Received: 22 March 2021 | Accepted: 11 May 2021

DOI: 10.1111/ene.14956

european journal of neurology
the official journal of the european academy of neurology

ORIGINAL ARTICLE

Two healthy lifestyle scores are associated with lower subsequent fatigue risk using inverse probability weighting in an international longitudinal cohort of people with multiple sclerosis

Tracey J. Weiland[1] | Nupur Nag[1] | Alysha De Livera[1,2] | George A. Jelinek[1] | Sandra L. Neate[1] | William Bevens[1] | Steve Simpson-Yap[1,3]

[1]Neuroepidemiology Unit, Melbourne School of Population and Global Health, The University of Melbourne, Melbourne, VIC, Australia

[2]School of Science, RMIT University, Melbourne, VIC, Australia

[3]Menzies Institute for Medical Research, University of Tasmania, Hobart, TAS, Australia

Correspondence
Tracey J. Weiland, Neuroepidemiology Unit, School of Population and Global Health, University of Melbourne, Melbourne, VIC, Australia.
Email: tweiland@unimelb.edu.au

Funding information
Mr Wal Pisciotta; Anonymous philanthropic donors

Abstract

Background and purpose: Several modifiable lifestyle factors have been associated with the onset and health outcomes of multiple sclerosis (MS), including clinically significant fatigue. A combined lifestyle score approach represents one method of assessing their relationship with clinical outcomes. The aim was to examine the association of two lifestyle scores with clinically significant fatigue and change thereof over 2.5 years' follow-up using inverse probability treatment weighting (IPTW).

Methods: Data on sociodemographic, lifestyle, and clinical characteristics surveyed from an international cohort of people with MS at baseline and at 2.5-year follow-up were used. Fatigue was defined by the Fatigue Severity Scale (FSS >5) and healthy lifestyle by the Healthy Lifestyle Index Score (HLIS) and the Smoking, Nutrition, Alcohol Consumption and Physical Activity (SNAP) score. Analyses were by IPTW accounting for age, sex, MS type, disability, treated comorbidity number, immunomodulatory medication use, prescription antifatigue medication use, and ongoing relapse symptoms.

Results: In total, 1268 participants completed the FSS at both time points; approximately 62% had fatigue. Using doubly robust IPTW, high (>11/20) HLIS (odds ratio [OR] 0.90, 95% confidence interval [CI] 0.81–0.98) and high (>3/5) SNAP (OR 0.82, 95% CI 0.73–0.90) were each associated with lower risk of fatigue at follow-up. Evaluating change in fatigue, a higher SNAP score was associated with a lower risk of fatigue (OR 0.89, 95% CI 0.80–0.97) but the score for HLIS did not reach statistical significance (OR 0.93, 95% CI 0.85–1.01).

Conclusion: These results suggest a robust role for key lifestyle factors in preventing clinically significant fatigue and may represent a place for lifestyle modification in improving clinical outcomes in MS.

KEYWORDS
epidemiology, fatigue, inverse probability treatment weighting, lifestyle, multiple sclerosis

INTRODUCTION

Multiple sclerosis (MS) is a chronic nervous system disease caused by an interplay of genetic and environmental factors [1]. Symptoms are heterogeneous, including motor, sensory and visual impairments, pain, fatigue, depression, cognitive dysfunction, incontinence and sexual dysfunction [2]. Fatigue is often the first symptom [3], affecting approximately 80% of people with MS [4]. Fatigue can be severe and highly disabling [5], limiting work capacity [6], social participation [7], and quality of life [8]. This combination of early onset, severity of impact, and high prevalence render fatigue management a priority [9–11].

Guidelines for health and chronic disease management recommend *simultaneous* reduction in risk factors [12], particularly smoking, poor diet, excessive alcohol use, and inactivity. A multimodal approach to risk factor reduction reflects real world conditions since health behaviours cluster together rather than being randomly distributed across the population [13]. Simultaneous modification of lifestyle components has been proposed as the foundation for health and symptom management in MS [14]. Lifestyle risk factor reduction has been associated with better clinical outcomes in MS [15–19], and is recommended alongside standard pharmacotherapy [20].

Inverse probability treatment weighting (IPTW) has emerged as a useful standardization method to control confounding [21]. Calculated from estimated propensity scores, each subject is weighted by the inverse of the probability of being assigned to their actual exposure group, creating what is effectively a weighted "pseudo-population". This technique of covariate adjustment uses a logistic regression model to estimate the probability of the exposure observed for each individual, and uses the predicted probability as a weight in subsequent analyses, transforming the exposure parameter to one that is independent of the model covariates [22]. A further development of IPTW methods is the IPTW regression adjustment (IPTW-RA) method, also known as doubly robust IPTW, which differs from standard IPTW in that the exposure and outcome variables have separate model components rather than each being obliged to have the same. This gives a greater degree of confidence since it means that only one of the models needs to be correctly specified in order to realize an unbiased measure of the exposure–outcome association [23].

The effects of baseline healthy lifestyle scores—the Healthy Lifestyle Index Score (HLIS) [24] and the Smoking, Nutrition, Alcohol Consumption and Physical Activity (SNAP) score [25]—on clinically significant fatigue at the 2.5-year follow-up in the Health Outcomes and Lifestyle In a Sample of people with Multiple sclerosis (HOLISM) longitudinal cohort were investigated using IPTW.

METHODS

Participants and recruitment

Participants were enrolled in the HOLISM study, the methodology for which has been described previously [26,27]. Briefly, participants were recruited via online platforms written in English, and SurveyMonkey® was used to provide consenting respondents with a participant information sheet and survey. Inclusion criteria were ≥18 years old and self-reporting a physician diagnosis of MS.

The University of Melbourne Health Sciences Human Ethics Sub-committee provided ethical approval (ID 1545102). Data may not be shared due to the conditions approved by this institutional ethics committee. All data are stored as re-identifiable information at The University of Melbourne in password-protected computer databases and only 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. Readers may contact Sandra Neate or Steve Simpson-Yap who can supply aggregate group data on request.

