The impact of smoking cessation on multiple sclerosis disease progression

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Abstract

The negative impact of smoking in MS is well established, however, there is much less evidence as to whether smoking cessation is beneficial to progression in MS.

Adults with MS registered on the United Kingdom MS Register (2011-2020) formed this retrospective and prospective cohort study. Primary outcomes were changes in 3 patient reported outcomes (PROs): normalised MS Physical Impact Scale (MSIS-29-Phys), normalised MS Walking Scale (MSWS-12) and the Hospital Anxiety and Depression Scale (HADS-Anxiety and HADS-Depression). Time to event outcomes were clinically significant increases in the PROs.

7983 participants were included, 4130 (51.7%) of these had ever smoked; of whom 1315 (16.5%) were current smokers and 2815/4130 (68.2%) were former smokers. For all PROs, current smokers at the time of completing their first questionnaire had higher PRO scores indicating higher disability compared to those who had never smoked (~10 points difference in MSIS-29-Phys and MSWS-12; 1.5-1.8 point for HADS-anxiety and HADS-depression). There was no improvement in PRO scores with increasing time since quitting in former smokers.

923 participants formed the prospective parallel group, which demonstrated that MSIS-29-phy 5.03, [3.71, 6.34], MSWS-12 5.28, [3.62, 6.94] and HADS-depression 0.71, [0.47, 0.96] worsened over a period of 4 years, whereas HADS-anxiety remained stable. Smoking status was significant at year 4; current smokers had higher MSIS-29-Phys and HADS-Anxiety scores

(3.05 [0.22, 5.88], 1.14 [0.52,1.76]) while former smokers had a lower MSIS-29 score of -2.91[-5.03, -0.79].

4642 participants comprised the time to event analysis. Still smoking was associated with a shorter time to worsening event in all PROs (MSIS-29-Phys: n=4436, p=0.0013; MSWS-12: n=3902, p=0.0061; HADS-anxiety: n=4511, p=0.0017; HADS-depression: n=4511, p<0.0001). Worsening in motor disability (MSIS-29-Phys and MSWS-12) was independent of baseline HADS-anxiety and HADS-depression scores. There was no statistically significant difference in the rate of worsening between never and former smokers.

When smokers quit, there is a slowing in the rate of motor disability deterioration so that it matches the rate of motor decline in those who have never smoked. This suggests that smoking cessation is beneficial for people with MS.

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Abbreviations: ANCOVA = Analysis of Covariance; DMT = Disease Modifying Therapy; EDSS = Expanded Disability Status Scale; HADS = Hospital Anxiety and Depression Scale; IQR = Interquartile Range; MS = Multiple Sclerosis; MSIS-29 = Multiple Sclerosis Impact Scale; MSWS-12 = MS Walking Scale; NHS = National Health Service; PRO = Patient reported outcome; pwMS = people with multiple sclerosis; REC = Research Ethics Committee; SD = Standard Deviation; UKMSR = United Kingdom MS Register

Introduction

Retrospective studies have shown that people with MS (pwMS) who smoke have more significant motor symptoms [1], increased MRI activity and brain atrophy[2,3] and more cognitive and psychological impairment [4,5]. In relapsing MS smoking can lead to earlier death [6], reaching disease milestones earlier [7] and earlier onset of secondary progressive MS [8,9]. While the negative impact of smoking in MS is well established, there is less evidence whether smoking cessation is beneficial. Retrospective analyses have shown that smoking cessation may reduce the risk of reaching disability milestones [9], and quitting earlier is associated with stronger reductions in risk [5]. These milestones, however, are confounded by other factors such as mood [10]

Studying the effects of exposures known to be harmful, such as smoking, poses specific challenges. One approach is to use registry data where the self-directed choice of each study subject determines their exposure. Registry studies are subject to several biases, in particular those associated with geographical and temporal variations in data-collection [11]. Some cross-site and longitudinal stability can be introduced by the use of patient reported outcomes (PROs) in which participants answer questions about certain aspects of their own health. PROs are not widely used as standardised clinical outcome measures in MS and preference has been for tools such as the Expanded Disability Status Scale (EDSS). However, PROs have been shown to be the better predictor of outcome when integrated into a patient-specific, personalised approach [12]. Two validated PROs have established use in assessing the motor impact of MS: the MS walking scale 12 (MSWS-12) [13], and the motor component of the MS impact scale 29 (MSIS-29-Phys) [14]. Clinically relevant changes, corresponding to established EDSS outcomes, have been validated both for the MSWS-12 [15] and the MSIS-29 [16,17]. The MSIS-29 has also been correlated with mortality[18].

The United Kingdom MS Register (UKMSR) is a primarily patient-driven registry of PRO based data that has been active since 2011. We have used UKMSR data from almost 8000 participants to conduct a PRO-based study investigating the effects of smoking, and of smoking cessation, in pwMS. To our knowledge, this represents the largest investigation into the effects of smoking cessation in MS and the largest study of smoking in any neurological disease to use PROs. We have used MSWS-12, MSIS-29-Phys and hospital anxiety and depression scales (HADS) [19]. Firstly, we utilised historical data on smoking and smoking cessation to assess

current impact on functional status. We then used prospectively collected data in the same cohort yearly over 4 years to measure average change in the PROs. Finally, we modelled the PRO results for use in time to event analyses using confirmed clinically relevant worsening events, to dissect out the impact of smoking and smoking cessation on disease progression in MS.

Methods

Population demographics

The UKMSR is an online, UK-wide register supported by National Health Service (NHS) clinical centres (REC: South West Central Bristol NRES 16/SW/0194). The register includes independent verification of treatments and EDSS outcomes from NHS centres in a separate but overlapping population. Participants enter data regularly (3 monthly from 2011 to 2018 and 6 monthly subsequently) and are sent reminders by email. Since September 2018 participants have a 28-day window in which to complete the PROs, although often they are all completed in one day. For this study demographics and disease specific data were assessed at the first questionnaire (baseline) or within 12 months prior or 6 months after completion of the first questionnaire. Demographic data collected included age, gender, ethnicity (Black Asian or minority ethnic group (BAME)/not). Disease-specific data was also obtained, including disease length (in years, from initial symptoms), disease type at diagnosis (secondary and primary progressive/not progressive) and whether the participant was on a disease modifying treatment (DMT) or not for their MS (highly active/normally active/none). Highly active treatments were defined as: alemtuzumab, cladribine, daclizumab, fingolimod, mitoxantrone, natalizumab, crelizumab, ofatumumab, and rituximab. A univariate statistical analysis was completed on these data; Chi-squared test for categorical, one way ANOVA tests for comparison of parametric means and Kruskal-Wallis tests for non-parametric data.

