerosis Impact Scale-29 (MSIS-29)[17] and Patient Determined Disease Steps (PDDS)[18] which are validated patient-based outcome measures. MSIS-29 accounts for MS impact on physical (twenty items) and psychological (nine items) dimensions [17]. Responses use a 5 point Likert type scale range from 1 to 5 (Not at all, A little, Moderately, Quite a bit, Extremely)[17]. The total score is the sum of points for all 29 questions (minimum score: 29; maximum score: 145)[17]. A change of ≥8 points in MSIS-29 (0 to 145 scale) is thought to reflect clinical change [19]. A higher score corresponds to more disability. We used the average score (the overall score divided by 29) which considers the number of questions that patient has answered, as we used previously [20]. The corresponding minimally clinically meaningful change on the scale used (1 to 5) is 0.27.

PDDS is a patient-reported outcome measure that reflects motor disability[18] and focuses on how well the patients walk. It has nine ordinal levels ranging between 0

(normal) and 8 (bedridden) of which the patient chooses the one that best describes his situation. PDDS scores can be converted into classifications of mild, moderate, or severe disability[18,21]. PDDS is a surrogate of the EDSS[21]. The higher score, the greater the degree of disability.

The study was approved by East Midlands Research Ethics Committee Derby-1.

Statistical analysis

To test the differences in median MSIS-29 and PDDS scores between smoking groups, we used two-sample Wilcoxon rank-sum (Mann-Whitney) and Kruskal–Wallis tests, and for testing the difference in proportions of males and females in different smoking categories Chi square test was used. Median regression models were used to compare MSIS-29 and PDDS between current, ex- and never-smokers while adjusting for disease duration, age at onset, sex, initial course (relapse-onset vs. PPMS) and DMTs for ≥1 year. Median regression coefficients are interpreted like ordinary regression coefficients. Cox proportional hazard regression models were used to estimate the risk of reaching EDSS 4.0 and 6.0. To investigate effects of smoking cessation we fit a model with smoke-free years. Final models were adjusted for potential confounders including initial course, DMT for ≥1 year, and sex. The time axis for the regression was age, with entry from date of MS onset. This ensured hazard ratios for all risk factors were adjusted for chronological age. Patients were followed to the first sustained EDSS score 4.0 or 6.0 or censored if they had not experienced the outcome by the time of last clinic visit, independent of the study end time. We did not correct for multiple comparisons as the factors analysed were not independent.

When fitting the smoke-free years variable in the model, we only included intensity of smoking to avoid collinearity and non-proportional hazard. Only current and ex-smokers were included in the smoke free-years analysis. The smoke-free years was set to 0 for current smokers and the interval between age at the disability milestone (if have reached the milestone) or last visit (if censored) and age at smoking cessation in ex-smokers. For example, if an individual starting smoking at age 22 had MS onset at 33, quit smoking at 47, and reached EDSS 6.0 at 55, the smoke-free years was set = 8 and smoking duration = 25 years. In models without smoke-free years, pack-years were used to adjust for the impact of duration and intensity of smoking.

Statistical analyses were performed using Stata version 13.1 (StataCorp. 2013. Stata Statistical Software. College Station, Texas, USA: StataCorp LP).

RESULTS

Patient characteristics

We originally identified 1412 patients who attended Nottingham university MS specific clinics between 2000 and 2013. Of those, 120 were deceased, 14 did not have clinically definite MS, eight had missing residential address and eight questionnaires were incomplete and were excluded. In all, 680 questionnaires with full data were returned, representing a 54% response rate. Mean age was 53 (SD ±11.33) with 2:1 female:male ratio. 57% had RRMS, 33% SP MS and 10 % PPMS. Mean MS duration was 19 (±10.4) years. 54% had ≥1 year of DMT exposure.