Data collection

The dataset consists of demographic, disease profile, medications and supplements, and modifiable lifestyle factors.

Modifiable lifestyle factors

Physical activity was assessed using the International Physical Activity Questionnaire Short Form (IPAQ-SF) [28], from which total physical activity was estimated in Metabolic Equivalent of Task (MET) units, classified into Inactive, Minimally Active, and Active as per IPAQ guidelines. Diet was assessed using a modified form [26] of the Diet Habits Questionnaire [29], querying aspects of food intake, as well as food selection and preparation, realizing a total score out of 100%. Body mass index (BMI) was estimated from self-reported height (m) and weight (kg) using the function weight/height^2, categorized into underweight (<18.5), normal (18.5–24.9), overweight (25.0–29.9), and obese (30.0+). Smoking behaviour was queried as never, ex-, and current smoker; for ex-smokers, duration since quitting was queried and for current smokers cigarettes smoked daily was queried. Alcohol consumption was queried as weekly frequency and volume per session, allowing the average daily grams of alcohol intake to be estimated (the definition of a standard drink was provided for different alcoholic beverages and volumes).

Clinical measures

Clinically significant fatigue was assessed by the Fatigue Severity Scale (FSS), with nine fatigue-related statements rated on a seven-point Likert scale (disagree to agree) [30], a mean score >5 [31] indicating clinically significant fatigue.

Disability was assessed using the Patient-Determined Disease Steps scale [32], from which the disease-duration-adjusted Patient-derived Multiple Sclerosis Severity Score (P-MSSS) was

calculated [33]. The number of treated comorbidities was assessed at baseline using the Self-administered Comorbidity Questionnaire [34]. Prescription medication use was queried at each review, including immunomodulatory, antidepressant, and antifatigue medications.

Healthy lifestyle indices

Two lifestyle indices were used as primary exposure covariates. HLIS was estimated based on quintiles for the continuous Diet Habits Questionnaire, IPAQ, and BMI, and specified absolute terms for alcohol intake and smoking [24] (Table S1). Scores were assigned to categories within variables with higher points corresponding to healthier lifestyle.

Five domain scores were summated realizing a total HLIS score ranging from 0 to 20, where 20 indicates healthiest behaviour. Since few participants scored below 3 (0, one; 1, none; 2, 11) and above 18 (19, six; 20, none), the total HLIS score was truncated to amalgamate scores 0–3 and 18–20, giving a total HLIS score ranging from 3 to 18.

The SNAP scores were derived using the revised framework of the Royal Australian College of General Practitioners which incorporated BMI [25], an amendment to the original.

Five domain scores were summated to realize a total SNAP score ranging from 0 to 5, where 5 indicates healthiest behaviour. Since few people had a SNAP score of 0 ($n = 4$), these were amalgamated with 1, giving a total SNAP score ranging from 1 to 5.

Data analysis

Outcomes

Two outcomes were evaluated: (i) the absolute risk of clinically significant fatigue (mean >5) at follow-up; (ii) the change in clinically significant fatigue between baseline and follow-up.

Exposures

For all analyses, exposures of interest were baseline HLIS and SNAP composite scores. To distinguish two groups, healthy lifestyle versus other, baseline HLIS and SNAP scales were dichotomized. For SNAP a healthy lifestyle was defined as a composite score >3 and for HLIS as a composite score >11. Varying cut-points were also explored as part of sensitivity analyses.

In addition to analyses using dichotomized composite scores, dichotomized subdomains for HLIS and SNAP scores were evaluated to determine if individual components of the respective healthy lifestyle composite had greater weighting on outcome. For HLIS, these subdomains were dichotomized as 0–3 versus 4. For SNAP, subdomains were already dichotomous terms of 0 or 1.

Characteristics by clinically significant fatigue

Analyses of the between-group difference for polychotomous variables were assessed by log-binomial regression, for normally distributed continuous variables by the two-tailed *t* test, and for non-normally distributed continuous variables by the Kruskal–Wallis test.

Inverse probability treatment weighting regression analyses

IPTW and IPTW-WA methods were used; weighted regression coefficients were used to estimate the probability of outcomes at each level of the treatment variable, from which risk ratios were estimated [35,36].

In verifying that the model covariates were balanced by treatment group, between-outcome group differences in model covariates before and after weighting were viewed graphically. The criterion of reducing the post-weighting standardized differences between groups to within an absolute value of 10% was adopted [21].

Since IPTW and IPTW-RA models can only evaluate dichotomous or polychotomous terms, but not continuous terms, a continuous HLIS score could not be quantitatively evaluated by these methods, nor could tests for trend for polychotomous variables be estimated.

Absolute risk of clinically significant fatigue

Baseline HLIS and SNAP score predictors of 2.5-year clinically significant fatigue were evaluated by four methods. The first was by logistic regression, adjusted for ongoing symptoms from recent relapse. Secondly, a fully adjusted model was evaluated, further adjusted for baseline age, sex, MS type, number of treated comorbidities, P-MSSS, immunomodulatory medication use, and antifatigue medication use; these covariates were included based on an a priori review of the literature and within-study associations with HLIS/SNAP and clinically significant fatigue. Thirdly, the standard IPTW model was applied, as described above. Fourthly, the doubly robust IPTW-RA model was applied, as described above. Note that further adjustment for vitamin D supplement use, which has been previously found to improve fatigue in MS [37], did not materially impact results (data not shown).

Change in clinically significant fatigue between baseline and follow-up

The models and statistical procedures used in evaluating change in clinically significant fatigue were the same as those described for

first outcome, absolute risk of fatigue, with the exception that adjustments were also made for baseline clinically significant fatigue.

Data were analysed using Stata/SE 16.0 (StataCorp).

