ORIGINAL ARTICLE

Self-reported cognitive function in a large international cohort of people with multiple sclerosis: associations with lifestyle and other factors

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Background and purpose: We aimed to estimate the prevalence of perceived cognitive impairment (PCI) and explore its associations with lifestyle and disease characteristics in a large international cohort of people with multiple sclerosis (MS).

Methods: This study was a cross-sectional analysis. Participants rated their cognitive function over the preceding 4 weeks using four questions in a subscale within the Multiple Sclerosis Quality of Life questionnaire (MSQOL-54). These questions assessed perceived concentration, attention and memory by the patient and family/friends. Four definitions of PCI were derived, ranging from lowest to highest specificity. Associations with PCI were assessed by log-binomial regression.

Results: The prevalence of PCI in our sample ranged from 41.0% (95% confidence interval, 39.0–43.0) using the least-specific definition to 11.6% (95% confidence interval, 10.3–12.9) using the most specific definition. A number of factors were associated with PCI, increasing in magnitude as the definition specificity increased, including positive associations for smoking and body mass index, whereas physical activity, dietary quality and use of vitamin D/omega-3 supplements were inversely associated with PCI.

Conclusions: Our study reports associations between healthy lifestyle behaviours and PCI in people with MS. Although reverse causality is a potential explanation for our findings, previous studies have shown comparable associations with healthy lifestyle and MS onset and progression. Subject to external validation, these results suggest benefits realized from a healthy lifestyle in people with MS.

Introduction

Cognitive impairment is seen in 40–60% of people with multiple sclerosis (MS) depending on definitions and measurement tools [1]. It occurs more commonly in males [2] and is frequently under-diagnosed [3,4]. Cognitive impairment includes deficits in complex attention, executive functioning, information processing efficiency and speed, and long-term memory [2,5–7]. These disabilities can negatively affect quality of life, employment, education and home life [5]. This is particularly relevant in younger adults with many competing pressures in work and family life [7]. Cognitive impairment and processing speed may be related to the severity and type of MS, i.e. those with

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greater disease progression are more likely to manifest cognitive symptoms, as well as differences between the relapsing-remitting and progressive MS types [6]. Perceived cognitive impairment (PCI) is important in itself, being a major determinant of health-related quality of life and work outcomes [8,9]. Additionally, self-reported cognitive measures can indicate objective cognitive impairment in people with MS [10].

Accurately assessing the prevalence of PCI is difficult, given the variability in how it is defined, either by longitudinal in-clinic assessment or by participant self-reporting symptoms [1]. Treating cognitive impairment in MS is also complex, with pharmacological treatments showing little efficacy in treating or preventing cognitive symptoms. Beyond disease-modifying drugs, an additional strategy may be modification of lifestyle such as physical activity, better diet and avoiding behaviours such as smoking, given their strong protective association against age-related cognitive decline in the general population [11]. Lifestyle factors such as diet, body mass index (BMI), smoking, physical activity and meditation have been associated with MS onset [12,13], as well as general health [14–16], suggesting potential for secondary prevention through lifestyle modification.

This study aimed to estimate the prevalence of PCI in a large international sample of people with MS and to explore associations between lifestyle and other factors with PCI.

Methods

Participants and data collection

Participants were enrolled in the HOLISM study for which methodology has previously been described [17]. Briefly, participants were recruited via online platforms and SurveyMonkey® was used to provide respondents with a participant information sheet, consent indicator and survey. Inclusion criteria required participants to be at least 18 years old and self-reporting a physician diagnosis of MS. The Health Sciences Human Ethics Sub-Committee at the University of Melbourne provided ethical approval (Ethics ID: 1545102) and all participants provided informed consent.

Data collected and tools used

A range of demographic, lifestyle and clinical parameters were queried using validated tools, where possible, as described previously [17], including sun exposure, vitamin D and omega-3 supplement use, biometrics for calculation of BMI and meditation frequency, among others. Physical activity was assessed by the International Physical Activity Questionnaire [18]. Diet was assessed using the Diet Habits Questionnaire, from which an overall diet quality score ranging from 0 to 100 was calculated [19]. Disability was assessed using the Patient-Determined Disease Steps (PDDS) scale [20], which has been validated against the Expanded Disability Status Scale and from which the disease duration-adjusted Patient-Derived Multiple Sclerosis Severity Score (P-MSSS) was calculated [21]. Fatigue was assessed using the Fatigue Severity Scale [22].

Perceived cognitive impairment measure

A subscale within the Multiple Sclerosis Quality of Life questionnaire (MSQOL-54) was used to assess cognitive function [23]. This is an interval scale based on the following four questions.

1 Have you had difficulty concentrating and thinking?
2 Did you have trouble keeping attention on an activity for long?
3 Have you had trouble with your memory?
4 Have others, such as family members or friends, noticed that you have trouble with your memory or problems with your concentration?

Respondents indicated how much of the time in the previous 4 weeks they had experienced each symptom (1 representing all of the time and 6 representing none of the time). We evaluated four definitions of PCI, ranging from those with at least one of the four MSQOL cognition-related parameters ‘a good bit of the time’, ‘most of the time’ or ‘all of the time’ to having all four parameters. Given the poorer specificity of the definition requiring one parameter and the poorer sensitivity of the definition requiring all four parameters, we further examined the middle two definitions, requiring at least two or at least three parameters.

Statistical analysis

Predictors of PCI were assessed by log-binomial regression, estimating a prevalence ratio. The primary adjusted model included adjustment for confounders identified from previous literature [1], i.e. age, sex, level of education completed and level of disability as measured by P-MSSS, except that of disease duration, which was adjusted for PDDS score. All analyses were conducted in STATA/SE 15.0 (Statacorp, College Park, TX, USA).

Results

The total cohort of 2464 participants was largely female (82.3%), with a mean age of 45.5 years and

median PDDS score of 3.0. The cohort generally engaged in healthy behaviours, 58.8% engaging in at least moderate physical activity, only 11.7% smoked tobacco and supplement use was frequent. Apart from a smaller proportion from North America and participants who were single, no covariates significantly differed between those who completed the MSQOL-54 cognition-related questions (n = 2314) and those who did not (n = 150, Table S1).

Distribution and determinants of perceived cognitive impairment (all definitions)

Perceived cognitive impairment decreased from 41.0% (95% confidence interval, 39.0–43.0) using the lowest specificity measure to 11.6% (95% confidence interval, 10.3–12.9) using the most specific measure (Table S2).

A number of factors were significantly associated with PCI, more with the less specific definition and fewer with the more stringent definitions of the outcome. Some of these, such as age and education, both associated with significantly lower frequency of PCI, may reflect participation and measurement biases. The significant associations of disease-related parameters, such as relapse rate, disability and fatigue, with greater frequency of PCI probably reflected covariance with greater disease activity.

Prevalent depression risk was also positively associated with PCI, whereas a greater number of social supports or being partnered were associated with a lower frequency of PCI. Multiple behavioural factors were significantly associated with PCI, including positive associations with smoking and BMI, and inverse associations with physical activity, dietary quality, supplement use and alcohol intake, as well as less consistent associations with meditation.

Determinants of perceived cognitive impairment (third- and second-most specific definitions)

The middle two definitions of PCI, those requiring at least two or at least three cognitive symptoms from the MSQOL-54, were evaluated further by adjustment for age, sex, education, P-MSSS and whether participants had ongoing symptoms from a relapse in the preceding 30 days (Table 1). Some, such as age and education were generally robust to adjustment, indicating independent effects. The associations of physical activity, BMI, alcohol intake, diet and supplement use were largely independent of age, sex, education and disability, whereas the association of smoking was attenuated by about 25% on adjustment, although still significant. The association of meditation, weak and inconsistent alone, was greatly reduced on adjustment, whereas the association of better diet was generally robust to adjustment. Disease-specific qualities, such as relapse frequency, disease trajectory and fatigue, were also largely robust to adjustment, substantiating the interpretation that these associations reflect more active disease being more likely to manifest as PCI. Adjusted associations of BMI (Fig. 1), dietary quality (Fig. 2) and smoking and supplement use (Fig. 3) are also shown graphically, demonstrating the comparability between the two definitions, but also showing the increase in magnitude with little increase in error as specificity is increased. Further adjustment for prevalent depression risk and fatigue attenuated but did not attenuate most associations, except for instances where the predictor was on a similar causal pathway, e.g. BMI and physical activity (attenuated on adjustment for fatigue) and marital status, number of social supports and alcohol intake (attenuated on adjustment for depression risk).