Smoking prevalence

62% of the patients reported they had tried tobacco at some point (ever-smoked), however, 51% reported having smoked regularly (regular smokers) and were further grouped into current or ex-smokers. At MS onset, 18% and 33% were ex-smokers and current smokers, respectively. At the time of the study 35% of smokers had quit smoking and 16% were current smokers. The percentages of non-, ex-, and current smokers were different between sexes. At the time of study 40 %, 45% and 14% of males were non-, ex-, and current smokers vs. 52%, 31% and 16% of females (P = 0.003). Mean age at the start of smoking was 17.5 (SD ±4.4) years. Smokers smoked for an average of 22.7 (±13.4) years with average smoking intensity of 14.6 (±8.7) cigarettes/ day.

MSIS-29 and PDDS scores

The median MSIS-29 and PDDS scores are shown in table 1. Both the average psychological and physical MSIS-29 scales, but not the overall scale, were higher in current-smokers compared to ex-smokers, who had higher scores than never-smokers. The higher scores reflect a higher level of disability.

The highest impact of smoking was on the MSIS-29 psychological scale where current and ex-smokers had a 0.8 (95%CI: 0.41 to 1.19, P < 0.001) and 0.56 (95%CI: 0.18 to 0.94 P = 0.004) increase in the median score compared with non-smokers, controlling for initial type of MS, disease duration, onset age, sex and exposure to treatment. Median overall scores were higher by 0.47 (95%CI: 0.14 to 0.80, P = 0.006) in current

smokers and by 0.33 (95%CI: 0.12 to 0.53, P = 0.002) in ex-smokers compared to non-smokers. The median MSIS-29 physical score was higher in current smokers (Coefficient (Coef): 0.58, 95%CI: 0.29 to 0.93, P = 0.001 and in ex-smokers (Coef: 0.32, 95%CI: 0.02 to 0.61, P 0.03) compared with non-smokers.

Both current and ex-smokers had higher PDDS scores than non-smokers (Table 1). The median adjusted PDDS score was 0.98 (95%CI: 0.53 to 1.43, P < 0.001) higher in current smokers compared with non-smokers. Ex-smokers had a non-significant trend to a higher median PDDS score compared with non-smokers (Coef: 0.34, 95%CI: -0.05 to 0.75, P =0.08). Coefficients of differences in median MSIS-29 and PDDS scores between non-, ex- and current smokers are shown in Table 2.

Smoking cessation and the risk of reaching EDSS scores 4.0 and 6.0

There were no differences in the assessment frequency between smoking groups. Patients who smoked between disease onset and the time of EDSS 4.0 and 6.0 had 2.42 (95%CI: 1.63 to 3.60, P < 0.001) and 1.86 (95%CI: 1.19 to 2.91, P = 0.006) times higher risk of reaching these two milestones compared with never-smokers. Total pack-years smoked up to each milestone showed no significant association with disability progression. In smokers, there was a significant difference in age at EDSS scores 4 and 6 between those who continued to smoke and those who quit smoking. Age at EDSS score 4 was 41 (95%CI: 36 to 43) in continuing smokers, 43 (95%CI: 40 to 46) in those with 1 to 15 smoke-free years and 52 (95%CI: 48 to 56) in the group with >15 smoke-free years (P<0.001). The corresponding age for EDSS score 6 was 45 (95%CI: 41 to 50), 49 (95%CI: 43 to 54) and 55 (95%CI: 50 to 59), respectively (P<0.001) (Figure 2).

Each year elapsed from smoking cessation was associated with 0.96 (95%CI: 0.95 to 0.97, P < 0.001) times decreased risk of reaching EDSS 4.0 and 0.97 (95%CI: 0.95 to 0.98, P < 0.001) times decreased risk of reaching EDSS 6 (Table 3). For example, an ex-smoker who stopped smoking 10 years earlier than a patient who continued smoking would have 33% and 26% lower risk of reaching EDSS scores 4.0 and 6.0, respectively (calculated as 1-(HR)^10).

DISCUSSION

In this study, we provide quantitative measures of the impact of smoking cessation on MS progression. These data are novel and can be used in smoking cessation trials in MS. We use for the first time 'smoke-free years' to quantify the impact of smoking cessation on disability progression. We show that each year after smoking cessation reduces the risk of reaching disability landmarks and the reduction in the risk of reaching advanced disability is greater if implemented early.