PRO Questionnaires

Three PROs were used: MSIS-29-Phys, MSWS-12 and the HADS scale. The MSIS-29-Phys subscore version 1 (MSIS-29v1[14]) was used prior to April 2012, and version 2 (MSIS-29v2[20]) was used subsequently. Answers to the 20 questions that form the MSIS-29 Phys sub-score are each scored between 1 and 5 in version 1, and between 1 and 4 in version 2. These scores give a total ranging from 20 to 100 for MSIS-29v1, and of 20 to 80 for MSIS-29v2. In order to account for the changes in scales, totals were rescaled to a value in the range of 0 to 100 using

a unity-based normalisation procedure [21]. A 10-point increase in the normalised score corresponds to an 8-point increase in the MSIS-29v1 physical score. This change reflects clinically relevant worsening [16,17]. MSWS-12 version 2 [13] was used to assess walking function. Participants were only excluded from the MSWS-12 assessment if they indicated that they could not walk. The score was normalised as above. A 10-point change in the normalised score corresponds to a 5.4-point change in the raw score which reflects a clinically relevant change [15]. The HADS provides scores for anxiety and depression [19] A 2-point change in either of these sub-scores corresponds to a clinically relevant change [22].

Retrospective and prospective cohort study design

The retrospective analysis was conducted using the population in whom valid data was available for date of birth, gender, and smoking status. Participants needed to have answered at least one of the three PROs and the first questionnaire answered for each PRO was used.

Two approaches were taken for the prospective cohort analysis. In the first, for the 4-year prospective parallel group analysis, participants were identified who had completed each of the 3 PROs at baseline and every year (±60 days) over a 4-year period. Secondly, for the time to event analyses 'streaks' of longitudinal data were obtained from participants who fulfilled specific criteria. To be included in a streak, participants had to have completed at least three sets of PRO questionnaires. The minimum time interval between each questionnaire was 15 days and the maximum interval could not be longer than 240 days. The longest sequence of questionnaires completed by each participant defined by these criteria was selected for each participant. In the event that a participant had more than one longest streak (of equal length), then the most recent was chosen. A separate set of streaks was built for each questionnaire. Clinically significant step changes were used as 'events' for time to event analysis. Information about the time to event was provided from timestamps which were automatically appended by the database tables. Censoring occurred at the date when the PRO score increased by a clinically significant step or, alternatively, when the last questionnaire of the streak was completed. The maximum number of PROs answered was used as a confounding variable in the time to event analysis.

Smoking status

Questions about smoking status were available to answer at any time and were reviewable at the time of every email reminder when the regular battery of PROs were completed. Participants were asked if they had ever smoked and, if they answered yes, whether they

continued to smoke. This provided three distinct categories: never, former, and current smoker. If the participant answered that they had stopped smoking, then the cessation date was requested. The number of cigarettes smoked per day in current and former smokers was also requested. This was classified as light (≤7), moderate (7-12) and heavy (≥13) based on the distribution of the data. Pack years smoked is defined by the rate of daily smoking in percentage of standard 20 cigarette packs multiplied by the total time smoked in days.

Statistical analysis

All statistical analysis was performed using the R statistical programming language, version 3.5.1, in the RStudio environment, version 1.1.463. Boxplots were used to illustrate the retrospective analysis (minimum score, lower quartile, median, upper quartile, maximum score). Generalised linear modelling was used for the retrospective analysis and Cox regression modelling was used to analyse the effects of being a never-, current- and former smoker on the rate of clinically significant events using the 'survival' package (v2.43-3) in R (v3.5.3). Baseline variables considered were age at first assessment, disease length, MS type at diagnosis (progressive as reference vs not progressive), gender (female as reference), ethnicity group (BAME vs white) and pack years smoked. DMT, either highly active, normally active or none, was modelled as a time varying covariate. Linear mixed models for repeated measures were used to analysis the prospective parallel groups using the 'lme4' package (v1.1-7) optimised using restricted maximum likelihood estimates. Dependent variables were the normalised MSIS-29 Phys, MSWS-12, HADS anxiety and depression scores. Fixed effects for time, smoking status, age, gender, time since onset, treatment type, pack years, and ethnicity were added, as well as the interaction terms between time and smoking status. The study participants were included as a random effect. Estimates of the fixed effects and their 95% confidence intervals are reported.

Data availability

Access to the data for this study is available in a secure environment subject to governance approval.

Results

Demographics

Seven thousand nine hundred and eighty-three pwMS who had a valid smoking status and had completed at least one PRO were identified from the UKMSR database (n=16187; valid date

of birth and gender). Details of the excluded population is provided in supplementary Table 1. Four thousand six hundred and forty-two pwMS in turn had the required information to produce a streak of prospective time to event data. For the 4-year prospective parallel cohort analysis 923 pwMS were available given the selection criteria (Table 1). Using simultaneously collected data (N=4591) we confirmed that the MSIS-29-Phys was highly correlated with the MSWS-12 (r=0.87, 95%CI [0.86, 0.87]). MSIS-29 was less so with the HADS-depression (r=0.61, 95%CI [0.59, 0.63]) and HADS-anxiety (r=0.37, 95%CI [0.35, 0.40]). The correlation of the MSWS-12 to the HADS-depression was higher (r=0.50, 95%CI [0.48, 0.53]) than the MSWS-12 correlation with the HADS-anxiety (r=0.21, 95%CI [0.18, 0.23]). HADS-depression and HADS-anxiety was also correlated with each other (r=0.60, 95%CI [0.59, 0.62]).

Smoking prevalence in the UKMSR population

Smoking status was independently verified in our data provided by NHS clinical centres. There were 858 pwMS who had smoking data on both the portal submitted by pwMS and in records collected by their clinical team. Of these, 265 records were independently collected within two months of each other since 2015. In the clinical data 11.0% were current smokers versus 14.7% for the online portal (p = 0.0491); 10 pwMS had told their healthcare team they do not smoke but revealed they did smoke on the portal.