Discussion

The PCI prevalence estimates ranged from 41% using the lowest specificity definition to 11.6% using the highest specificity definition. Although this measure is not an objective clinical assessment of cognitive impairment, it is nonetheless an important outcome, in both the context of its potential indication of clinical cognitive impairment and reflecting the patient's perception of cognitive dysfunction, which is relevant in joint patient–practitioner decision-making. We found associations of multiple lifestyle and clinical covariates with PCI, increasing in magnitude and significance as definition specificity increased, suggesting true associations. Not all factors were causal in nature, however, and may instead reflect measurement/participation biases. However, many factors were strong candidates for causal relationships, including smoking, physical activity, BMI, dietary quality and vitamin D and omega-3 supplement use.

Defining perceived cognitive impairment and prevalence estimate comparisons

Current neuropsychological tests for people with MS are time-consuming, require specialist training and are often administered face to face, leading to potential under-diagnosis [3]. Subjective reporting of PCI has been shown to correlate with objective testing in some studies [24], but not in others [25,26]. However, surrogate or self-reported markers for cognitive impairment are frequently used in epidemiological studies.

To assess PCI, we utilized four definitions, ranging from having frequent cognitive symptoms in one domain of the MSQOL-54 to having them in all four.

Table 1 Distribution and determinants of cognitive impairment as defined by third- and second-most specific definition

	Third-most specific (at least two symptoms all of the time, most of the time, good bit of the time) [766 (33.1%; 95% CI, 31.1–35.0)]					Second-most specific (at least three symptoms all of the time, most of the time, good bit of the time) [562 (24.3%; 95% CI, 22.5–26.0)]				
	Not impaired [*n* (%)]	Impaired [*n* (%)]	PR (95% CI) Univariable	PR (95% CI) Adjusted[a]	PR (95% CI) Adjusted[b]	Not impaired [*n* (%)]	Impaired [*n* (%)]	PR (95% CI) Univariable	PR (95% CI) Adjusted[a]	PR (95% CI) Adjusted[b]
Sex										
Male	273 (17.9%)	133 (17.5%)	1.00 (reference)	1.00 (reference)	1.00 (reference)	318 (18.4%)	88 (15.7%)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Female	1256 (82.2%)	627 (82.5%)	1.02 (0.87–1.19)	1.02 (0.88–1.19)	0.94 (0.81–1.10)	1412 (81.6%)	471 (84.3%)	1.15 (0.94–1.41)	1.18 (0.96–1.45)	1.06 (0.87–1.30)
			P = 0.84	*P* = 0.80	*P* = 0.44			*P* = 0.16	*P* = 0.12	*P* = 0.55
Age (years)										
18–38	388 (25.8%)	250 (33.5%)	1.00 (reference)	1.00 (reference)	1.00 (reference)	457 (26.9%)	181 (33.1%)	1.00 (reference)	1.00 (reference)	1.00 (reference)
>38–46	385 (25.6%)	171 (22.9%)	**0.79 (0.67–0.92)**	**0.76 (0.65–0.89)**	**0.81 (0.70–0.94)**	423 (24.9%)	133 (24.3%)	0.84 (0.70–1.02)	**0.80 (0.67–0.97)**	0.88 (0.74–1.06)
>46–54	388 (25.8%)	185 (24.8%)	**0.82 (0.71–0.96)**	**0.78 (0.67–0.91)**	**0.18 (0.70–0.94)**	439 (25.8%)	134 (24.5%)	0.82 (0.68–1.00)	**0.77 (0.63–0.93)**	**0.82 (0.68–0.99)**
>54–87	342 (22.8%)	140 (18.8%)	**0.74 (0.63–0.88)**	**0.73 (0.62–0.87)**	**0.79 (0.67–0.93)**	383 (22.5%)	99 (18.1%)	**0.72 (0.58–0.90)**	**0.72 (0.59–0.89)**	**0.78 (0.64–0.96)**
Trend			***P* = 0.001**	***P* < 0.001**	***P* = 0.005**			***P* = 0.003**	***P* = 0.001**	***P* = 0.017**
Region of residence										
Australasia	580 (37.5%)	217 (28.3%)	1.00 (reference)	1.00 (reference)	1.00 (reference)	659 (37.6%)	138 (24.6%)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Europe	423 (27.3%)	187 (24.4%)	1.13 (0.96–1.33)	1.11 (0.94–1.30)	1.11 (0.95–1.30)	465 (26.5%)	145 (25.8%)	**1.37 (1.12–1.69)**	**1.30 (1.05–1.60)**	**1.27 (1.04–1.55)**
North America	511 (33.0%)	338 (44.1%)	**1.46 (1.27–1.68)**	**1.42 (1.23–1.63)**	**1.33 (1.16–1.53)**	586 (33.5%)	263 (46.8%)	**1.79 (1.49–2.15)**	**1.62 (1.35–1.94)**	**1.50 (1.25–1.79)**
Other	34 (2.2%)	24 (3.1%)	**1.52 (1.10–2.11)**	1.29 (0.94–1.77)	1.04 (0.74–1.45)	42 (2.4%)	16 (2.9%)	**1.59 (1.02–2.48)**	1.27 (0.82–1.96)	1.04 (0.69–1.57)
BMI										
Underweight (<18.5)	72 (4.7%)	23 (3.1%)	0.90 (0.63–1.31)	0.92 (0.64–1.33)	0.92 (0.65–1.31)	77 (4.4%)	18 (3.3%)	1.05 (0.68–1.62)	1.08 (0.71–1.64)	1.05 (0.71–1.56)
Normal (18.5–<25)	897 (58.4%)	328 (43.9%)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1004 (57.8%)	221 (40.3%)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Overweight (25–<30)	331 (21.6%)	192 (25.7%)	**1.37 (1.19–1.59)**	**1.28 (1.11–1.48)**	1.11 (0.96–1.28)	379 (21.8%)	144 (26.3%)	**1.53 (1.27–1.83)**	**1.40 (1.16–1.68)**	1.15 (0.96–1.37)
Obese (≥30)	236 (15.4%)	205 (27.4%)	**1.74 (1.52–1.99)**	**1.56 (1.36–1.79)**	**1.30 (1.13–1.48)**	276 (15.9%)	165 (30.1%)	**2.07 (1.75–2.46)**	**1.83 (1.54–2.17)**	**1.47 (1.24–1.74)**
Trend			***P* < 0.001**	***P* < 0.001**	***P* < 0.001**			***P* < 0.001**	***P* < 0.001**	***P* < 0.001**
Marital status										
Married	955 (62.4%)	438 (58.2%)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1068 (61.85%)	325 (58.7%)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Cohabiting/ partnered	205 (13.4%)	94 (12.5%)	1.00 (0.83–1.20)	0.99 (0.82–1.18)	0.99 (0.84–1.18)	229 (13.3%)	70 (12.6%)	1.00 (0.80–1.26)	0.98 (0.79–1.23)	1.04 (0.85–1.27)
Single	208 (13.6%)	118 (15.7%)	1.15 (0.98–1.36)	1.11 (0.94–1.31)	1.03 (0.88–1.22)	244 (14.1%)	82 (14.8%)	1.08 (0.87–1.33)	1.02 (0.83–1.27)	0.94 (0.76–1.15)
Separated/divorced/ widowed	162 (10.6%)	102 (13.6%)	**1.23 (1.04–1.46)**	1.18 (0.99–1.40)	1.02 (0.85–1.22)	187 (10.8%)	77 (13.9%)	**1.25 (1.01–1.54)**	1.15 (0.92–1.43)	0.96 (0.77–1.21)
Social supports in place										
0–1	361 (24.2%)	230 (31.9%)	1.00 (reference)	1.00 (reference)	1.00 (reference)	417 (24.7%)	174 (33.0%)	1.00 (reference)	1.00 (reference)	1.00 (reference)
≥2	1132 (75.8%)	490 (68.1%)	**0.78 (0.69–0.88)**	**0.80 (0.70–0.90)**	0.95 (0.85–1.07)	1269 (75.3%)	353 (67.0%)	**0.74 (0.63–0.86)**	**0.76 (0.65–0.89)**	0.94 (0.81–1.09)
			***P* < 0.001**	***P* < 0.001**	*P* = 0.43			***P* < 0.001**	***P* < 0.001**	*P* = 0.39
Employment status										
Working full-time	550 (36.4%)	204 (27.4%)	1.00 (reference)	1.00 (reference)	1.00 (reference)	610 (35.7%)	144 (26.3%)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Working part-time	376 (24.9%)	121 (16.2%)	0.90 (0.74–1.09)	0.92 (0.76–1.11)	0.89 (0.74–1.07)	414 (24.2%)	83 (15.2%)	0.87 (0.68–1.12)	0.89 (0.69–1.13)	0.85 (0.67–1.08)
Stay at home parent/carer	114 (7.5%)	60 (8.1%)	**1.28 (1.01–1.61)**	1.19 (0.95–1.50)	1.12 (0.89–1.39)	129 (7.5%)	45 (8.2%)	**1.35 (1.01–1.81)**	1.23 (0.93–1.63)	1.13 (0.87–1.48)
Full-time student	35 (2.3%)	20 (2.7%)	1.34 (0.93–1.94)	1.04 (0.70–1.54)	**1.46 (1.02–2.10)**	43 (2.5%)	12 (2.2%)	1.14 (0.68–1.93)	0.79 (0.43–1.43)	1.13 (0.64–1.99)