RESULTS

Cohort characteristics

Of 2466 baseline participants, 1268 completed the FSS at baseline and 2.5-year follow-up. Whole sample fatigue prevalence remained consistent across study duration; however, a significantly smaller proportion of individuals reporting fatigue at baseline did so also at 2.5 years.

At baseline this cohort was predominantly female (82.7%), of mean age 46.1 years (Table 1). The majority had relapsing–remitting MS (68.3%) with mild disability (median P-MSSS 1.7), and 62.1% had clinically significant fatigue, with 46.6% using immunomodulatory medication. Lifestyle scores were moderate, with an average HLIS of 10.8% and 38% having SNAP score >3. As would be expected, HLIS and SNAP score were strongly correlated ($r = 0.64$, $p < 0.001$).

Comparing these characteristics with clinically significant fatigue at follow-up (Table 1), those with fatigue were more likely to be older, with progressive MS type and higher P-MSSS at baseline, although sex and immunomodulatory medication use did not differ. Participants with clinically significant fatigue at follow-up had lower HLIS and SNAP scores at baseline (Figure 1); total FSS at follow-up was inversely associated with both HLIS and SNAP, those with HLIS >8 and SNAP >2 having significantly lower FSS.

Baseline determinants of clinically significant fatigue risk at follow-up

Weighted standardized differences in model covariates were markedly reduced compared to unweighted scores for both HLIS and SNAP, falling well within the −10% to 10% interval and generally lying close to 0%, indicative of balance between groups (Figure S1).

Using standard logistic regression, higher truncated HLIS was associated with 11% lower risk of subsequent clinically significant fatigue and higher (>11) HLIS was associated with 48% lower risk of subsequent fatigue (Table 2). Both attenuated on adjustment but remained strongly significant. By IPTW, higher HLIS was associated with 11% lower subsequent risk of fatigue, but using IPTW-RA higher HLIS was associated with 10% lower subsequent risk of fatigue ($p = 0.018$). Examining the subdomains of HLIS, although none reached statistical significance, non-smokers and higher physical activity showed robust associations by IPTW-RA, such that non-smokers had 8% and those with physical activity over 134 METs/week had 16% lower risk of subsequent fatigue.

For SNAP, a strong and dose-dependent inverse association was seen between higher SNAP and lower subsequent risk of fatigue, such that those of SNAP 4 and 5 had 59% and 72% lower risk compared to those of SNAP 2. Accordingly, those of SNAP >3 had 60% lower subsequent risk of fatigue. Both of these attenuated on adjustment but remained highly significant. By IPTW, the polychotomous SNAP became much less dose-dependent, with those of SNAP 4 and 5 having 16% and 20% lower risk of fatigue, whilst for dichotomous SNAP those of higher SNAP had 19% lower risk of subsequent fatigue. Similar results were seen for IPTW-RA. Examining subdomains of SNAP, in contrast to HLIS, all domains but alcohol showed strong and significant inverse associations with subsequent fatigue risk, the strongest associations by IPTW-RA being for diet and smoking (both 18% lower fatigue risk).

Sensitivity analyses exploring dichotomized HLIS and SNAP at different cut-points revealed that for HLIS inverse associations were evident across much of the range up to HLIS >12, whereupon no differences were seen. For SNAP, on the other hand, significant and materially reduced fatigue risk was evident throughout the range (Table S2).

Baseline determinants of change in clinically significant fatigue, baseline to 2.5-year review

Weighted standardized differences in model covariates were markedly reduced compared to the raw data for both HLIS and SNAP, falling well within the −10% to 10% interval and generally lying close to 0%, indicative of balance between groups (Figure S2).

Baseline truncated continuous HLIS was associated with 7% lower change in clinically significant fatigue, although on adjustment this became non-significant (Table 3). HLIS >11 was associated with 36% lower change in clinically significant fatigue, attenuating on adjustment to 27%. By IPTW and IPTW-RA, HLIS >11 showed a trend to lower change in clinically significant fatigue, albeit not reaching statistical significance for either. Examining subdomains, non-smoking showed a robust inverse association, being associated with 10% lower risk of fatigue change by IPTW.

For SNAP, there was a mixed inverse trend that did not persist by IPTW or IPTW-RA. For higher (>3) SNAP, a consistent and robust inverse association was seen, such that by IPTW-RA SNAP >3 was associated with 11% lower risk of change in fatigue. Examining SNAP subdomains, the healthy diet subdomain showed a consistent inverse association, being associated with a 12% lower risk of fatigue change by IPTW-RA. Non-smoking showed a strong inverse trend (14% lower) that was nearly significant.

Sensitivity analyses for differing cut-points of dichotomized HLIS and SNAP showed inverse trends up to HLIS 12 but only for the 3 cutpoint for SNAP (Table S3).

DISCUSSION

This study demonstrates evidence of protective associations of two baseline healthy lifestyle scores with subsequent risk of clinically significant fatigue 2.5 years later. Importantly, using sophisticated IPTW methods, which control for confounding more