The prevalence of smokers and the intensity of smoking in our population are close to those reported in other studies[6,22]. 16% of the patients in our cohort were current smokers at the time of the study, vs. 16.7% in a study on smoking from the North American Research Committee on MS (NARCOMS) Registry[23], 15.2% in a self-reported National MS Society Rhode Island Chapter study[24] and 14% in a recent Swedish study[8]. Few participants began smoking after MS onset. Many ex-smokers quit after disease onset, suggesting that a diagnosis of MS may influence smoking patterns, as reported[25]. In our cohort, the proportion of smokers was higher in males.

Although at the time of the study the sex-specific proportion of current smokers was close (16.5% in women vs. 14.5% in males), more women were current smokers. Smoking in women, could have a bearing on the increasing female:male ratio in MS[26].

In our population, the proportion of smokers at onset of MS was the highest (40%) in patients who had already converted to SPMS at the time of the study. The SPMS group also had the highest proportion of current smokers. Several factors can account for this. Firstly, most people with RRMS will convert over time to SPMS, and continued smoking hastens this transition to SPMS[6,8]. Secondly, people in the SPMS group are older than those in the RRMS group, and smoking prevalence was higher in the past decades [27]. Finally, people with SPMS generally have higher degrees of disability and longer disease duration than RRMS, and the use of tobacco could be a coping mechanism, as is seen in other chronic diseases[28-31]. Of note, 1/3 of all patients with MS in this study were current smokers at the onset of MS. This high prevalence of smoking at onset indicates that many patients are candidates for cessation interventions.

The data used in this study are novel and come from a well-established cohort of patients with MS[4]. We estimated the risk of reaching EDSS scores of 4.0 and 6.0, which are robust outcome measures and milestones of disability in MS. Generally, MS patients reaching EDSS 4.0 have already entered secondary progression[32]. A study by Koch et al. used time to EDSS 4.0 and 6.0, however, it did not find significant evidence of an association between cigarette smoking and progression[33]. Differences in sample size (364 patients in that study, 680 in ours) and longer follow-up make our estimates more robust. Our data are in agreement with those of D'Hooghe et al.[10], who showed

higher risk of reaching EDSS 6.0 amongst occasional and daily cigarette smokers. Importantly, by adjusting for major confounders, we show that the effect of smoking on progression is independent of disease duration, age at onset, sex, initial type of MS, and DMTs exposure. While total pack-years smoked before each disability landmark were not associated with the risk of reaching EDSS 4.0 and 6.0, the smoke-free years had an impact on reaching both outcomes. Of note, Hedstrom et al.[3] found that the risk of developing MS in people who smoke decreases slowly after cessation regardless of the dose-response association between smoking and the risk of MS.

Our findings show that 10 smoke-free years can account for a 33% and 26% lower risk of reaching EDSS scores 4.0 and 6.0 in ex-smokers compared to current smokers. Interestingly, our estimated risk reduction of 33%, 10 years after smoking cessation, confirms the findings by Ramanujam et al.[8] and Hedstrom et al.[3] and suggests that the mechanism responsible for increased susceptibility to MS in smokers also impacts disease course after MS onset. The impact of smoking and smoking cessation on smoking-related diseases is time-dependent [34]. Our findings show that the earlier smokers with MS quit, the better the effect on progression in the long term. Data from the general population show that recovery after cessation is slow and incomplete. Smoking is associated with white matter hyperintensity progression[35] and accelerated cortical thinning[36]. Although partial recovery of cortical thinning is possible in ex-smokers, it takes time[36]. Epigenetic changes may be involved in the development and progression of MS[37]. Specific methylation status is sensitive and specific for smoking status[38]. Some methylation sites revert to levels typical of never-smokers within

decades, but others remain differentially methylated more than 35 years after smoking cessation[39].

In this study we showed that the physical and psychological impact of MS from the patient perspective is worse in smokers than in non-smokers. MSIS-29[17] physical and psychological scales measure related but distinct constructs and it was suggested that a combined score may mask differential effects on physical and psychological health[17]. In our study, the unadjusted MSIS-29 scores showed an ascending trend from non- to current-smokers when physical and psychological scales were measured separately, but not for the overall score.