(continued)

Table 1 *(Continued)*

	Third-most specific (at least two symptoms all of the time, most of the time, good bit of the time) [766 (33.1%; 95% CI, 31.1–35.0)]					Second-most specific (at least three symptoms all of the time, most of the time, good bit of the time) [562 (24.3%; 95% CI, 22.5–26.0)]				
	Not impaired [*n* (%)]	Impaired [*n* (%)]	PR (95% CI) Univariable	PR (95% CI) Adjusted[a]	PR (95% CI) Adjusted[b]	Not impaired [*n* (%)]	Impaired [*n* (%)]	PR (95% CI) Univariable	PR (95% CI) Adjusted[a]	PR (95% CI) Adjusted[b]
Unemployed, seeking	44 (2.9%)	31 (4.2%)	**1.53 (1.14–2.05)**	**1.45 (1.08–1.95)**	1.29 (0.97–1.72)	53 (3.1%)	22 (4.0%)	**1.54 (1.05–2.25)**	1.45 (0.99–2.11)	1.28 (0.90–1.82)
Unemployed, not seeking	60 (4.0%)	40 (5.4%)	**1.48 (1.13–1.93)**	1.27 (0.94–1.71)	1.14 (0.85–1.52)	70 (4.1%)	30 (5.5%)	**1.57 (1.13–2.19)**	1.36 (0.95–1.96)	1.13 (0.80–1.61)
Retired due to age	65 (4.3%)	6 (0.8%)	**0.31 (0.14–0.68)**	**0.40 (0.18–0.86)**	**0.41 (0.20–0.84)**	67 (3.9%)	4 (0.7%)	**0.30 (0.11–0.77)**	0.41 (0.16–1.09)	0.42 (0.17–1.05)
Retired for medical reasons	269 (17.8%)	263 (35.3%)	**1.83 (1.58–2.11)**	**1.79 (1.52–2.10)**	**1.39 (1.19–1.63)**	325 (19.0%)	207 (37.8%)	**2.04 (1.70–2.44)**	**2.02 (1.65–2.48)**	**1.48 (1.22–1.79)**
Level of education completed										
None/primary/ secondary	320 (20.8%)	243 (31.9%)	1.00 (reference)	1.00 (reference)	1.00 (reference)	373 (21.4%)	190 (33.9%)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Vocational school	217 (14.1%)	155 (20.3%)	0.97 (0.83–1.13)	0.98 (0.84–1.14)	1.02 (0.88–1.19)	258 (14.8%)	114 (20.4%)	0.91 (0.75–1.10)	0.93 (0.77–1.13)	1.00 (0.83–1.21)
Bachelor's degree	595 (38.6%)	237 (31.1%)	**0.66 (0.57–0.76)**	**0.70 (0.61–0.81)**	**0.81 (0.70–0.93)**	667 (38.2%)	165 (29.5%)	**0.59 (0.49–0.70)**	**0.62 (0.52–0.75)**	**0.76 (0.64–0.91)**
Post-graduate study	410 (26.6%)	128 (16.8%)	**0.55 (0.46–0.66)**	**0.59 (0.49–0.71)**	**0.72 (0.60–0.86)**	447 (25.6%)	91 (16.3%)	**0.50 (0.40–0.63)**	**0.57 (0.45–0.70)**	**0.74 (0.60–0.92)**
Trend			***P* < 0.001**	***P* < 0.001**	***P* < 0.001**			***P* < 0.001**	***P* < 0.001**	***P* = 0.001**
Smoke tobacco currently?										
No	1408 (92.1%)	603 (80.6%)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1576 (91.2%)	435 (79.2%)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Yes	121 (7.9%)	145 (19.4%)	**1.82 (1.60–2.07)**	**1.46 (1.28–1.68)**	**1.22 (1.06–1.41)**	152 (8.8%)	114 (20.8%)	**1.98 (1.69–2.33)**	**1.53 (1.29–1.82)**	**1.25 (1.05–1.49)**
			***P* < 0.001**	***P* < 0.001**	***P* = 0.005**			***P* < 0.001**	***P* < 0.001**	***P* = 0.011**
Alcohol intake										
Non-drinker	248 (16.3%)	165 (22.0%)	1.00 (reference)	1.00 (reference)	1.00 (reference)	288 (16.7%)	125 (22.8%)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Rarely	364 (23.9%)	213 (28.4%)	0.93 (0.79–1.08)	1.00 (0.85–1.17)	0.96 (0.82–1.12)	414 (24.0%)	163 (29.7%)	0.93 (0.77–1.14)	1.01 (0.83–1.23)	0.98 (0.81–1.19)
<Once per week	206 (13.5%)	110 (14.7%)	0.87 (0.72–1.06)	0.98 (0.81–1.18)	1.00 (0.83–1.19)	238 (13.8%)	78 (14.2%)	0.82 (0.64–1.04)	0.93 (0.73–1.18)	0.96 (0.76–1.21)
1–3 days per week	408 (26.8%)	156 (20.8%)	**0.69 (0.58–0.83)**	**0.79 (0.66–0.95)**	0.88 (0.74–1.05)	457 (26.5%)	107 (19.5%)	**0.63 (0.50–0.79)**	**0.73 (0.58–0.91)**	0.87 (0.70–1.09)
4–7 days per week	298 (19.6%)	105 (14.0%)	**0.65 (0.53–0.80)**	**0.80 (0.65–0.97)**	0.86 (0.71–1.04)	328 (19.0%)	75 (13.7%)	**0.62 (0.48–0.79)**	**0.77 (0.60–1.00)**	0.86 (0.67–1.11)
Trend			***P* < 0.001**	***P* = 0.002**	*P* = 0.12			***P* < 0.001**	***P* = 0.002**	*P* = 0.17
Physical activity, by IPAQ										
Low activity	560 (37.5%)	354 (48.8%)	1.00 (reference)	1.00 (reference)	1.00 (reference)	644 (38.1%)	270 (51.0%)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Moderate activity	495 (33.1%)	211 (29.1%)	**0.77 (0.67–0.89)**	0.87 (0.76–1.01)	1.04 (0.91–1.19)	559 (33.0%)	147 (27.8%)	**0.71 (0.59–0.84)**	**0.81 (0.68–0.97)**	1.01 (0.85–1.20)
High activity	440 (29.4%)	161 (22.2%)	**0.69 (0.59–0.81)**	**0.77 (0.66–0.91)**	1.04 (0.89–1.21)	489 (28.9%)	112 (21.2%)	**0.63 (0.52–0.77)**	**0.72 (0.59–0.88)**	1.04 (0.85–1.26)
Trend			***P* < 0.001**	***P* = 0.003**	*P* = 0.50			***P* < 0.001**	***P* = 0.003**	*P* = 0.63
How often in preceding 12 months have you got adequate sun exposure?										
Never/<once per week	432 (31.0%)	218 (32.3%)	1.00 (reference)	1.00 (reference)	1.00 (reference)	499 (31.6%)	151 (30.7%)	1.00 (reference)	1.00 (reference)	1.00 (reference)
1–2 times per week	393 (28.2%)	197 (29.2%)	1.00 (0.85–1.17)	0.99 (0.85–1.15)	0.99 (0.86–1.15)	438 (27.8%)	152 (30.9%)	1.11 (0.91–1.35)	1.11 (0.91–1.34)	1.14 (0.95–1.38)
3–4 times per week	311 (22.3%)	129 (19.1%)	0.87 (0.73–1.05)	0.88 (0.73–1.05)	0.92 (0.78–1.10)	347 (22.0%)	93 (18.9%)	0.91 (0.72–1.14)	0.93 (0.74–1.17)	1.01 (0.81–1.25)
5–6 times per week	150 (10.8%)	67 (9.9%)	0.92 (0.73–1.16)	0.90 (0.71–1.13)	0.98 (0.78–1.23)	166 (10.5%)	51 (10.4%)	1.01 (0.77–1.34)	1.04 (0.79–1.36)	1.15 (0.87–1.51)
Every day	109 (7.8%)	63 (9.4%)	1.09 (0.87–1.37)	1.01 (0.81–1.26)	1.00 (0.81–1.23)	127 (8.1%)	45 (9.2%)	1.13 (0.85–1.50)	1.04 (0.79–1.37)	1.07 (0.82–1.40)
Trend			*P* = 0.79	*P* = 0.47	*P* = 0.76			*P* = 0.90	*P* = 0.91	*P* = 0.66