TABLE 1 Baseline characteristics by clinically fatigued status at follow-up

		No fatigue at follow-up (n = 476, 37.5%)	Fatigue at follow-up (n = 792, 62.5%)	Test for difference
Sex				
Male	216 (17.3%)	85 (18.0%)	131 (16.8%)	
Female	1035 (82.7%)	388 (82.0%)	647 (83.2%)	p = 0.61
MS type				
RRMS	844 (68.3%)	356 (75.7%)	488 (63.8%)	
SPMS	133 (10.8%)	28 (6.0%)	105 (13.7%)	**p < 0.001**
PPMS	90 (7.3%)	19 (4.0%)	71 (9.3%)	**p < 0.001**
Unsure/other	168 (13.6%)	67 (14.3%)	101 (13.2%)	p = 0.58
(Missing)	(16 (1.3%))	(3 (0.6%))	(13 (1.7%))	p = 0.074
Baseline clinically significant fatigue				
No	433 (37.9%)	306 (70.3%)	127 (17.9%)	
Yes	710 (62.1%)	129 (29.7%)	581 (82.1%)	**p < 0.001**
(Missing)	(108 (8.6%))	(38 (8.0%))	(70 (9.0%))	**p < 0.001**
Immunomodulatory medication use?				
No	668 (53.4%)	266 (56.2%)	402 (51.7%)	
Yes	583 (46.6%)	207 (43.8%)	376 (48.3%)	p = 0.12
SNAP				
0–1	55 (4.9%)	9 (2.1%)	46 (6.6%)	
2	219 (19.4%)	63 (14.4%)	156 (22.5%)	p = 0.066
3	427 (37.8%)	141 (32.2%)	286 (41.3%)	**p = 0.015**
4	343 (30.3%)	172 (39.3%)	171 (24.7%)	**p < 0.001**
5	87 (7.7%)	53 (12.1%)	34 (4.9%)	**p < 0.001**
(Missing)	(120 (9.6%))	(35 (7.4%))	(85 (10.9%))	p = 0.074
Age, years; data are mean (SD; range)	46.1 (10.5; 18.0–79.0)	44.6 (11.0; 18.0–79.0)	47.0 (10.1; 20.4–78.5)	**p < 0.001**
HLIS, original; data are mean (SD; range)	10.8 (3.2; 3–18)	11.9 (3.0; 3–18)	10.7 (3.3; 3–18)	**p < 0.001**
P-MSSS, median (IQR)	1.7 (0.6–4.7)	0.8 (0.4–2.2)	2.8 (0.8–5.3)	**p < 0.001**

Note: Analyses of between-group difference for polytomous variables assessed by log-binomial regression, for normally distributed continuous variables by two-tailed t test, and for non-normally distributed continuous variables by Kruskal-–Wallis test.

Results in boldface denote statistical significance ($p < 0.05$).

Abbreviations: HLIS, Healthy Lifestyle Index Score; IQR, interquartile range; P-MSSS, Participant-reported Multiple Sclerosis Severity Score; PPMS, primary progressive multiple sclerosis; RRMS, relapsing–remitting multiple sclerosis; SNAP, Smoking, Nutrition, Alcohol Consumption and Physical Activity; SPMS, secondary progressive multiple sclerosis.

comprehensively than standard multivariable regression, robust protective associations of higher healthy lifestyle scores with risk of clinically significant fatigue were found. In our cohort, higher HLIS was associated with 10% reduced risk of fatigue (p = 0.018), whilst those with higher SNAP had 18% reduced risk ($p < 0.001$). Higher baseline HLIS was associated with 7% lower subsequent change in fatigue, albeit not reaching statistical significance (p = 0.080), whereas higher baseline SNAP was associated with 11% lower risk of increased fatigue 2.5 years later (p = 0.011). Close inspection within subdomains suggested that the observed associations between HLIS and SNAP and both absolute and change in fatigue were driven by physical activity, diet, and smoking.

Fatigue affects a majority of people with MS [4,5] and is responsible for a significant burden of disease, with social, economic, and quality of life impacts [6–8]. Despite growing evidence highlighting the benefits of a healthy lifestyle, the value of lifestyle risk factor reduction in alleviating MS symptoms and/or disease course remains under-utilized, particularly when healthy lifestyle is conceptualized as a collection of behavioural choices. For heterogeneous conditions, such as MS, which probably [22] have several pathological processes driving disease, multimodal interventions offer the potential to target different pathological mechanisms simultaneously [38].

Main findings

In our sample of adults with MS, baseline SNAP and HLIS were both associated with lower risk of fatigue at the 2.5-year follow-up, even after controlling for confounders. For both composite scores, this effect was demonstrated using three methods: multivariable logistic