Overall, smokers fared worse on both physical and psychological MSIS-29 scales and on overall scores. The absolute differences in MSIS-29 scores between current- and never-smokers are likely to be clinically meaningful (>0.27 points on the MSIS-29 scale 1 to 5).[19]

Interestingly, the highest impact of smoking was noted on the MSIS-29 psychological scale. MSIS-29 psychological is more valid for detecting group differences in anxiety and depression[17] and smoking is associated with increased risk of anxiety and depression in people with MS[25,40]. Our study did not assess if smoking is a marker of risk or a causal factor for psychological change. Importantly, despite the belief among many smokers that quitting will lead to worsened mental health, smoking cessation is associated with reduced anxiety and depression[25].

Cognitive impairment occurs in approximatively half of all people with MS, and typically involves information processing speed, attention, working memory and executive functions [41]. The MSIS-29 score is a predictor of self-efficacy in MS[42], which in turn correlates with attention, reaction time variability and speed of memory[42]. We have not assessed cognition in this group of patients. It would be of value in the future to consider the influence of smoking on cognition in people with MS.

Here we show that the scores of the two patient-reported outcome measures MSIS-29 physical and PDDS were lower in ex-smokers than in current-smokers. We suggest that MSIS-29 and PDDS are reliable measures for monitoring of people with MS undertaking smoking cessation interventions. MSIS-29 physical has been used in long-term phase III treatment studies [19]. The PDDS, a surrogate of EDSS[18], is used in clinical research and practice alongside EDSS or when EDSS is impractical or costly[18].

Strengths of this study include the large cohort and the use of validated patient-based outcomes with questionnaires previously employed in MS. The main limitations of the study include the retrospective design (retrospective reports of smoking status with possibility of recall bias), and the low response rate (54%) making generalizability uncertain. Another limitation is the lack of biochemical verification of smoking status (e.g. exhaled CO or urine nicotine/cotinine) in the participants to the study. The response rate in our study is similar to the response rate seen in other population questionnaire-based studies in MS [43,44]. More of those who did not return the questionnaire could have been smokers. Smokers with MS have generally higher levels of disability [4]which could have precluded them from participating in the study, and

smokers from disadvantaged groups tend to participate at lower rate in research studies [45,46]. However, bias due to the response rate is less likely as the group of respondents was representative of the population studied (similar rates of smokers, ex- and never smokers as the cohort in Manouchehrinia et al.[4]). Moreover, this study focused on the impact of cessation in the respondents and not on the prevalence of smoking in the overall MS population. Another limitation is the reliance on self-reported adverse health behaviours, which may be susceptible to reporting bias, common to many similar studies[25] . Also, the cross-sectional assessment of the MS disability with MSIS-29 and PDDS questionnaires cannot provide information about how the impact of MS changes over time. Future studies assessing that impact at different time points could address this issue.

This study is novel in the effort to quantify the effect of smoking cessation. We provide for the first time estimates of the likelihood of reduction of progression in MS. These data can be used for calculation of sample size and effect size in intervention trials of smoking cessation in people with MS. Notably, the clear effect of smoking cessation on MS progression suggests the need to consider adjusting for smoking cessation when assessing for treatment effects in clinical trials of treatments in MS.

In conclusion, smoking cessation is associated with a significant reduction of the risk of disability progression. Smoking cessation should be an early intervention in people with MS.