(continued)

Table 1 *(Continued)*

	Third-most specific (at least two symptoms all of the time, most of the time, good bit of the time) [766 (33.1%; 95% CI, 31.1–35.0)]					Second-most specific (at least three symptoms all of the time, most of the time, good bit of the time) [562 (24.3%; 95% CI, 22.5–26.0)]				
	Not impaired [*n* (%)]	Impaired [*n* (%)]	PR (95% CI) Univariable	PR (95% CI) Adjusted[a]	PR (95% CI) Adjusted[b]	Not impaired [*n* (%)]	Impaired [*n* (%)]	PR (95% CI) Univariable	PR (95% CI) Adjusted[a]	PR (95% CI) Adjusted[b]
At risk of depression as measured by PHQ-2?										
No	1370 (19.5%)	421 (58.6%)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1512 (89.4%)	279 (53.2%)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Yes	127 (8.5%)	298 (41.5%)	**2.98 (2.69–3.31)**	**2.52 (2.25–2.82)**	**2.09 (1.87–2.35)**	180 (10.6%)	245 (46.8%)	**3.70 (3.23–4.24)**	**3.03 (2.62–3.51)**	**1.39 (1.20–1.60)**
			***P* < 0.001**	***P* < 0.001**	***P* < 0.001**			***P* < 0.001**	***P* < 0.001**	***P* < 0.001**
Taking a vitamin D supplement?										
No	270 (17.4%)	190 (24.8%)	1.00 (reference)	1.00 (reference)	1.00 (reference)	307 (17.5%)	153 (27.2%)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Yes	1278 (82.6%)	576 (75.2%)	**0.75 (0.66–0.86)**	**0.86 (0.75–0.98)**	1.03 (0.90–1.18)	1445 (82.5%)	409 (72.8%)	**0.66 (0.57–0.78)**	**0.78 (0.66–0.91)**	0.94 (0.81–1.10)
			***P* < 0.001**	***P* = 0.021**	*P* = 0.66			***P* < 0.001**	***P* = 0.002**	*P* = 0.46
Taking an omega-3 supplement?										
No	499 (32.2%)	378 (49.4%)	1.00 (reference)	1.00 (reference)	1.00 (reference)	590 (33.7%)	287 (51.1%)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Yes	1049 (67.8%)	388 (50.7%)	**0.63 (0.56–0.70)**	**0.72 (0.64–0.80)**	**0.85 (0.76–0.96)**	1162 (66.3%)	275 (48.9%)	**0.59 (0.51–0.67)**	**0.69 (0.60–0.80)**	**0.84 (0.73–0.98)**
			***P* < 0.001**	***P* < 0.001**	***P* = 0.008**			***P* < 0.001**	***P* < 0.001**	***P* = 0.022**
Type of omega-3 supplement used										
None	499 (32.5%)	378 (49.8%)	1.00 (reference)	1.00 (reference)	1.00 (reference)	590 (34.0%)	287 (51.4%)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Fish oil including high potency	570 (37.2%)	236 (31.1%)	**0.68 (0.60–0.78)**	**0.75 (0.66–0.86)**	0.89 (0.78–1.02)	639 (36.8%)	167 (29.9%)	**0.63 (0.54–0.75)**	**0.72 (0.61–0.85)**	0.87 (0.74–1.03)
Flaxseed oil	158 (10.3%)	44 (5.8%)	**0.51 (0.39–0.66)**	**0.60 (0.46–0.79)**	0.78 (0.60–1.01)	171 (9.9%)	31 (5.6%)	**0.47 (0.34–0.66)**	**0.58 (0.41–0.81)**	0.80 (0.59–1.10)
Both fish/flaxseed	307 (20.0%)	101 (13.3%)	**0.57 (0.48–0.69)**	**0.68 (0.57–0.83)**	**0.80 (0.67–0.96)**	335 (19.3%)	73 (13.1%)	**0.55 (0.44–0.69)**	**0.69 (0.55–0.87)**	0.98 (0.64–1.01)
Type of MS at completion of survey										
Benign	77 (5.0%)	19 (2.5%)	**0.59 (0.39–0.89)**	0.77 (0.51–1.15)	0.92 (0.63–1.34)	82 (4.7%)	14 (2.5%)	**0.59 (0.36–0.97)**	0.81 (0.50–1.31)	1.01 (0.64–1.57)
RRMS	943 (61.3%)	476 (62.1%)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1068 (61.3%)	351 (62.5%)	1.00 (reference)	1.00 (reference)	1.00 (reference)
PPMS	117 (7.6%)	50 (6.5%)	0.89 (0.70–1.14)	0.88 (0.68–1.14)	0.79 (0.61–1.02)	135 (7.8%)	32 (5.7%)	0.78 (0.56–1.07)	0.78 (0.55–1.10)	**0.70 (0.50–0.99)**
PRMS	173 (11.2%)	89 (11.6%)	1.01 (0.84–1.22)	1.01 (0.83–1.23)	0.95 (0.79–1.16)	194 (11.1%)	68 (12.1%)	1.05 (0.84–1.31)	1.04 (0.81–1.33)	1.01 (0.80–1.28)
PRMS	27 (1.8%)	19 (2.5%)	1.23 (0.87–1.75)	1.08 (0.74–1.57)	0.91 (0.64–1.28)	32 (1.85%)	14 (2.5%)	1.23 (0.79–1.92)	1.04 (0.64–1.69)	0.83 (0.52–1.32)
Unsure/other	202 (13.1%)	113 (14.8%)	1.07 (0.91–1.26)	1.05 (0.89–1.25)	1.04 (0.88–1.23)	232 (13.3%)	83 (14.8%)	1.07 (0.87–1.31)	1.05 (0.85–1.30)	1.07 (0.87–1.32)
Number of doctor-diagnosed relapses in preceding 12 months										
0	980 (66.4%)	326 (45.2%)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1078 (64.7%)	228 (42.9%)	1.00 (reference)	1.00 (reference)	1.00 (reference)
1	326 (22.1%)	227 (31.4%)	**1.65 (1.43–1.89)**	**1.36 (1.17–1.58)**	**1.31 (1.13–1.52)**	387 (23.2%)	166 (31.3%)	**1.72 (1.45–2.05)**	**1.40 (1.16–1.70)**	**1.35 (1.13–1.62)**
2	120 (8.1%)	105 (14.5%)	**1.87 (1.58–2.21)**	**1.39 (1.15–1.68)**	**1.31 (1.10–1.56)**	143 (8.6%)	82 (15.4%)	**2.09 (1.69–2.57)**	**1.48 (1.18–1.87)**	**1.39 (1.11–1.73)**
≥3	49 (3.3%)	64 (8.9%)	**2.27 (1.88–2.74)**	**1.61 (1.31–1.98)**	**1.44 (1.17–1.78)**	58 (3.5%)	55 (10.4%)	**2.79 (2.23–3.49)**	**1.91 (1.48–2.45)**	**1.72 (1.34–2.21)**
Trend			***P* < 0.001**	***P* < 0.001**	***P* < 0.001**			***P* < 0.001**	***P* < 0.001**	***P* < 0.001**
Number of doctor-diagnosed relapses in preceding 5 years										
0	465 (32.7%)	149 (21.6%)	1.00 (reference)	1.00 (reference)	1.00 (reference)	512 (32.0%)	102 (19.9%)	1.00 (reference)	1.00 (reference)	1.00 (reference)
1	324 (22.8%)	126 (18.3%)	1.15 (0.94–1.42)	1.12 (0.91–1.38)	1.01 (0.83–1.24)	356 (22.2%)	94 (18.4%)	1.26 (0.98–1.62)	1.25 (0.96–1.62)	1.10 (0.86–1.41)
2	294 (20.7%)	133 (19.3%)	**1.28 (1.05–1.57)**	1.17 (0.95–1.44)	1.06 (0.88–1.29)	338 (21.1%)	89 (17.4%)	1.26 (0.97–1.62)	1.12 (0.86–1.47)	1.00 (0.77–1.29)
3	145 (10.2%)	95 (13.8%)	**1.63 (1.32–2.01)**	**1.38 (1.10–1.72)**	1.18 (0.95–1.45)	163 (10.2%)	77 (15.0%)	**1.93 (1.50–2.49)**	**1.61 (1.22–2.12)**	**1.35 (1.04–1.76)**