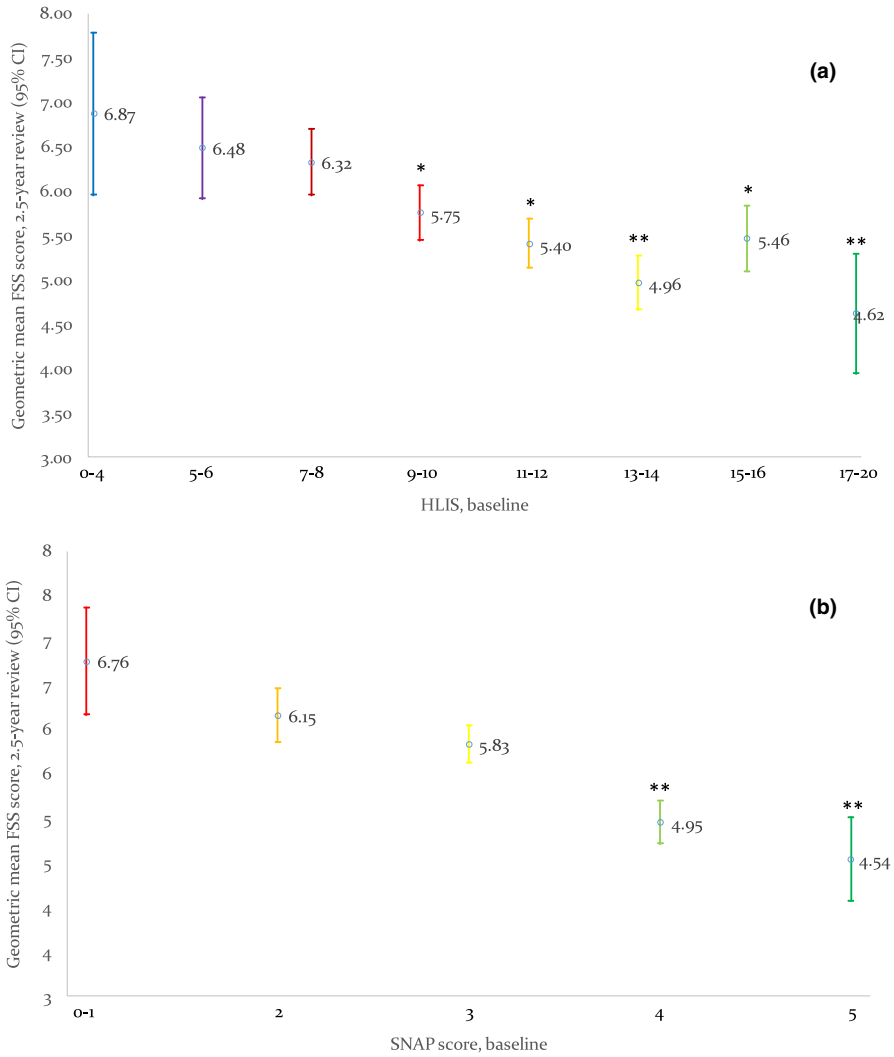

FIGURE 1 Fatigue Severity Score sum at follow-up against (a) HLIS and (b) SNAP at baseline. The plots show geometric mean follow-up FSS (95% confidence interval) by level of baseline HLIS (a) and SNAP (b) scores, adjusted for ongoing symptoms from recent relapse. *$p < 0.05$. **$p < 0.001$ [Colour figure can be viewed at wileyonlinelibrary.com]

regression, IPTW, and IPTW-RA. Whilst HLIS >11 was associated with a 33% lower risk of subsequent fatigue using standard multivariable logistic regression, using IPTW and IPTW-RA the magnitudes of effect were reduced to an 11% and 10% lower subsequent risk of fatigue. Similarly, SNAP >3 was associated with 46% lower fatigue risk using multivariable logistic regression, and although the magnitude reduced to 19% and 18% using IPTW and IPTW-RA, respectively, it nonetheless showed a robust positive association. In evaluating the subdomains, HLIS association was evident only in the physical activity and smoking subdomains, although not reaching statistical significance, whilst for SNAP significant inverse associations were seen for all but the alcohol subdomain.

Despite the association observed for baseline SNAP and HLIS and a lower risk of fatigue 2.5 years post-baseline, the effects observed for change in fatigue over 2.5 years were less clear. Our analyses of differing cut-points of dichotomized SNAP and HLIS produced conflicting results for HLIS and SNAP. Higher SNAP scores—the equivalent of adopting at least four of five healthy behaviours—were associated with reductions in fatigue over 2.5 years across all analytical methods. HLIS showed weaker associations by standard logistic regression and IPTW, failing to reach statistical significance by IPTW despite having similar magnitudes as seen for SNAP. Amongst subdomains, the smoking domains of both HLIS and SNAP were inversely associated with subsequent change in clinically significant fatigue, as well as the physical activity subdomain of SNAP, but no other subdomains were associated.

The disparity in results for the two lifestyle scores is possibly attributable to their different underlying scoring structures. SNAP is simple and efficient, with a single cut-off for whether the lifestyle for each subdomain is healthy or not, allowing easy comparability and interpretation. HLIS subdomains are in quintiles which may over-complicate the lifestyle factors assessed. For instance, for smoking, SNAP assigns current non-smoker as healthy, and HLIS assigns a gradation of healthiness to both number of cigarettes per day for current smokers and duration since quitting for ex-smokers; the latter may depart from a linear association. In trying to capture more elements than the comparatively simple SNAP, HLIS may not be as sound a measure of healthy lifestyle in people with MS.

Disparity in measurement may explain why the association of HLIS with change in fatigue at follow-up failed to reach significance. For absolute fatigue risk, HLIS shows a prospective association that is in line with but weaker than that seen for SNAP. For

TABLE 2 Associations between baseline characteristics and fatigue at follow-up as determined by logistic regression models and inverse probability weighting

Baseline characteristic	*n/N* (%)	Model 1	Model 2	Model 3	Model 4 Doubly robust
Sex					
Male	131/216 (60.7%)	1.00 [Reference]	1.00 [Reference]		
Female	647/1035 (62.5%)	1.19 (0.87, 1.63) $p = 0.29$	1.27 (0.89, 1.79) $p = 0.18$		
Age, years		**1.02 (1.01, 1.04)** ***p* < 0.001**	1.01 (0.99, 1.02) $p = 0.31$		
Number of treated comorbidities		**1.66 (1.42, 1.92)** ***p* < 0.001**	**1.43 (1.22, 1.67)** ***p* < 0.001**		
MS type					
RRMS	488/844 (57.8%)	1.00 [Reference]	1.00 [Reference]		
SPMS	105/133 (79.0%)	**2.92 (1.85, 4.60)**	1.53 (0.90, 2.59)		
PPMS	71/90 (78.9%)	**2.72 (1.55, 4.80)**	1.45 (0.74, 2.86)		
Unsure/other	101/168 (60.1%)	1.04 (0.73, 1.48)	–		
P-MSSS		**1.33 (1.25, 1.41)** ***p* < 0.001**	**1.26 (1.18, 1.35)** ***p* < 0.001**		
Immunomodulatory medication use?					
No	402/668 (60.2%)	1.00 [Reference]	1.00 [Reference]		
Yes	376/583 (64.5%)	1.25 (0.98, 1.58) $p = 0.070$	**1.37 (1.04, 1.82)** ***p* = 0.026**		
Prescription antidepressant medication use?					
No	614/1046 (58.7%)	1.00 [Reference]	1.00 [Reference]		
Yes	164/205 (80.0%)	**2.81 (1.94, 4.08)** ***p* < 0.001**	1.32 (0.85, 2.06) $p = 0.22$		
Prescription antifatigue medication use?					
No	697/1158 (60.2%)	1.00 [Reference]	1.00 [Reference]		
Yes	81/93 (87.1%)	**5.19 (2.72, 9.93)** ***p* < 0.001**	**4.08 (2.03, 8.20)** ***p* < 0.001**		
HLIS		**0.89 (0.86, 0.93)** ***p* < 0.001**	**0.92 (0.88, 0.97)** ***p* < 0.001**		
≤11	396/574 (69.0%)	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
>11	273/518 (52.7%)	**0.52 (0.40, 0.67)** ***p* < 0.001**	**0.67 (0.51, 0.89)** ***p* = 0.005**	**0.89 (0.80, 0.97)** ***p* = 0.010**	**0.90 (0.81, 0.98)** ***p* = 0.018**
HLIS diet					
≤80%	574/886 (64.8%)	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
>80%	173/323 (53.6%)	**0.66 (0.51, 0.87)** ***p* = 0.003**	0.85 (0.63, 1.13) $p = 0.26$	0.95 (0.86, 1.04) $p = 0.31$	0.97 (0.80, 1.06) $p = 0.55$
HLIS physical activity					
≤80%	663/1064 (62.3%)	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
>80%	26/55 (47.3%)	**0.55 (0.31, 0.96)** ***p* = 0.034**	0.68 (0.38, 1.23) $p = 0.20$	0.82 (0.60, 1.03) $p = 0.10$	0.84 (0.65, 1.03) $p = 0.094$
HLIS alcohol consumption					
≤80%	431/741 (58.2%)	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
>80%	304/452 (67.3%)	**1.44 (1.12, 1.85)** ***p* = 0.005**	1.28 (0.97, 1.69) p = 0.077	1.06 (0.96, 1.15) p = 0.21	1.06 (0.97, 1.15) $p = 0.18$
HLIS smoking					
≤80%	370/559 (66.2%)	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]