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Conflict of Interest Disclosures:

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References:

1. Hedstrom AK, Sundqvist E, Baarnhielm M, et al. Smoking and two human leukocyte antigen genes interact to increase the risk for multiple sclerosis. *Brain.* 2011;134(Pt 3):653-664.
2. Hernan MA, Olek MJ, Ascherio A. Cigarette smoking and incidence of multiple sclerosis. *Am J Epidemiol.* 2001;154(1):69-74.
3. Hedstrom AK, Hillert J, Olsson T, Alfredsson L. Smoking and multiple sclerosis susceptibility. *Eur J Epidemiol.* 2013;28(11):867-874.
4. Manouchehrinia A, Tench CR, Maxted J, Bibani RH, Britton J, Constantinescu CS. Tobacco smoking and disability progression in multiple sclerosis: United Kingdom cohort study. *Brain.* 2013;136(Pt 7):2298-2304.
5. Hernan MA, Jick SS, Logroscino G, Olek MJ, Ascherio A, Jick H. Cigarette smoking and the progression of multiple sclerosis. *Brain.* 2005;128(Pt 6):1461-1465.
6. Healy BC, Ali EN, Guttmann CR, et al. Smoking and disease progression in multiple sclerosis. *Arch Neurol.* 2009;66(7):858-864.
7. Wingerchuk DM. Smoking: effects on multiple sclerosis susceptibility and disease progression. *Ther Adv Neurol Disord.* 2012;5(1):13-22.
8. Ramanujam R, Hedstrom AK, Manouchehrinia A, et al. Effect of Smoking Cessation on Multiple Sclerosis Prognosis. *JAMA Neurol.* 2015:1-7.
9. Katz DL, Jekel JF. *Jekel's epidemiology, biostatistics, preventive medicine, and public health.* 4th ed. Philadelphia, Pa. ; London: Saunders; 2014.
10. D'Hooghe M B, Haentjens P, Nagels G, De Keyser J. Alcohol, coffee, fish, smoking and disease progression in multiple sclerosis. *Eur J Neurol.* 2012;19(4):616-624.
11. Manouchehrinia A, Weston M, Tench CR, Britton J, Constantinescu CS. Tobacco smoking and excess mortality in multiple sclerosis: a cohort study. *J Neurol Neurosurg Psychiatry.* 2014;85(10):1091-1095.
12. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology.* 1983;33(11):1444-1452.
13. Health survey for England-2010, respiratory health. 2011.
14. Burney PG, Luczynska C, Chinn S, Jarvis D. The European Community Respiratory Health Survey. *Eur Respir J.* 1994;7(5):954-960.
15. Poser CM, Paty DW, Scheinberg L, et al. New diagnostic criteria for multiple sclerosis: guidelines for research protocols. *Ann Neurol.* 1983;13(3):227-231.
16. McDonald WI, Compston A, Edan G, et al. Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the diagnosis of multiple sclerosis. *Ann Neurol.* 2001;50(1):121-127.
17. Hobart J, Lamping D, Fitzpatrick R, Riazi A, Thompson A. The Multiple Sclerosis Impact Scale (MSIS-29): a new patient-based outcome measure. *Brain.* 2001;124(Pt 5):962-973.