(continued)

Table 1 *(Continued)*

	Third-most specific (at least two symptoms all of the time, most of the time, good bit of the time) [766 (33.1%; 95% CI, 31.1–35.0)]					Second-most specific (at least three symptoms all of the time, most of the time, good bit of the time) [562 (24.3%; 95% CI, 22.5–26.0)]				
	Not impaired [*n* (%)]	Impaired [*n* (%)]	PR (95% CI) Univariable	PR (95% CI) Adjusted[a]	PR (95% CI) Adjusted[b]	Not impaired [*n* (%)]	Impaired [*n* (%)]	PR (95% CI) Univariable	PR (95% CI) Adjusted[a]	PR (95% CI) Adjusted[b]
4	72 (5.1%)	47 (6.8%)	**1.63 (1.25–2.12)**	1.25 (0.94–1.65)	1.10 (0.84–1.44)	83 (5.2%)	36 (7.0%)	**1.82 (1.32–2.52)**	1.36 (0.96–1.94)	1.13 (0.82–1.57)
≥5	124 (8.7%)	140 (20.3%)	**2.19 (1.83–2.62)**	**1.69 (1.38–2.05)**	**1.27 (1.05–1.54)**	150 (9.4%)	114 (22.3%)	**2.60 (2.08–3.26)**	**1.94 (1.51–2.48)**	**1.42 (1.12–1.80)**
Trend			***P* < 0.001**	***P* < 0.001**	***P* = 0.009**			***P* < 0.001**	***P* < 0.001**	***P* = 0.002**
Doctor-defined disease activity over the previous 12 months										
Decreasing	557 (39.4%)	208 (30.3%)	0.99 (0.84–1.16)	1.08 (0.91–1.27)	0.97 (0.83–1.14)	613 (38.5%)	152 (29.9%)	1.01 (0.83–1.24)	1.09 (0.89–1.33)	0.95 (0.78–1.16)
Stable	548 (38.7%)	209 (30.5%)	1.00 (reference)	1.00 (reference)	1.00 (reference)	608 (38.2%)	149 (29.3%)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Increasing	310 (21.9%)	269 (39.2%)	**1.68 (1.46–1.95)**	**1.45 (1.24–1.69)**	**1.25 (1.08–1.45)**	371 (23.3%)	208 (40.9%)	**1.83 (1.52–2.19)**	**1.47 (1.21–1.78)**	**1.21 (1.01–1.46)**
Trend			***P* < 0.001**	***P* < 0.001**	***P* = 0.001**			***P* < 0.001**	***P* = 0.002**	***P* = 0.013**
Have ongoing symptoms from a relapse in the last 30 days?										
No	1239 (80.0%)	475 (62.0%)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1379 (78.7%)	335 (59.6%)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Yes	309 (20.0%)	291 (38.0%)	**1.75 (1.56–1.96)**	**1.58 (1.41–1.78)**	**1.32 (1.18–1.48)**	373 (21.3%)	227 (40.4%)	**1.94 (1.68–2.23)**	**1.70 (1.47–1.97)**	**1.39 (1.20–1.60)**
			***P* < 0.001**	***P* < 0.001**	***P* < 0.001**			***P* < 0.001**	***P* < 0.001**	***P* < 0.001**
P-MSSS disability										
Mild disability (0–3)	565 (36.9%)	168 (22.3%)	1.00 (reference)	1.00 (reference)	1.00 (reference)	622 (35.9%)	111 (20.2%)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Moderate disability (4–6)	400 (26.1%)	236 (31.3%)	**1.62 (1.37–1.91)**	**1.53 (1.29–1.81)**	**1.20 (1.02–1.41)**	451 (26.0%)	185 (33.6%)	**1.92 (1.56–2.37)**	**1.83 (1.48–2.26)**	**1.35 (1.10–1.66)**
Severe disability (>6)	567 (37.0%)	349 (46.4%)	**1.66 (1.42–1.94)**	**1.54 (1.31–1.81)**	1.04 (0.89–1.22)	662 (38.2%)	254 (46.2%)	**1.83 (1.50–2.24)**	**1.68 (1.36–2.06)**	1.06 (0.86–1.30)
Trend			***P* < 0.001**	***P* < 0.001**	*P* = 0.86			***P* < 0.001**	***P* < 0.001**	*P* = 0.87
Fatigue, as defined by FSS score >35										
No fatigue	644 (44.9%)	87 (12.6%)	1.00 (reference)	1.00 (reference)	1.00 (reference)	686 (42.3%)	45 (8.9%)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Fatigue	792 (55.2%)	606 (87.5%)	**3.64 (2.96–4.48)**	**3.32 (2.68–4.12)**	**2.70 (2.17–3.37)**	935 (57.7%)	463 (91.1%)	**5.38 (4.02–7.21)**	**4.80 (3.52–6.53)**	**3.70 (2.70–5.07)**
			***P* < 0.001**	***P* < 0.001**	***P* < 0.001**			***P* < 0.001**	***P* < 0.001**	***P* < 0.001**
Disease duration (years)										
1–4	592 (38.4%)	276 (36.1%)	1.00 (reference)	1.00 (reference)	1.00 (reference)	673 (38.6%)	195 (34.8%)	1.00 (reference)	1.00 (reference)	1.00 (reference)
>4–7	304 (19.7%)	146 (19.1%)	1.02 (0.87–1.20)	1.15 (0.98–1.35)	1.00 (0.86–1.18)	339 (19.4%)	111 (19.8%)	1.10 (0.90–1.35)	1.22 (1.00–1.50)	0.99 (0.81–1.21)
>7–13	333 (21.6%)	183 (24.0%)	1.12 (0.96–1.30)	**1.25 (1.07–1.46)**	1.06 (0.91–1.23)	377 (21.6%)	139 (24.8%)	1.20 (0.99–1.45)	**1.34 (1.11–1.62)**	1.05 (0.88–1.27)
>13–54	311 (20.2%)	159 (20.8%)	1.06 (0.91–1.25)	**1.26 (1.06–1.50)**	1.07 (0.90–1.26)	355 (20.4%)	115 (20.5%)	1.09 (0.89–1.33)	1.24 (1.00–1.55)	0.94 (0.76–1.16)
Trend			*P* = 0.25	***P* = 0.004**	*P* = 0.43			*P* = 0.19	***P* = 0.011**	*P* = 0.91
Number of comorbidities as defined by SCQ										
0	633 (41.0%)	133 (17.4%)	1.00 (reference)	1.00 (reference)	1.00 (reference)	679 (38.8%)	87 (15.5%)	1.00 (reference)	1.00 (reference)	1.00 (reference)
1	425 (27.5%)	176 (23.0%)	**1.69 (1.38–2.06)**	**1.62 (1.32–1.98)**	**1.40 (1.15–1.71)**	484 (27.7%)	117 (20.8%)	**1.71 (1.33–2.21)**	**1.60 (1.23–2.08)**	**1.30 (1.01–1.69)**
2	281 (18.2%)	188 (24.5%)	**2.31 (1.91–2.79)**	**2.25 (1.86–2.73)**	**1.70 (1.40–2.06)**	335 (19.2%)	134 (23.8%)	**2.52 (1.97–3.21)**	**2.46 (1.92–3.15)**	**1.69 (1.32–2.17)**
≥3	206 (13.3%)	269 (35.1%)	**3.26 (2.74–3.88)**	**2.95 (2.47–3.53)**	**1.91 (1.59–2.31)**	251 (14.4%)	224 (39.9%)	**4.15 (3.33–5.17)**	**3.64 (2.90–4.58)**	**2.14 (1.69–2.71)**
Trend			***P* < 0.001**	***P* < 0.001**	***P* < 0.001**			***P* < 0.001**	***P* < 0.001**	***P* < 0.001**
Taking any of the 11 specified immunomodulatory medications?[c]										
No	813 (52.5%)	370 (48.3%)	1.00 (reference)	1.00 (reference)	1.00 (reference)	920 (52.5%)	263 (46.8%)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Yes	735 (47.5%)	396 (51.7%)	1.12 (1.00–1.26)	**1.14 (1.01–1.28)**	1.04 (0.93–1.17)	832 (47.5%)	299 (53.2%)	**1.19 (1.03–1.37)**	**1.19 (1.03–1.38)**	1.06 (0.92–1.22)
			P = 0.056	***P* = 0.031**	*P* = 0.46			***P* = 0.019**	***P* = 0.020**	*P* = 0.42