(Continues)

TABLE 2 (Continued)

Baseline characteristic	*n/N* (%)	Model 1	Model 2	Model 3	Model 4 Doubly robust
>80%	370/641 (57.7%)	**0.69 (0.54, 0.88) *p=0.003***	**0.76 (0.58, 1.00) *p=0.047***	**0.92 (0.84, 1.00) *p=0.048***	0.92 (0.84, 1.00) *p=0.050*
HLIS BMI					
≤80%	533/826 (64.5%)	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
>80%	241/420 (57.4%)	**0.77 (0.60, 0.99) *p* = 0.039**	0.91 (0.69, 1.20) p = 0.50	0.98 (0.89, 1.07) *p* = 0.66	0.97 (0.88, 1.06) *p* = 0.52
SNAP score					
0–1	46/55 (83.6%)	1.88 (0.86, 4.14)	1.52 (0.65, 3.55)	0.95 (0.62, 1.28)	1.05 (0.83, 1.26)
2	156/219 (71.2%)	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
3	286/427 (67.0%)	0.86 (0.60, 1.24)	1.05 (0.70, 1.55)	1.01 (0.89, 1.14)	1.01 (0.89, 1.13)
4	171/343 (49.9%)	**0.41 (0.28, 0.59)**	**0.62 (0.41, 0.93)**	**0.84 (0.73, 0.96)**	**0.85 (0.73, 0.97)**
5	34/87 (39.1%)	**0.28 (0.16, 0.48)**	**0.39 (0.22, 0.69)**	**0.80 (0.63, 0.98)**	**0.77 (0.62, 0.93)**
Trend		***p* < 0.001**	***p* < 0.001**		
0–3	488/701 (69.6%)	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
>3	205/430 (47.7%)	**0.40 (0.31, 0.52) *p* < 0.001**	**0.54 (0.41, 0.71) *p* < 0.001**	**0.81 (0.73, 0.89) *p* < 0.001**	**0.82 (0.74, 0.91) *p* < 0.001**
SNAP diet domain					
Unhealthy	643/1000 (64.3%)	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Healthy	98/200 (49.0%)	**0.52 (0.38, 0.72) *p* < 0.001**	**0.52 (0.36, 0.73) *p* < 0.001**	**0.81 (0.70, 0.91) *p* < 0.001**	**0.82 (0.72, 0.92) *p* < 0.001**
SNAP physical activity domain					
Unhealthy	288/380 (75.8%)	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Healthy	416/765 (54.4%)	**0.40 (0.30, 0.54) *p* < 0.001**	**0.65 (0.48, 0.90) *p* = 0.008**	**0.87 (0.79, 0.96) *p* = 0.007**	**0.86 (0.78, 0.95) *p* = 0.003**
SNAP alcohol intake domain					
Unhealthy	117/204 (57.4%)	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Healthy	630/1005 (62.7%)	1.25 (0.91, 1.72) *p* = 0.16	1.10 (0.78, 1.56) *p* = 0.59	1.00 (0.86, 1.13) *p* = 0.97	1.00 (0.88, 1.13) *p* = 0.95
SNAP smoking domain					
Unhealthy	82/100 (82.0%)	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Healthy	660/1104 (59.8%)	**0.35 (0.20, 0.61) *p<0.001***	**0.48 (0.27, 0.85) *p=0.013***	**0.82 (0.69, 0.95) *p=0.022***	**0.82 (0.69, 0.95) *p=0.019***
SNAP BMI domain					
Unhealthy	375/537 (69.8%)	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Healthy	401/712 (56.3%)	**0.55 (0.43, 0.70) *p* < 0.001**	**0.72 (0.55, 0.94) *p* = 0.017**	**0.90 (0.83, 0.98) *p* = 0.022**	**0.91 (0.83, 0.99) *p* = 0.033**

Note: Model 1 utilizes logistic regression adjusted for whether participants were experiencing ongoing symptoms from recent relapse at either review. Model 2 utilizes logistic regression adjusted for the covariates in model 1, as well as age, sex, MS type, P-MSSS, number of treated comorbidities, and prescription antifatigue medication use. Model 3 utilizes inverse probability treatment weighting adjusted for the covariates in model 2. Model 4 utilizes inverse probability-weighted regression adjustment adjusted for the covariates in models 2 and 3.