18. Learmonth YC, Motl RW, Sandroff BM, Pula JH, Cadavid D. Validation of patient determined disease steps (PDDS) scale scores in persons with multiple sclerosis. *BMC Neurol.* 2013;13(1):37.
19. Costelloe L, O'Rourke K, Kearney H, et al. The patient knows best: significant change in the physical component of the Multiple Sclerosis Impact Scale (MSIS-29 physical). *J Neurol Neurosurg Psychiatry.* 2007;78(8):841-844.
20. Manouchehrinia A, Edwards LJ, Roshanisefat H, Tench CR, Constantinescu CS. Multiple sclerosis course and clinical outcomes in patients with comorbid asthma: a survey study. *BMJ Open.* 2015;5(5):e007806.
21. Marrie RA, Goldman M. Validity of performance scales for disability assessment in multiple sclerosis. *Mult Scler.* 2007;13(9):1176-1182.
22. Hedstrom A, Hillert J, Olsson T, Alfredsson L. Nicotine might have a protective effect in the etiology of multiple sclerosis. *Mult Scler.* 2013;19(8):1009-1013.
23. Marrie RA, Cutter G, Tyry T, Campagnolo D, Vollmer T. Smoking status over two years in patients with multiple sclerosis. *Neuroepidemiology.* 2009;32(1):72-79.
24. Friend KB, Mernoff ST, Block P, Reeve G. Smoking rates and smoking cessation among individuals with multiple sclerosis. *Disability and Rehabilitation.* 2006;28(18):1135-1141.
25. McKay KA, Tremlett H, Fisk JD, et al. Adverse health behaviours are associated with depression and anxiety in multiple sclerosis: A prospective multisite study. *Mult Scler.* 2015.
26. Westerlind H, Bostrom I, Stawiarz L, Landtblom AM, Almqvist C, Hillert J. New data identify an increasing sex ratio of multiple sclerosis in Sweden. *Mult Scler.* 2014;20(12):1578-1583.
27. Hiscock R, Bauld L, Amos A, Fidler JA, Munafo M. Socioeconomic status and smoking: a review. *Ann N Y Acad Sci.* 2012;1248:107-123.
28. Ditre JW, Langdon KJ, Kosiba JD, Zale EL, Zvolensky MJ. Relations between pain-related anxiety, tobacco dependence, and barriers to quitting among a community-based sample of daily smokers. *Addict Behav.* 2015;42:130-135.
29. Goesling J, Brummett CM, Meraj TS, Moser SE, Hassett AL, Ditre JW. Associations Between Pain, Current Tobacco Smoking, Depression, and Fibromyalgia Status Among Treatment-Seeking Chronic Pain Patients. *Pain Med.* 2015;16(7):1433-1442.
30. Novy DM, Lam C, Gritz ER, Hernandez M, Driver LC, Koyyalagunta D. Distinguishing features of cancer patients who smoke: pain, symptom burden, and risk for opioid misuse. *J Pain.* 2012;13(11):1058-1067.
31. Weber T, Boggero IA, Carlson CR, Bertoli E, Okeson JP, de Leeuw R. Smoking and Posttraumatic Stress Disorder Symptomatology in Orofacial Pain. *J Dent Res.* 2016;95(10):1161-1168.
32. Scalfari A, Neuhaus A, Degenhardt A, et al. The natural history of multiple sclerosis: a geographically based study 10: relapses and long-term disability. *Brain.* 2010;133(Pt 7):1914-1929.
33. Koch M, van Harten A, Uyttenboogaart M, De Keyser J. Cigarette smoking and progression in multiple sclerosis. *Neurology.* 2007;69(15):1515-1520.
34. Mons U, Muezzinler A, Gellert C, et al. Impact of smoking and smoking cessation on cardiovascular events and mortality among older adults: meta-analysis of individual

participant data from prospective cohort studies of the CHANCES consortium. *Bmj-British Medical Journal.* 2015;350.
35. Power MC, Deal JA, Sharrett AR, et al. Smoking and white matter hyperintensity progression The ARIC-MRI Study. *Neurology.* 2015;84(8):841-848.
36. Karama S, Ducharme S, Corley J, et al. Cigarette smoking and thinning of the brain's cortex. *Mol Psychiatry.* 2015;20(6):778-785.
37. Koch MW, Metz LM, Kovalchuk O. Epigenetic changes in patients with multiple sclerosis. *Nature Reviews Neurology.* 2013;9(1):35-43.
38. Zeilinger S, Kuhnel B, Klopp N, et al. Tobacco smoking leads to extensive genome-wide changes in DNA methylation. *PLoS One.* 2013;8(5):e63812.
39. Guida F, Sandanger TM, Castagne R, et al. Dynamics of smoking-induced genome-wide methylation changes with time since smoking cessation. *Human Molecular Genetics.* 2015;24(8):2349-2359.
40. Marrie R, Horwitz R, Cutter G, Tyry T, Campagnolo D, Vollmer T. High frequency of adverse health behaviors in multiple sclerosis. *Mult Scler.* 2009;15(1):105-113.
41. Borghi M, Cavallo M, Carletto S, et al. Presence and significant determinants of cognitive impairment in a large sample of patients with multiple sclerosis. *PLoS One.* 2013;8(7):e69820.
42. Jongen PJ, Wesnes K, van Geel B, et al. Does Self-Efficacy Affect Cognitive Performance in Persons with Clinically Isolated Syndrome and Early Relapsing Remitting Multiple Sclerosis? *Mult Scler Int.* 2015;2015:960282.
43. Turner AP, Hawkins EJ, Haselkorn JK, Kivlahan DR. Alcohol misuse and multiple sclerosis. *Arch Phys Med Rehabil.* 2009;90(5):842-848.
44. Hadjimichael O, Vollmer T, Oleen-Burkey M, North American Research Committee on Multiple S. Fatigue characteristics in multiple sclerosis: the North American Research Committee on Multiple Sclerosis (NARCOMS) survey. *Health Qual Life Outcomes.* 2008;6:100.
45. Bonevski B, Randell M, Paul C, et al. Reaching the hard-to-reach: a systematic review of strategies for improving health and medical research with socially disadvantaged groups. *BMC Med Res Methodol.* 2014;14:42.
46. Goldberg M, Chastang JF, Leclerc A, et al. Socioeconomic, demographic, occupational, and health factors associated with participation in a long-term epidemiologic survey: a prospective study of the French GAZEL cohort and its target population. *Am J Epidemiol.* 2001;154(4):373-384.