4130/7983 (51.7%) of the total MS population were ever smokers; 1315/7983 (16.5%) were current smokers which is similar to the 10-year average prevalence across the entire UK from 2011 (16.68%, p = 0.619)[23] 2815/4130 (68.2%) of the smokers had stopped at the time of data collection; this proportion is higher than for the total UK population between 2011 and 2019, (57.2%, p = <0.001). In the time to event population, 675/4642 (14.5%) were current smokers and 130/923 (13.7%) of the 4-year prospective population were current smokers. As the populations studied became more selective and required longer follow-up (total > time to event > 4-year parallel group) age and disease length increased as did the proportion of pwMS with progressive diagnoses but also the proportion of males (Table 1).

Retrospective analysis of smoking impact

The total population was used for the retrospective analysis (n=7983; Table 1). For all PROs, those who were current smokers at the time of completing their first questionnaire had higher disability, depression and anxiety compared to those who had never smoked (Figure 1A). Smoking cessation was associated with a range of PRO scores depending on the PRO. HADS-

depression scores were similar in former smokers compared to never smokers (Fig1A-panel 4). MSIS-29-Phys and HADS-anxiety scores were lower in former smokers than those of current smokers but higher than those of never smokers (Fig1A-panels 1 and 3). There was no change in the MSWS-12 scores compared to current smokers (Fig1A-panel 2). In those who were still smoking, heavier smoking burden (light, moderate, heavy) was associated with a higher PRO score in all cases (Figure 1B). In those who were former smokers, the effects of increased smoking burden were still evident except for in the HADS-anxiety score (Figure 1C). PRO score was not correlated with time since quitting in former smokers in all PROs; MSIS-29-Phys (r=0.04, 95%CI [0.003, 0.078], n=2754), MSWS-12 (0.11, 95%CI [0.07, 0.15], n=2581), HADS anxiety Score (-0.19, 95%CI [-0.22, -0.15], n=2779) and HADS depression score (-0.08, 95%CI [-0.11, -0.04], n=2779).

Carrying out a multi variable linear regression adjusting for age at baseline, time since onset, MS type at diagnosis, ethnicity and whether the subject was receiving a DMT (Table 2) confirmed the expected impact of age and disease length and having progressive disease on PRO scores but also demonstrated benefits of being on a DMT and being non-white. The analysis confirmed that smokers had higher PROs scores than never smokers with a mean increase in 4.7 and 3.7 points for the MSIS-29-Phys and MSWS-12 respectively and 0.79 and 0.74 for the HADS-anxiety and depression respectively. There was no significant difference between former smokers and never smokers in any of the PROs. However, for each additional pack year of smoking there was a significant increase in all PROs: 0.19 point for the MSIS-29-Phys, 0.21 point for the MSWS-12 and 0.03 points for both HADS scores indicating a cumulative effect of smoking on disability.

Prospective parallel group analysis of smoking impact over 4 years

To determine the impact of smoking on PROs over the longer term we utilised a subgroup of pwMS (n=923; Table 1) who had completed the PROs every year over 4 years. Average scores were plotted for each category of smoking status (Figure 2). The MSIS-29-phy, MSWS-12 and HADS-depression score worsened over time whereas the HADS anxiety remained stable. Smoking status was significant controlling for time across all PROs. Linear mixed modelling demonstrated that at year 4 MSIS-29-Phys (5.03, [3.71, 6.34]), MSWS-12 (5.28, [3.62, 6.94]), and HADS-Depression (0.71, [0.47, 0.96]) scores increased whereas the HADS-Anxiety did

not change. Being a current smoker was associated with a higher score than never smokers for MSIS-29-Phys 3.05 [0.22, 5.88] and HADS-Anxiety 1.14 [0.52,1.76], whereas former smokers had a lower score at year 4 by -2.91[-5.03, -0.79] MSIS-29-Phys points. Average scores for MSIS-29, MSWS-12 and HADS depression increased steadily for each year after baseline when accounting for both fixed and random effects (see supplementary Table 2 for full results).

Time to event analyses

The prospective time to event analysis was performed using streaks of data created using the criteria described above. Streak length ranged from 180 days to 8 years. Median streak length (in years) for MSIS-29-Phys was 3.22 (interquartile range (IQR) 3.65), MSWS 2.82 (IQR 3.65) and HADS 3.19 (IQR 3.63). Median time (in days) between each questionnaire in the streak was 115 (IQR 77) for the MSIS-29-Phys, 111 (IQR 65) for the MSWS and 114 (IQR 74) for the HADS.

Cumulative event probabilities for time to worsening event were calculated for each PRO (Figures 3 and 4). Cox regression models were created for time to worsening, controlling for age at baseline, gender, baseline score, MS type at diagnosis with DMT treatment as a time-varying covariate (Table 3). Together, these demonstrated that current smoking was associated with a shorter time to worsening of MSIS-29-Phys (Table 3, Figure 3A), MSWS-12 (Table 3, Figure 3B), HADS-anxiety events (Table 3, Figure 4A) and HADS-depression (Table 3, Figure 4B). There was no significant difference in the rate of events between never and former smokers.

The relationship between anxiety, depression and motor events.

The HADS-anxiety and HADS-depression PROs were separately modelled against each motor PRO (Table 4). 1860 participants shared time to event data starting at the same time for all PROs. Using Cox modelling controlling for baseline MSIS-29-Phys (Table 4, column 1) and MSWS-12 (Table 4, column 2) score, age, gender, MS Type at diagnosis, ethnicity and DMT as a time-varying covariate, current smoking was associated with an increased risk of having a higher MSIS-29-Phys and MSWS-12 score independently of the baseline HADS-anxiety and HADS-depression score. An increasing baseline HADS-depression score was independently associated with a worsening of both the MSIS-29-Phys and MSWS-12. Next, we used Cox models to investigate the impact of the MSIS-29-motor on the HADS-anxiety (Table 4, column

3) and HADS-depression scores (Table 4, column 4). In both cases, being a current smoker was associated with a higher MSIS-29-Phys score and HADS-anxiety score controlling for age, gender, MS Type at diagnosis, ethnicity and DMT as a time-varying covariate.

Discussion

The UK MS Register has enabled the identification of a UK wide, community-based registry population of almost 8000 people to demonstrate the benefits of smoking cessation in MS. Smoking is associated with a dose related worsening of motor function and smokers experience an accelerated rate of worsening compared to non-smokers. Once accrued, the damage does not resolve when smoking is stopped. Importantly however, we have shown that, following smoking cessation, there is a deceleration in the rate of motor deterioration so that it matches the rate of motor decline in those who have never smoked.