Results in boldface denote statistical significance ($p < 0.05$).

Abbreviations: BMI, body mass index; HLIS, Healthy Lifestyle Index Score; MS, multiple sclerosis; P-MSSS, Patient-reported MS Severity Score; PPMS, primary progressive MS; RRMS, relapsing–remitting MS; SNAP, Smoking, Nutrition, Alcohol Consumption and Physical Activity; SPMS, secondary-progressive MS.

change in fatigue, despite both HLIS and SNAP showing similar magnitudes, that for HLIS was consistently weaker and less significant. This is interpreted as a positive finding from a superior measure, with the conclusion that the SNAP composite lifestyle score, and particularly the subdomains of smoking and diet, shows a robust prospective association with fatigue and change thereof over 2.5 years of follow-up.

Our findings that never smoking and a healthy diet are associated with both absolute fatigue and change in fatigue over time point to a role for these behaviours in the prevention and management

TABLE 3 Associations between baseline characteristics and change in fatigue over follow-up as determined by logistic regression models and inverse probability weighting

Baseline characteristic	*n/N* (%)	Model 1	Model 2	Model 3	Model 4
Sex					
Male	122/199 (61.3%)	1.00 [Reference]	1.00 [Reference]		
Female	586/944 (62.1%)	0.98 (0.67, 1.43) $p = 0.93$	1.06 (0.71, 1.57) $p = 0.77$		
Age, years		**1.02 (1.01, 1.03) $p = 0.004$**	1.01 (1.00, 1.03) $p = 0.13$		
Number of treated comorbidities		**1.30 (1.10, 1.55) $p = 0.003$**	**1.20 (1.00, 1.43) $p = 0.045$**		
MS type					
RRMS	453/783 (57.9%)	1.00 [Reference]	1.00 [Reference]		
SPMS	97/123 (78.9%)	**1.91 (1.13, 3.23)**	1.24 (0.68, 2.24)		
PPMS	65/81 (80.3%)	**2.17 (1.11, 4.21)**	1.34 (0.63, 2.83)		
Unsure/other	92/153 (60.1%)	0.85 (0.55, 1.30)	-		
P-MSSS		**1.18 (1.10, 1.26) $p < 0.001$**	**1.14 (1.06, 1.23) $p < 0.001$**		
Immunomodulatory medication use?					
No	349/587 (59.5%)	1.00 [Reference]	1.00 [Reference]		
Yes	359/556 (64.6%)	1.14 (0.86, 1.52) $p = 0.36$	1.23 (0.89,1.69) $p = 0.21$		
Prescription antidepressant medication use?					
No	553/949 (58.3%)	1.00 [Reference]	1.00 [Reference]		
Yes	155/194 (79.9%)	**1.85 (1.21, 2.84) $p = 0.005$**	1.20 (0.74, 1.97) $p = 0.46$		
Prescription antifatigue medication use?					
No	631/1054 (59.9%)	1.00 [Reference]	1.00 [Reference]		
Yes	77/89 (86.5%)	**2.64 (1.31, 5.30)**	**2.43 (1.17, 5.03)**		
		$p = 0.006$	**$p = 0.017$**		
HLIS		**0.93 (0.89, 0.98) $p = 0.006$**	0.96 (0.91, 1.01) $p = 0.088$		
≤11	378/550 (68.7%)	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
>11	263/494 (53.2%)	**0.64 (0.48, 0.87) $p = 0.004$**	**0.73 (0.53, 0.99) $p = 0.046$**	0.92 (0.85, 1.00) $p = 0.068$	0.93 (0.85, 1.01) $p = 0.080$
HLIS diet					
≤80%	538/831 (64.7%)	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
>80%	170/312 (54.5%)	0.95 (0.69, 1.30) $p = 0.74$	1.04 (0.75, 1.45) $p = 0.81$	1.01 (0.92, 1.10) $p = 0.84$	1.02 (0.93, 1.11) $p = 0.66$
HLIS physical activity					
≤80%	636/1018 (62.5%)	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
>80%	25/52 (48.1%)	0.59 (0.30, 1.14) $p = 0.12$	0.66 (0.33, 1.30) $p = 0.23$	0.83 (0.59, 1.08) $p = 0.19$	0.88 (0.68, 1.07) $p = 0.22$
HLIS alcohol consumption					
≤80%	412/704 (58.5%)	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
>80%	284/423 (67.1%)	1.04 (0.77, 1.41) $p = 0.78$	1.02 (0.74, 1.40) $p = 0.91$	0.99 (0.90, 1.07) $p = 0.76$	0.99 (0.91, 1.07) $p = 0.85$
HLIS smoking					
Unhealthy	346/523 (66.2%)	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]	

(Continues)

TABLE 3 (Continued)