Tables

Table 1: The median (interquartile range) MSIS-29 and PDDS scores by smoking status at the time of study.

	Never smoked	Ex-smokers	Current smokers	P-value *
MSIS-29 overall scale	2.72 (1.93-3.48)	3.19 (2.31-3.79)	3.10 (2.31-3.93)	< 0.001
MSIS-29 physical	2.85 (1.95-3.55)	3.25 (2.35-3.95)	3.35 (2.25-4.15)	< 0.001
MSIS-29 psychological	2.33 (1.67-3.32)	2.89 (2-3.67)	3.11 (2.11-3.67)	< 0.001
PDDS	4 (2-6)	5 (3-6)	5 (3-6)	0.02

* P-values from Kruskal–Wallis one-way analysis of variance for differences between never-, ex- and current smokers.
MSIS-29: Multiple Sclerosis Impact Scale; PDDS: Patient Determined Disease Steps.

Table 2: Coefficients of differences in median MSIS-29 and PDDS scores between non-, ex- and current smokers.

	Median overall MSIS-29 score *	**Median MSIS-29 physical score ***	**Median MSIS-29 Psychological score ***	**Median PDDS score ***
Non-smokers	Ref.	Ref.	Ref.	Ref.
Ex-smokers	0.33 (0.12 to 0.53)	0.32 (0.02 to 0.61)	0.56 (0.18 to 0.94)	0.35 (-0.05 to 0.75)
Current smokers	0.47 (0.14 to 0.80)	0.59 (0.24 to 0.94)	0.80 (0.42 to 1.19)	0.99 (0.53 to 1.43)

* Coefficients from median regression models adjusted for disease duration, disease initial phenotype, sex, age at disease onset and exposure to disease modifying treatments. MSIS-29: Multiple Sclerosis Impact Scale; PDDS: Patient Determined Disease Steps.

Table 3: Hazard ratios of reaching EDSS scores 4 and 6

	Hazard of reaching EDSS 4.0 †	**Hazard of reaching EDSS 6.0** †
Non-smokers	Ref.	Ref.
Ex-smokers	1.09 (0.81 to 1.46)	0.96 (0.69 to 1.32)
Current smokers	2.42 (1.63 to 3.60)	1.86 (1.19 to 2.91)
Years elapsed from smoking cessation ‡	0.96 (0.95 to 0.97)	0.97 (0.95 to 0.98)

† Hazard ratios from Cox regression models adjusted for disease initial phenotype, sex, exposure to disease modifying treatment and pack-years smoked.
‡ Hazard ratios from Cox regression models adjusted for disease initial phenotype, sex, smoking intensity and exposure to disease modifying treatments.
EDSS: Expanded Disability Status Scale.

Figure titles

Figure 1. Flow chart of the questionnaires included in the study

Figure 2. Kaplan-Meier plots of age at EDSS scores 4 and 6. P-values from log-ranked tests of equality of survival.