The use of registry data has allowed us to overcome some of the challenges associated with studying harmful interventions. The use of PROs has, in turn, negated some of the limitations which are associated with registry data. One drawback of registry data is the potential variability associated with data drawn from multiple sites and multiple operators. This variability is particularly true of the EDSS, a quantifiable neurological examination and the most commonly used outcome in MS [24]. The use of validated PROs has allowed a more uniform UK-wide approach to data collection. It is especially reassuring that the retrospective analysis highlights the known benefits of DMTs in MS as this has previously been shown with other registries using the EDSS [25]. Interestingly we found that non-white ethnicity is associated with lower PRO scores. Generally non-white populations have similar disability to white populations. However socioeconomic factors including participation, health literacy and health behaviours differ in non-white populations. As our population is a volunteer population therefore this non-white population could be biased towards those with a better outcome. [26] Furthermore, we have reinforced the appropriateness of PROs in this setting by using a prospective parallel group analysis to show that PROs related to motor disability worsen over 4 years irrespective of smoking status, as has been previously documented with the EDSS.

We have extended the use of PROs by adapting them for use in time to event analyses. Such analyses are common in MS trials [27]. Regular data capture has allowed us to identify a population in whom smoking status can be confirmed at each data timepoint and in whom clinically significant PRO step changes can be identified and timestamped over a period of up to 8 years. PROs tied to clinically relevant outcomes in this way offer the opportunity to determine the interaction with key potential confounders such as depression and anxiety. Here, we have shown that, uniquely among the tested PROs, anxiety does not worsen over time, even though anxiety is higher in current smokers, improves with smoking cessation and is independently associated with the motor score. This implies that anxiety it is not directly linked to MS. Depression on the other hand, does appear to be linked with the disease itself, worsening over time and, notably, deteriorating more rapidly in former smokers compared to never smokers. There is a potential that depression could drive both continued smoking and lack of exercise.

There are several limitations of our study. The UKMSR is predominantly a self-declared register but here we have confirmed smoking status against independent healthcare team verification. Interestingly, we find that the rate of smoking declaration is higher in the self-reported data than in the clinical documentation. This discrepancy raises questions about how clinical teams can target smoking cessation advice if they are not aware of a patient's true smoking status. A further major issue with registries is that selection bias can be augmented when participants are effectively allocating themselves into study groups. Therefore, we cannot exclude the indirect effects of other beneficial health related activity that may go hand in hand with smoking cessation. The UKMSR is representative of the UK MS population [11] but here, by using a subset of the total study population, we find that completing more PROs and with greater regularity is associated with lower rates of smoking. Participants who have completed more PROs also tend to be older, male, and to have more progressive MS. Despite these apparent biases, we are still able to demonstrate the impact of smoking cessation in all populations.

Despite longstanding knowledge that smoking is associated with a poor outcome in MS, we show that the rate of smoking in pwMS is on par with the national rates. The number of former smokers is higher than the national average indicating the rates of smoking may have previously been higher still in pwMS in common with prior populations studied [7,9]. This suggests that pwMS may not be receiving sufficient encouragement and support to stop

smoking. This failure is in common with a number of other conditions in which smoking is known to have a negative impact. Recognition of such a failure has led to calls for advice about smoking cessation to be included in standard clinical guidelines for relevant diseases [28] and adds to the arguments for generating evidence for the effectiveness of smoking cessation interventions [29]. Here we have provided further impetus for pwMS to stop smoking by showing that the rate of motor deterioration is not only accelerated in smokers, but that it returns to the rate of deterioration in non-smokers following smoking cessation.

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BS - Writing - Review & Editing (supporting), Data Curation (supporting), Funding acquisition (supporting)

AS - Writing - Review & Editing (supporting), Data Curation (supporting), Funding acquisition (supporting)

HW - Writing - Review & Editing (supporting), Data Curation (supporting), Funding acquisition (supporting)

DVF - DVF - Writing - Review & Editing (supporting), Resources (supporting), Funding acquisition (equal), Project administration (supporting)
RMM - Conceptualization (equal), Investigation (supporting), Resources (lead), Data Curation (supporting), Supervision (equal), Writing - Original Draft (equal), Writing - Review & Editing (equal), Project administration (equal), Funding acquisition (equal)
RN - Conceptualization (equal), Methodology (equal), Validation (equal), Formal Analysis (equal), Investigation (equal), Data Curation (supporting), Supervision (lead), Writing - Original Draft (equal), Writing - Review & Editing (equal), Project (equal), Funding acquisition (equal), Project administration (equal), Funding acquisition (equal)

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Figure legends

Figure 1. Boxplots demonstrating the effect of smoking cessation **(A)** and smoking amount (light, moderate, heavy) in current **(B)** and former smokers **(C)** for the MSIS-29-phy (panel 1), MSWS-12 (panel 2), HADS-anxiety (panel 3) and HADS-depression (panel 4).

Figure 2. Parallel group analysis of mean change (±standard error) for former (grey line), current (black dashes) and never (light grey dots) smokers. Plots are over 4 years for MSIS-29-Phys (A: n=731:382 never-smokers, 105 current-smokers and 244 former smokers), MSWS-12 (B: n=573: 317 never-smokers, 81 current-smokers and 175 former smokers), HADS-anxiety (C) and HADS-depression (D: n=766: 407 never-smokers, 107 current-smokers and 252 former smokers).

Figure 3. Cumulative event (1-Kaplan-Meier) curves for MSIS-29-phy (A: n=4436) and MSWS-12 (B: n=3902). Being a current smoker (dots) was associated with a higher rate of worsening events in both MSIS-29-Phys (Wald test chi-square, [df=2] =13.32, p=0.0013; median time [95%CI]: 673 days [600, 787]) and MSWS-12 (Wald test chi-square, [df=2] =10.16, p=0.0061; median time 936 days [803, 1135]) compared to never (line; MSIS-phys median time 883 days [819, 960]; MSWS-12 median time 1131 [1035, 1317]) and former smokers (dashes; MSIS-phys median time 829 days [772, 930]; MSWS-12 median time 1250 [1029, 14567]).