(continued)

Table 1 *(Continued)*

	Third-most specific (at least two symptoms all of the time, most of the time, good bit of the time) [766 (33.1%; 95% CI, 31.1–35.0)]					Second-most specific (at least three symptoms all of the time, most of the time, good bit of the time) [562 (24.3%; 95% CI, 22.5–26.0)]				
	Not impaired [*n* (%)]	Impaired [*n* (%)]	PR (95% CI) Univariable	PR (95% CI) Adjusted[a]	PR (95% CI) Adjusted[b]	Not impaired [*n* (%)]	Impaired [*n* (%)]	PR (95% CI) Univariable	PR (95% CI) Adjusted[a]	PR (95% CI) Adjusted[b]
On average, how often meditated in previous 12 months?										
Never	674 (44.7%)	380 (52.3%)	1.00 (reference)	1.00 (reference)	1.00 (reference)	771 (45.3%)	283 (53.5%)	1.00 (reference)	1.00 (reference)	1.00 (reference)
<1 per week	332 (22.0%)	173 (23.8%)	0.95 (0.82–1.10)	0.99 (0.85–1.14)	1.03 (0.90–1.18)	387 (22.7%)	118 (22.3%)	0.87 (0.72–1.05)	0.91 (0.76–1.10)	0.95 (0.80–1.14)
1–2 per week	213 (14.1%)	72 (9.9%)	**0.70 (0.57–0.87)**	**0.76 (0.61–0.94)**	0.90 (0.74–1.10)	229 (13.4%)	56 (10.6%)	**0.73 (0.57–0.95)**	0.80 (0.62–1.04)	0.96 (0.75–1.22)
3–4 per week	123 (8.2%)	37 (5.1%)	**0.64 (0.48–0.86)**	**0.72 (0.54–0.97)**	0.80 (0.59–1.07)	134 (7.9%)	26 (4.9%)	**0.61 (0.42–0.87)**	**0.67 (0.46–0.97)**	0.72 (0.50–1.04)
5-6 per week	67 (4.5%)	22 (3.0%)	**0.69 (0.47–0.99)**	0.72 (0.50–1.05)	0.80 (0.55–1.17)	74 (4.3%)	15 (2.8%)	0.63 (0.39–1.01)	0.71 (0.45–1.13)	0.77 (0.48–1.24)
Every day	98 (6.5%)	42 (5.8%)	0.83 (0.64–1.09)	0.88 (0.68–1.14)	0.98 (0.76–1.26)	109 (6.4%)	31 (5.9%)	0.83 (0.60–1.14)	0.87 (0.63–1.20)	0.94 (0.68–1.31)
			***P* < 0.001**	***P* = 0.007**	*P* = 0.15			***P* = 0.003**	***P* = 0.021**	*P* = 0.16
DHQ total score										
32–70	293 (19.1%)	272 (36.2%)	1.00 (reference)	1.00 (reference)	1.00 (reference)	356 (20.6%)	209 (38.0%)	1.00 (reference)	1.00 (reference)	1.00 (reference)
>70–80	350 (22.9%)	220 (29.3%)	**0.80 (0.70–0.92)**	**0.86 (0.75–0.98)**	0.96 (0.84–1.09)	408 (23.6%)	162 (29.5%)	**0.77 (0.65–0.91)**	**0.82 (0.70–0.97)**	0.94 (0.80–1.11)
>80–90	507 (33.1%)	173 (23.0%)	**0.53 (0.45–0.62)**	**0.63 (0.54–0.73)**	**0.74 (0.63–0.86)**	556 (32.1%)	124 (22.6%)	**0.49 (0.41–0.60)**	**0.60 (0.50–0.73)**	**0.73 (0.61–0.89)**
>90–100	381 (24.9%)	86 (11.5%)	**0.38 (0.31–0.47)**	**0.47 (0.38–0.58)**	**0.66 (0.54–0.81)**	412 (23.8%)	55 (10.0%)	**0.32 (0.24–0.42)**	**0.42 (0.32–0.55)**	**0.62 (0.47–0.80)**
Trend			***P* < 0.001**	***P* < 0.001**	***P* < 0.001**			***P* < 0.001**	***P* < 0.001**	***P* < 0.001**

All results estimated using log-binomial regression estimating prevalence ratio (PR) [95% confidence interval (CI)]. Results in boldface denote statistical significance ($P < 0.05$). BMI, body mass index; DHQ, Diet Habits Questionnaire; FSS, Fatigue Severity Scale; IPAQ, International Physical Activity Questionnaire; MS, multiple sclerosis; PHQ-2, Patient Health Questionnaire-2; P-MSSS, Patient-Derived Multiple Sclerosis Severity Score; PPMS, primary progressive MS; PRMS, progressive-relapsing MS; RRMS, relapsing-remitting MS; SCQ, Self-Administered Comorbidity Questionnaire; SPMS, secondary progressive MS. [a]Adjusted models adjusted for age, sex, education and level of disability as measured by P-MSSS and whether participants were experiencing ongoing symptoms from a relapse in the preceding 30 days. [b]Adjusted models adjusted for age, sex, education and level of disability as measured by P-MSSS, whether participants were experiencing ongoing symptoms from a relapse in the preceding 30 days, fatigue as measured by FSS and depression as measured by PHQ-2. [c]Immunomodulatory medications queried include interferon-beta-based medication, glatiramer acetate, alemtuzumab, cladribine, daclizumab, dimethyl fumarate, fingolimod, laquinimod, rituximab, teriflunomide and natalizumab.

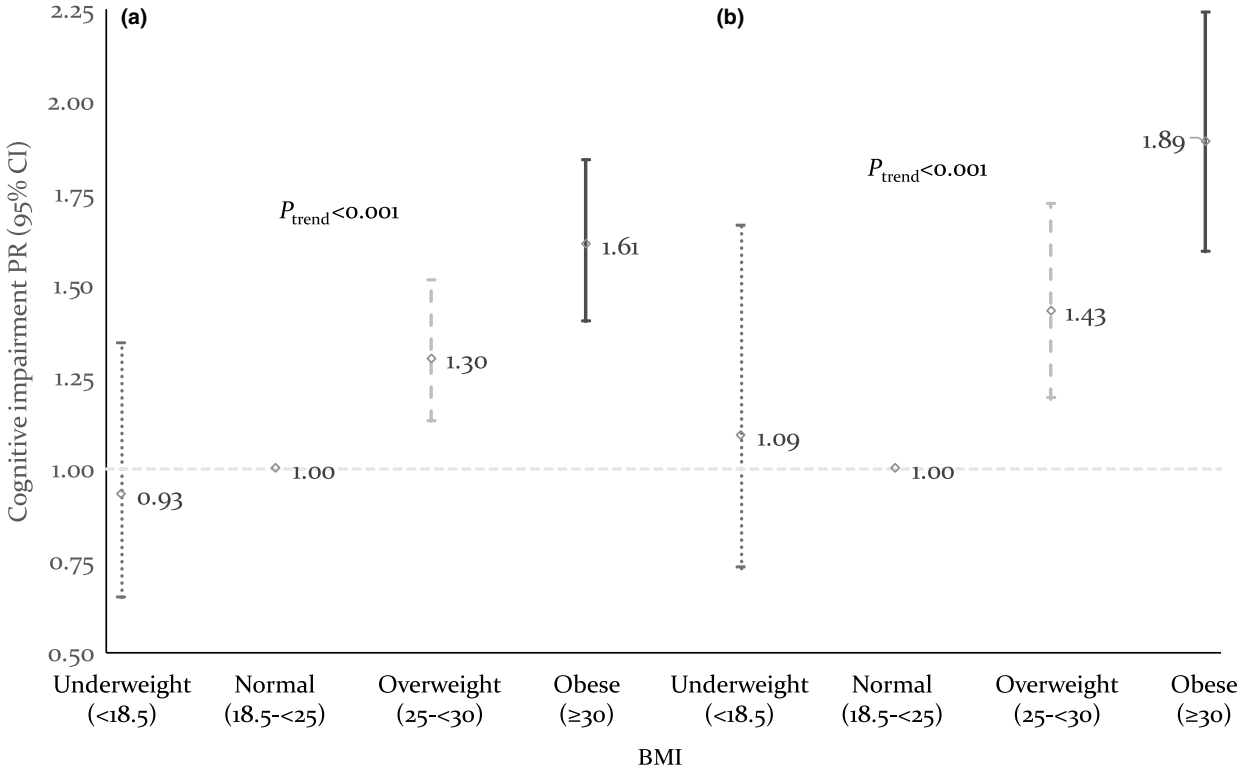

Figure 1 Association of body mass index (BMI) with perceived cognitive impairment by (a) third-most and (b) second-most specific definitions. Coefficients adjusted for age, sex, education and Patient-Determined Multiple Sclerosis Severity Score. CI, confidence interval; PR, prevalence ratio.

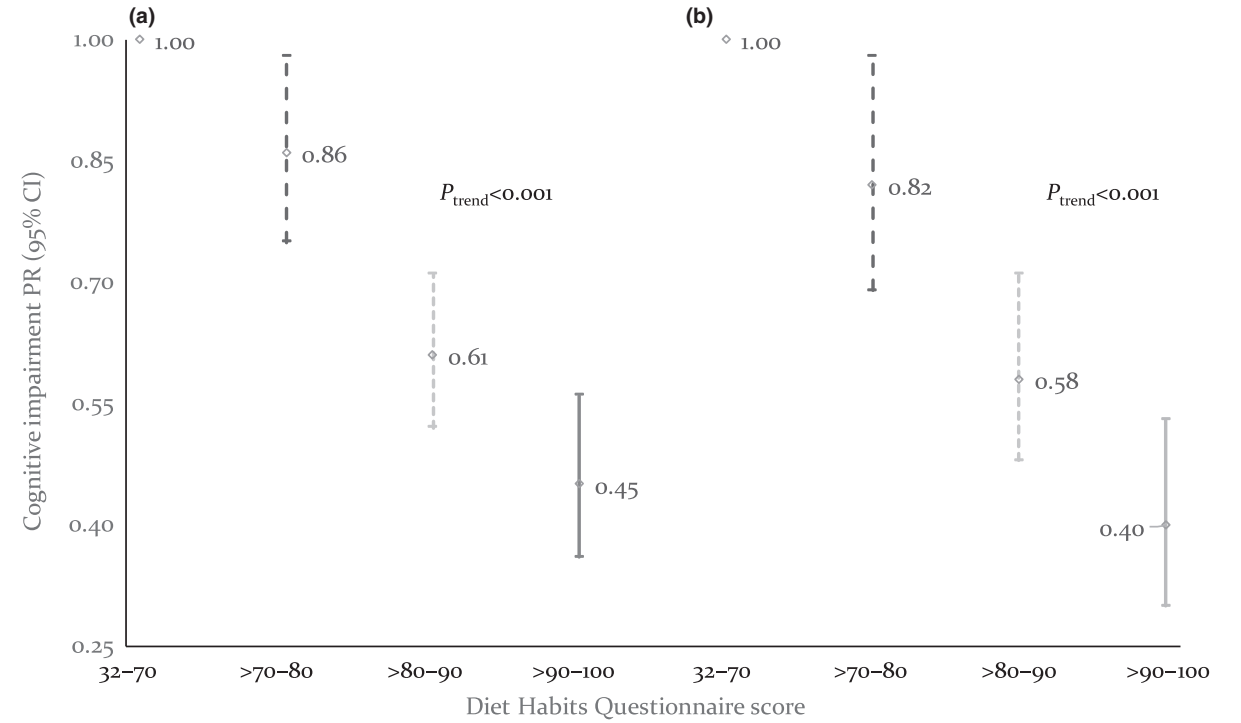

Figure 2 Association of diet quality score (higher score indicates more healthy diet quality) with perceived cognitive impairment by (a) third-most and (b) second-most specific definitions. Coefficients adjusted for age, sex, education and Patient-Determined Multiple Sclerosis Severity Score. CI, confidence interval; PR, prevalence ratio.