Figure 4. Cumulative event (1-Kaplan-Meier) curves for HADS-anxiety (A: n=4511) and HADS-depression (B: n=4511). Being a current smoker (dots) was associated with a higher rate of both HADS-anxiety (Wald test chi-square, [df=2] =12.68, p=0.0017; median time 907 days [742, 1239]) and -depression (Wald test chi-square, [df=2] =54.25, p<0.0001; median time 760 days [629, 934]). PRO worsening events compared to never (line; HADS-anxiety median time 1318 days [1168, 1519]; HADS-depression median time 1392 [1207, 1563]) and former smokers (dashes; HADS-anxiety median time 1318 days [1118, 1483]; HADS-depression median time 1110 [1034, 1270]).

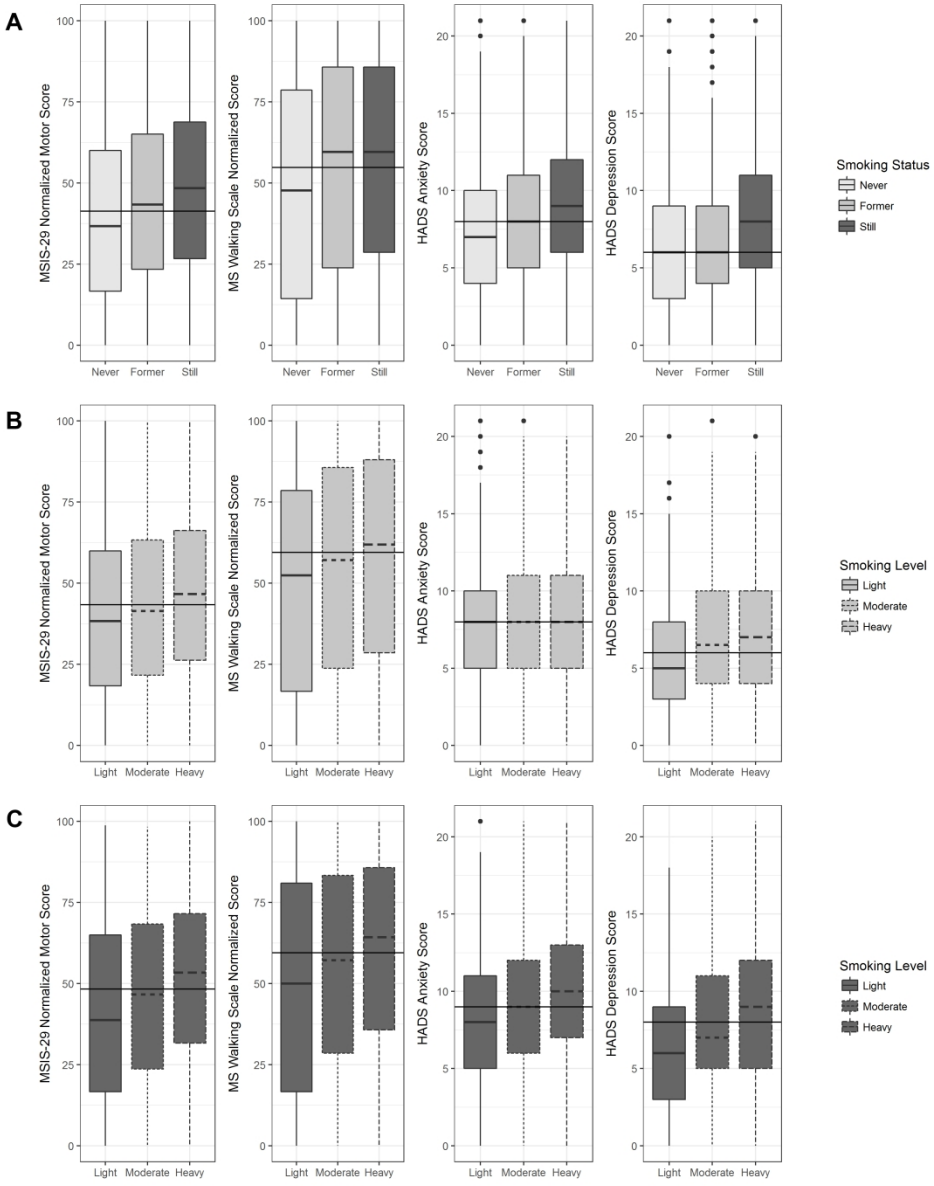

Figure 1

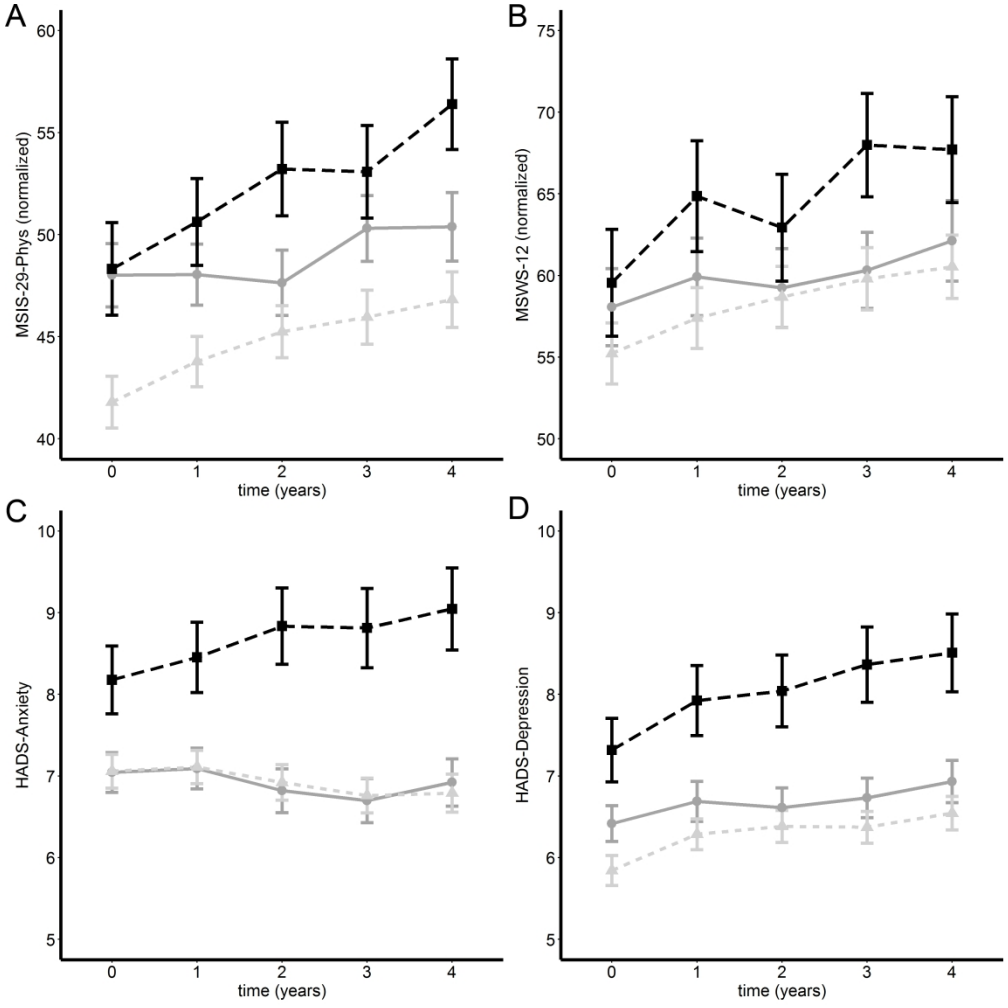

Figure 2

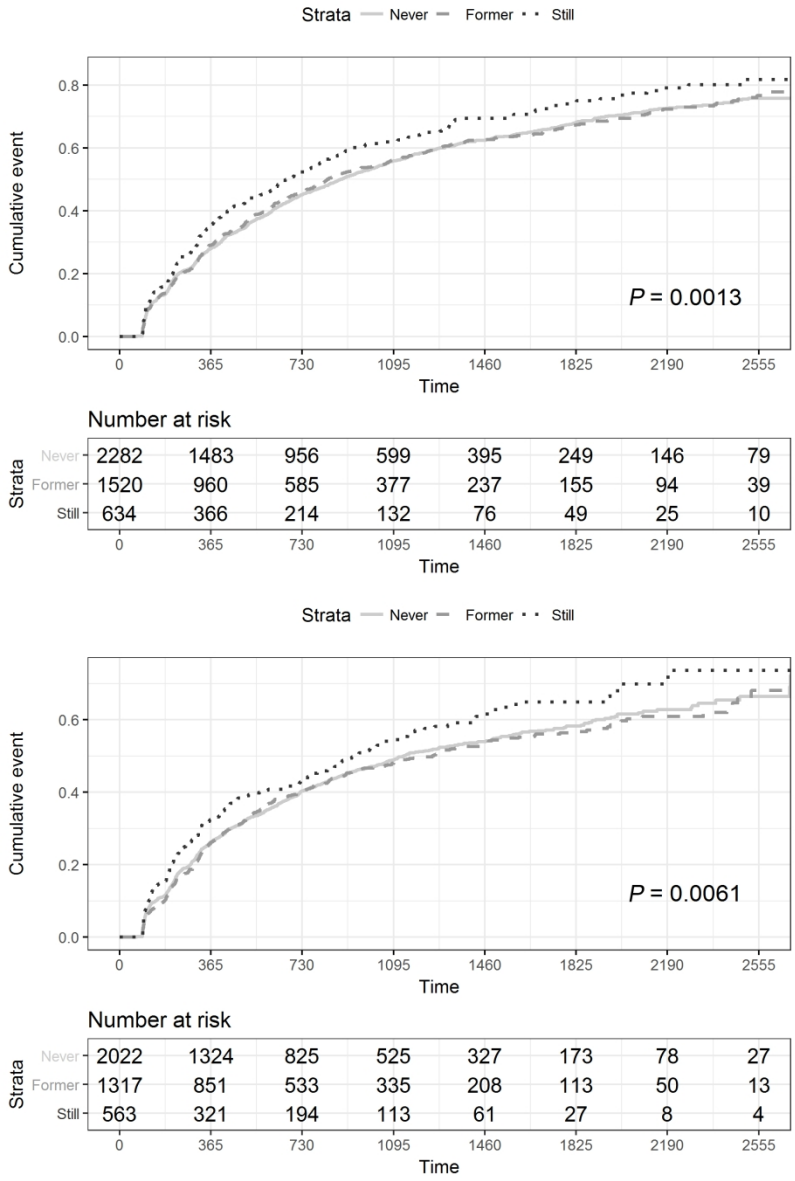

Figure 3

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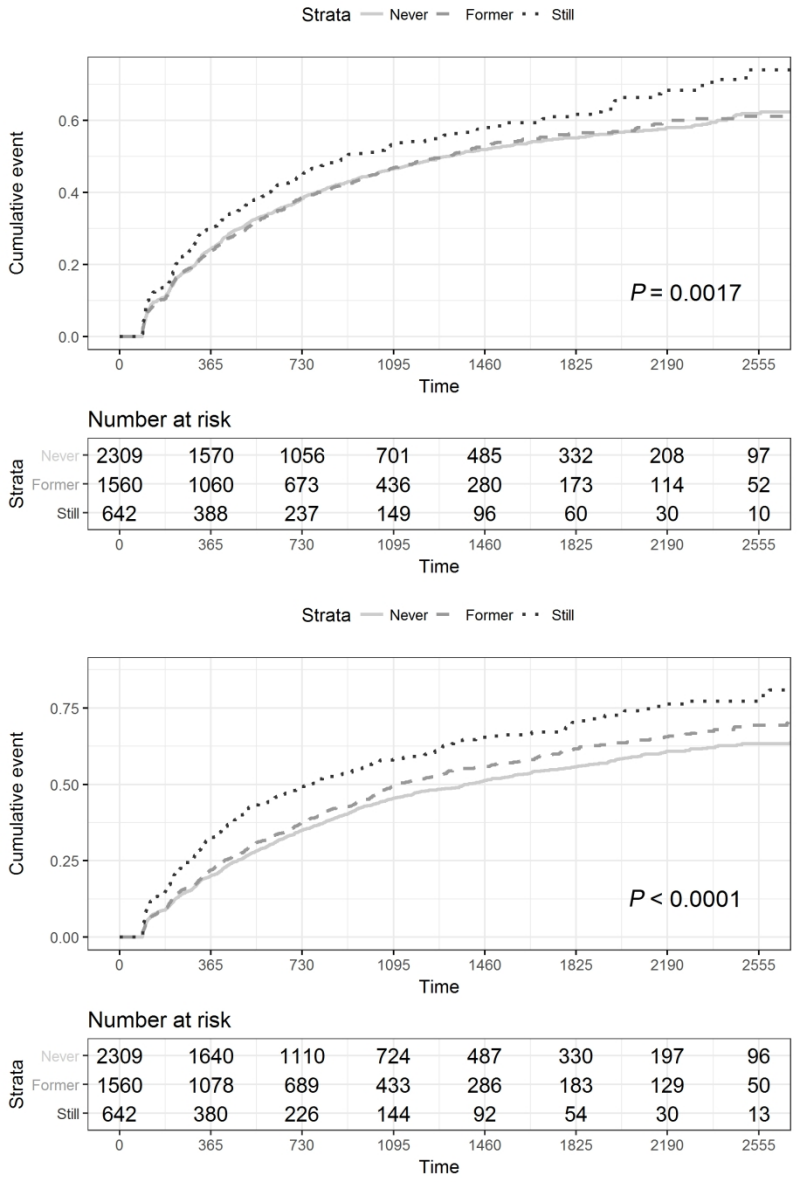