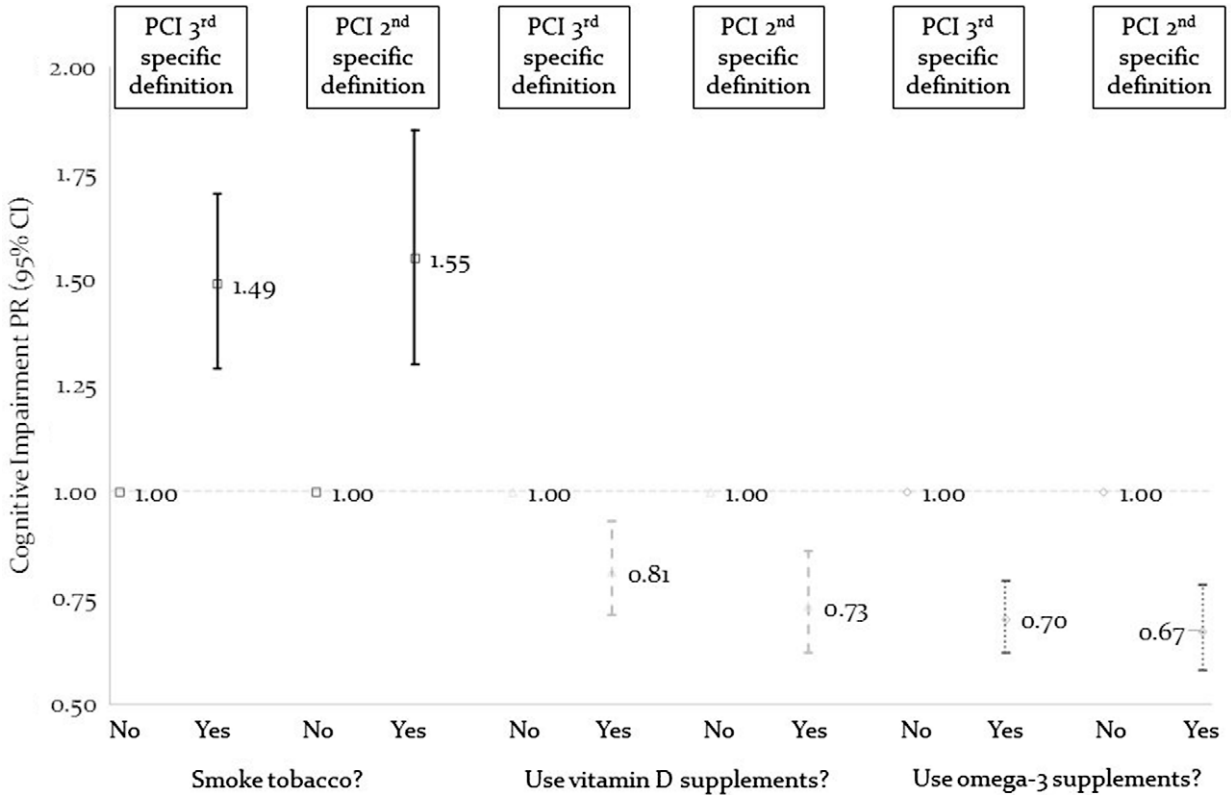

Figure 3 Association of tobacco and supplement use with perceived cognitive impairment by third-most and second-most specific definitions. Coefficients adjusted for age, sex, education and Patient-Determined Multiple Sclerosis Severity Score. CI, confidence interval; PR, prevalence ratio.

Although results using all four definitions are presented, the definitions that we regard as most appropriate balance the needs of specificity and sensitivity, namely the second- and third-most specific, which estimate prevalences of 24.3% and 33.1% respectively. The reason for selecting these definitions was twofold: first, we aimed to maximize specificity and sensitivity, and secondly, by examination of the proportions with PCI between definitions and the change in coefficients, there was a good reason to select the second-most specific measure. However, we have also presented results for the third-most specific definition.

Julian *et al*. assessed PCI in moderately depressed patients with MS using the four-item cognitive scale of the MSQOL-54, as we have done, using participant responses to produce a 'Subjective Cognitive Impairment Index' [26]. The study showed that depression confounded the association between subjective and objective scores of PCI, but for those whose depression lifted following treatment, the concordance between this subjective score and formal neuropsychiatric testing of cognitive function was reasonable. Similarly, Deloire *et al* used the same four items from a French adaptation of the MSQOL-54, finding that depression and fatigue were more predictive of PCI [27]. Both studies, however, had only small sample sizes and were thus significantly limited in comparison with our study.

A much larger study, the NARCOMS study, containing information from over 35 000 people with MS, examined cognition as one of 11 domains commonly affected in MS [28]. They used a self-reported tool similar to the MSQOL-54, assessing PCI by disease duration; at one end of the spectrum (disease duration ≤1 year), the prevalence estimate of PCI was approximately 25–30% and, at the other end of the spectrum (disease duration 29–30 years), PCI prevalence was approximately 50%. In our sample, although our participants had a lower mean disease duration (8.7 years), we estimated similar PCI prevalence estimates, about 22.5% and 32% using the second- and third-most specific definitions. This provides some external support for our mode of assessing PCI, realizing similar proportions using analogous methods.

Perceived cognitive impairment determinants

Some of the factors significantly associated with PCI were probably not causal in nature but rather reflected

selection or participation biases. For instance, the inverse association of older age with PCI probably reflects differential participation with age. Some factors examined may have been modulators of response to the questions posed. For instance, the inverse association of higher education with PCI probably reflected the impact of greater educational exposure with the memory and attention queried. The associations of disease-specific parameters, such as relapse number or disease trajectory, probably reflected correlation of disease activity with PCI.

Other factors may have legitimate relationships with PCI. Smoking and BMI showed consistent and significant deleterious associations with PCI, increasing in magnitude with definition specificity. On the contrary, beneficial behaviours, such as physical activity, dietary quality and vitamin D and omega-3 supplement use, showed significant inverse associations with PCI, enhancing with increased specificity. However, the potential for reverse causality is an issue with all of these determinants, especially in a cross-sectional analysis. Greater social support showed a significant and robust inverse association with PCI, although there was also a potential for reverse causality here. Also, there was the potential that differential social environments might impact upon the measurement of PCI used, such that those with fewer contacts might not recognize cognitive changes as early.

A recent study of over 2000 older participants from the general population showed that, after adjusting for age, sex and comorbidities, physical activity, healthy diet and light-to-moderate alcohol consumption were all associated with better cognitive function [29], in keeping with our findings. An intervention study published in 2017 showed promise for lifestyle modifications, where people with MS reported less fatigue, improved mood and cognitive function following a 12-month multimodal lifestyle modification programme [24].

Strengths and limitations

In this large, multinational web-based study, we made use of self-reported exposure and clinical outcome data. Some of these, like the PDDS score and P-MSSS, have been validated against in-clinic measures. We acknowledge that we lacked an objective clinical cognitive impairment measure with which to compare, as this was not logistically feasible given the study design. However, our findings have considerable importance for self-perceived cognitive function in people with MS and our data indicate the extent to which this cohort perceives difficulties in cognitive functioning. Our analyses show that lifestyle factors may play an important role in addressing these perceived difficulties.

Defining PCI is a complex process, particularly via self-report-based questionnaire methods like those employed here or elsewhere [26–28]. Although the use of MSQOL-54 and related self-reported questionnaire methods is a promising mode of assessing PCI in large cohort studies, this method should be validated against standard clinical measures. Also, these results are based on a cross-sectional study design and therefore causal directionality cannot be ascribed. Although external consistency with the results of other studies adds weight to our findings, replication, ideally in a prospective cohort study design, is required before any guidance can be inferred from these results. We also cannot rule out the possibility that symptoms of cognitive impairment could be due to non-MS pathology, such as stroke, trauma or other processes. Finally, our study is, like many observational cohort studies, susceptible to healthy participant bias. There is also an unknown proportion of potential participants who may not have participated due to perceived or diagnosed cognitive impairment. Thus, our estimates of the prevalence of PCI may be underestimates.

Conclusions

These results show that the prevalence estimate of PCI in this sample ranged from 11.6% to 41.0%. These results add to the literature, which suggests that cognitive impairment is a significant issue in the MS clinical course that should be studied further. Our data showed PCI to be strongly associated with the modifiable risk factors smoking, diet and obesity, after adjusting for other relevant demographic and clinical covariates. Although reverse causality is a potential explanation of our results, many of the identified significant covariates have been previously associated with MS onset and progression. Modification of risk factors such as smoking, diet and obesity may form the basis of a secondary preventive approach to preventing and managing PCI in people with MS.

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Disclosure of conflicts of interest

G.A.J. receives royalties for his books, *Overcoming Multiple Sclerosis* and *Recovering from Multiple Sclerosis*. G.A.J., S.L.N. and K.L.T. have received remuneration for conducting lifestyle educational workshops for people with MS. The other authors declare no financial or other conflicts of interest.

Availability of data and material

Data may not be shared due to the conditions approved by our institutional ethics committee, in that all data are stored as reidentifiable information at the University of Melbourne in the form of password-protected computer databases and only the listed investigators have access to the data. All data have been reported on a group basis, summarizing the group findings rather than individual findings so that personal information cannot be identified. Therefore, we can supply aggregate group data on request. Readers may contact George Jelinek or Tracey Weiland.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Cohort characteristics, both overall and between those with and without data on a subscale within the Multiple Sclerosis Quality of Life (MSQOL-54) cognition questions.

Table S2. Distribution and determinants of cognitive impairment (gradation of definitions). Results estimate a prevalence ratio (95% confidence interval).

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