Figure 4

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Table 1 Demographics and PRO outcomes of the total population with a given smoking status (n=7983), the time-to-event (n=4642) and parallel group (n=923) population

	N, smoking status p value			Never			Former			Current		
	Total	Time to event	Parallel	Total	Time to event	Parallel	Total	Time to event	Parallel	Total	Time to event	Parallel
	n below	n below	n below	(n = 3853)	(n = 2378)	(n = 487)	(n = 2815)	(n = 1589)	(n = 309)	(n = 1315)	(n = 675)	(n = 127)
Age at Baseline, mean (SD)	7983	4642	923	48 (11.5)	49.6 (11)	51.5 (10)	50.7 (11.2)	52.6 (10.7)	54.7 (9.8)	45.3 (11.1)	47.3 (10.9)	49.1 (10.6)
Time Since MS Onset, mean (SD)	7826	4596	919	13.3 (10.6)	14.3 (10.8)	16.1 (10.7)	15.6 (11.8)	16.5 (12)	17.5 (11.4)	11.9 (9.8)	13 (10.2)	14.2 (10.5)
Gender: female, N (%)	7983	4642	923	3016 (78.3)	1856 (78)	375 (77)	1934 (68.7)	1070 (67.3)	185 (59.9)	940 (71.5)	457 (67.7)	84 (66.1)
MS at Diagnosis: Known-Progressive, N (%)	7983	4642	923	682 (17.7)	459 (19.3)	116 (23.8)	602 (21.4)	380 (23.9)	98 (31.7)	225 (17.1)	134 (19.9)	32 (25.2)
On DMT: Known-DMT, N (%)	7983	4642	923	1167 (30.3)	810 (34.1)	171 (35.1)	656 (23.3)	407 (25.6)	73 (23.6)	359 (27.3)	209 (31)	41 (32.3)
On Highly Active DMT N(%)	7983	4642	923	59 (1.5)	38 (1.6)	6 (1.2)	38 (1.3)	21 (1.3)	2 (0.6)	25 (1.9)	13 (1.9)	4 (3.1)
Black, Asian and minority ethnic, N (%)	7534	4408	868	271 (7)	137 (5.8)	17 (3.5)	177 (6.3)	75 (4.7)	7 (2.3)	118 (9)	57 (8.4)	9 (7.1)
MSIS-29-Phys, median [IQR]	7840	4436	922	36.7 [16.7–60]	36.7 [18.3–58.6]	40.6 [21.7–61.7]	43.3 [23.3–64.4]	45 [25–65]	48.3 [28.3–66.7]	48.3 [26.7–69.1]	50 [30–70]	48.8 [30–65.6]
MSWS-12, median [IQR]	7318	3902	885	47.6 [14.3–78.6]	50 [16.7–78.6]	61.9 [26.2–85.7]	59.5 [23.8–85.7]	59.5 [26.2–85.7]	71.4 [40.5–90.5]	59.5 [28.6–85.7]	64.3 [31–85.7]	66.7 [39.3–86.9]
HADS Anxiety, median [IQR]	7923	4511	923	7 [4–10]	7 [4–10]	7 [4–10]	8 [5–11]	7 [5–11]	7 [4–9]	9 [6–12]	9 [6–12]	8 [5–11]
HADS Depression, median [IQR]	7923	4511	923	6 [3–9]	6 [3–9]	5 [3–8.5]	6 [4–9]	6 [4–10]	6 [4–9]	8 [5–11]	7 [5–10]	7 [4–10]

SD – standard deviation; IQR –interquartile range.

Table 2 Multivariable linear regression of retrospective data (MSIS-29-Phys n=7840, MSWS-12 n= 7318, HADS n = 7923)

		MSIS-29-Phys		MSWS-12	
		Estimate, 95% CI	p-value	Estimate, 95% CI	p-value
(Intercept)		31.45, [28.45, 34.44]	<0.0001	26.25, [22.36, 30.13]	<0.0001
Smoking status (ref: Never)	Former	−0.21, [−2.12, 1.7]	0.83	−0.63, [−3.11, 1.84]	0.62
	Current	4.65, [1.87, 7.42]	0.001	3.68, [0.09, 7.28]	0.044
Age		0, [−0.07, 0.07]	0.97	0.24, [0.15, 0.32]	<0.0001
Gender (ref: Female)	Male	−0.86, [−2.12, 0.39]	0.18	1.04, [−0.6, 2.68]	0.21
Time since onset		0.54, [0.48, 0.59]	<0.0001	0.7, [0.62, 0.78]	<0.0001
Progressive (ref: No)	Yes	12.67, [11.14, 14.2]	<0.0001	20.9, [18.87, 22.93]	<0.0001
Treatment (Ref: No Treatment)	Normally Active	−5.41, [−6.71, −4.12]	<0.0001	−6.37, [−8.02, −4.72]	<0.0001
	Highly Active	−6.63, [−11.06, −2.2]	0.0034	−6.37, [−11.9, −0.85]	0.024
Black, Asian, Minority Ethnic (ref: No)	Yes	−3.71, [−5.83, −1.59]	0.00059	−5.54, [−8.29, −2.79]	<0.0001
Pack Years		0.19, [0.11, 0.26]	<0.0001	0.21, [0.11, 0.31]	<0.0001
		HADS-Anxiety		HADS-Depression	
(Intercept)		11.79, [11.27, 12.3]	<0.0001	6.7, [6.21, 7.2]	<0.0001
Smoking status (ref: Never)	Former	0.15, [−0.18, 0.47]	0.38	−0.13, [−0.45, 0.18]	0.41
	Current	0.79, [0.31, 1.26]	0.0012	0.74, [0.28, 1.2]	0.0015
Age		−0.09, [−0.1, −0.07]	<0.0001	−0.02, [−0.03, −0.01]	0.00016
Gender (ref: Female)	Male	−0.84, [−1.05, −0.62]	<0.0001	0.06, [−0.14, 0.27]	0.56
Time since onset		0.02, [0.01, 0.03]	0.0031	0.03, [0.02, 0.04]	<0.0001
Progressive (ref: No)	Yes	0.14, [−0.12, 0.4]	0.29	0.81, [0.56, 1.06]	<0.0001
Treatment (Ref: No Treatment)	Normally Active	−0.3, [−0.52, −0.08]	0.0081	−0.52, [−0.74, −0.31]	<0.0001
	Highly Active	−1.52, [−2.27, −0.76]	<0.0001	−1.25, [−1.98, −0.52]	0.00075
Black, Asian, Minority Ethnic (ref: No)	Yes	−0.18, [−0.54, 0.18]	0.32	−0.24, [−0.59, 0.11]	0.18
Pack Years		0.03, [0.01, 0.04]	<0.0001	0.03, [0.02, 0.05]	<0.0001

Table 3 Cox regression models for the time to worsening of the PROs (hazard ratios and 95% confidence intervals)

Hazard ratio,95% CI		MSIS-29-Phys	MSWS-12	HADS-Anxiety	HADS-Depression
Smoking status (ref: Never)	Former	1.02, [0.88, 1.17]	0.97, [0.84, 1.13]	1.02, [0.88, 1.17]	1.01, [0.88, 1.17]
	Still	**1.3, [1.04, 1.62]**	1.16, [0.92, 1.47]	**1.25, [1, 1.57]**	**1.25, [1, 1.56]**
PRO baseline score		0.99, [0.99, 1]	**1, [1, 1.01]**	1, [0.99, 1.01]	1, [0.99, 1.01]
Max number of PROs		1, [0.99, 1.01]	1, [0.99, 1.01]	1, [0.99, 1]	1, [0.99, 1.01]
Age at baseline (Years)		**1, [1, 1.01]**	1, [0.99, 1]	**1, [1, 1.01]**	**1, [1, 1.01]**
Gender (ref: Female)	Male	0.97, [0.88, 1.06]	0.96, [0.87, 1.06]	0.98, [0.89, 1.07]	0.98, [0.89, 1.07]
Time Since Onset (Years)		**1, [1, 1.01]**	1, [0.99, 1]	1, [0.99, 1]	1, [0.99, 1]
Progressive (ref: No)	Yes	**1.22, [1.09, 1.36]**	1.05, [0.94, 1.18]	**1.11, [1, 1.24]**	**1.11, [1, 1.24]**
Treatment (Ref: No Treatment)	Normally Active	1, [0.91, 1.1]	1.06, [0.96, 1.17]	1.03, [0.94, 1.13]	1.03, [0.94, 1.14]
	Highly Active	1.11, [0.77, 1.62]	1.1, [0.76, 1.6]	1.13, [0.77, 1.64]	1.13, [0.78, 1.65]
Black, Asian, Minority Ethnic (ref: No)	Yes	0.86, [0.72, 1.04]	0.85, [0.7, 1.04]	0.88, [0.73, 1.06]	0.88, [0.74, 1.06]
Pack Years		**1, [1, 1.01]**	1, [0.99, 1.01]	1, [0.99, 1.01]	1, [0.99, 1.01]

Table 4 Cox regression models for the time to worsening of the PROs incorporating anxiety and depression (hazard ratios and 95% confidence intervals)

Hazard ratio,95% CI		MSIS-29-Phys	MSWS-12	HADS-Anxiety	HADS-Depression
Smoking status (ref: Never)	Former	1.02, [0.88, 1.18]	0.98, [0.84, 1.14]	1, [0.86, 1.16]	0.99, [0.85, 1.15]
	Still	**1.28, [1.02, 1.6]**	1.16, [0.92, 1.47]	**1.27, [1.01, 1.6]**	1.22, [0.97, 1.55]
MSIS-29-Phys		**0.99, [0.99, 0.99]**		**0.97, [0.96, 0.97]**	**0.96, [0.96, 0.97]**
MSWS-12			**1, [1, 1.01]**	**1.03, [1.02, 1.03]**	**1.03, [1.02, 1.03]**
HADS-Anxiety		0.99, [0.98, 1.01]	0.99, [0.98, 1.01]	1.04, [1.02, 1.05]	
HADS-Depression		**1.05, [1.03, 1.06]**	0.99, [0.98, 1.01]		**1.05, [1.04, 1.07]**
Max MSIS-29		1.02, [0.97, 1.07]		1.02, [0.97, 1.07]	1.01, [0.96, 1.07]
Max MSWS-12			**1.03, [1, 1.05]**	1.01, [0.99, 1.03]	1.01, [0.99, 1.03]
Max HADS		0.98, [0.94, 1.03]	**0.97, [0.96, 0.99]**	0.97, [0.93, 1.03]	0.98, [0.93, 1.03]
Age at baseline		**1, [1, 1.01]**	1, [0.99, 1]	1, [0.99, 1]	1, [0.99, 1]
Gender (ref: Female)	Male	0.94, [0.86, 1.04]	0.96, [0.87, 1.05]	0.94, [0.86, 1.04]	**0.9, [0.82, 0.99]**
Time since onset		**1, [1, 1.01]**	1, [0.99, 1]	1, [0.99, 1]	1, [0.99, 1]
Progressive (ref: No)	Yes	1**.24, [1.12, 1.39]**	1.06, [0.94, 1.19]	1.01, [0.89, 1.13]	1.02, [0.91, 1.15]
Treatment (Ref: No Treatment)	Normally Active	0.99, [0.9, 1.09]	1.05, [0.95, 1.16]	1.03, [0.93, 1.14]	1.02, [0.93, 1.13]
	Highly Active	1.11, [0.76, 1.62]	1.07, [0.73, 1.57]	1.06, [0.74, 1.53]	1.07, [0.75, 1.54]
Black, Asian, Minority Ethnic (ref: No)	Yes	0.86, [0.72, 1.03]	0.85, [0.7, 1.04]	0.87, [0.71, 1.05]	0.87, [0.72, 1.06]
Pack Years		**1, [1, 1.01]**	**1, [1, 1.01]**	**1, [1, 1.01]**	**1, [1, 1.01]**