Baseline characteristic	*n/N* (%)	Model 1	Model 2	Model 3	Model 4
Healthy	355/611 (58.1%)	**0.62 (0.46, 0.83) *p* = 0.001**	**0.67 (0.49, 0.91) *p* = 0.009**	**0.90 (0.83, 0.97) *p* = 0.011**	**0.90 (0.83, 0.97) *p* = 0.011**
HLIS BMI					
Unhealthy	482/751 (64.2%)	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Healthy	222/388 (57.2%)	0.91 (0.67, 1.23) $p = 0.54$	1.01 (0.74, 1.38) $p = 0.95$	1.01 (0.92, 1.09) $p = 0.87$	1.00 (0.91, 1.08) $p = 0.97$
SNAP score					
0–1	43/52 (82.7%)	1.47 (0.61, 3.51)	1.29 (0.53, 3.14)	0.78 (0.43, 1.14)	0.89 (0.73, 1.05)
2	146/208 (70.2%)	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
3	278/413 (67.3%)	1.15 (0.75, 1.75)	1.23 (0.79, 1.90)	1.05 (0.92, 1.17)	1.04 (0.92, 1.17)
4	166/328 (50.6%)	**0.64 (0.42, 0.99)**	0.78 (0.50, 1.23)	0.90 (0.78, 1.03)	0.90 (0.78, 1.03)
5	31/79 (39.2%)	0.63 (0.33, 1.18)	0.66 (0.34, 1.27)	1.02 (0.84, 1.21)	0.96 (0.78, 1.14)
Trend		***p* = 0.003**	***p* = 0.038**		
0–3	467/673 (69.4%)	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
>3	197/407 (48.4%)	**0.57 (0.42, 0.77) *p<0.001***	**0.65 (0.47, 0.89) *p = 0.007***	**0.88 (0.80, 0.97) *p = 0.008***	**0.89 (0.80, 0.97) *p = 0.011***
SNAP diet domain					
Unhealthy	612/952 (64.3%)	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Healthy	91/184 (49.5%)	**0.66 (0.45, 0.98) *p* = 0.037**	**0.63 (0.42, 0.94) *p* = 0.024**	**0.88 (0.78, 0.99) *p* = 0.036**	**0.88 (0.77, 0.98) *p* = 0.022**
SNAP physical activity domain					
Unhealthy	273/361 (75.6%)	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Healthy	402/732 (54.9%)	**0.65 (0.47, 0.91) *p* = 0.012**	0.84 (0.59, 1.19) $p = 0.32$	0.96 (0.87, 1.06) $p = 0.46$	0.96 (0.87, 1.05) $p = 0.36$
SNAP alcohol intake domain					
Unhealthy	110/195 (56.4%)	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Healthy	598/948 (63.1%)	1.20 (0.82, 1.74) $p = 0.36$	1.11 (0.75, 1.65) $p = 0.60$	0.99 (0.87, 1.12) $p = 0.89$	1.02 (0.90, 1.14) $p = 0.70$
SNAP smoking domain					
Unhealthy	77/95 (81.1%)	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Healthy	626/1043 (60.0%)	**0.49 (0.27, 0.91) *p* = 0.023**	0.57 (0.31, 1.06) $p = 0.075$	**0.84 (0.70, 0.99) *p* = 0.048**	0.86 (0.72, 1.00) $p = 0.060$
SNAP BMI domain					
Unhealthy	336/487 (69.0%)	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Healthy	370/654 (56.6%)	0.78 (0.58, 1.05) $p = 0.096$	0.88 (0.64, 1.19) $p = 0.40$	0.97 (0.89, 1.05) $p = 0.44$	0.97 (0.89, 1.05) $p = 0.47$

Note: Model 1 utilizes logistic regression adjusted for baseline fatigue and whether participants were experiencing ongoing symptoms from recent relapse at either review. Model 2 utilizes logistic regression adjusted for the covariates in model 1, as well as age, sex, MS type, P-MSSS, number of treated comorbidities, and prescription antifatigue medication use. Model 3 utilizes inverse probability treatment weighting adjusted for the covariates in model 2. Model 4 utilizes inverse probability-weighted regression adjustment adjusted for the covariates in models 2 and 3.

Results in boldface denote statistical significance ($p < 0.05$).

Abbreviations: BMI, body mass index; HLIS, Healthy Lifestyle Index Score; MS, multiple sclerosis; P-MSSS, Patient-reported MS Severity Score; PPMS, primary progressive MS; RRMS, relapsing–remitting MS; SNAP, Smoking, Nutrition, Alcohol Consumption and Physical Activity; SPMS, secondary progressive MS.

of MS fatigue. This finding is unsurprising given the role ascribed to smoking and poor diet in molecular mechanisms that drive MS pathogenesis, indirectly via the intestinal microbiome [39] or directly by affecting cellular metabolism oxidative stress, giving rise to immune dysregulation, chronic inflammation, modulation of glial function, and neurodegeneration [40]. The exact nature of a healthy diet which may improve MS progression is uncertain, although many diet programmes have been proposed for people with MS, including lifestyle programmes like the Wahls Elimination diets which were recently demonstrated to improve fatigue in people with MS [41,42] as well as non-MS-specific diets like the ketogenic diet which a single-arm pilot randomized clinical trial (RCT) suggested

may improve fatigue [43]. Further research on this topic should be pursued.

These data are consistent with our previously reported observational data from this cohort at baseline [44], findings from other cohorts regarding the importance of diet quality and composite healthy lifestyle and fatigue [18], and a recent review of activity and fatigue in MS [45].

Increasingly, composite scores of lifestyle risk factors are being applied to data collected from observational studies of people with MS [18,19,46,47], including longitudinal cohorts. Whilst such cohorts enable evaluation of causal inferences and permit long-term monitoring of conditions, residual confounding in multivariable modelling limits interpretation. The use of propensity weighting allows a superior regression methodology that more approximates, but naturally does not replace, RCTs.

Given the challenges associated with longitudinal RCTs of lifestyle change, obtaining a preliminary indication of risk reduction benefits is invaluable. In cohorts for whom relevant lifestyle data are collected, the application of lifestyle composites in combination with newer statistical methods as shown in the present study adds further weight to the rationale for such RCTs.

Strengths and limitations

Our study was strengthened by the longitudinal collection of lifestyle data that allowed the application of known lifestyle composites. The use of a large, international cohort of people with MS, with differing types of MS, a broad spectrum of disability, and a fatigue prevalence comparable to other cohorts [3,48–50], is a further strength.

Our study was affected by appreciable attrition, exacerbating the healthy participant bias present at baseline. Our recruitment strategy may have contributed to bias; participants were recruited online and were healthier than participants recruited to other cohorts. It is therefore conceivable that their health behaviours may not reflect those of the broader population with MS. In addition, the recruitment online and consequent mode of re-contacting for the follow-up by email may have contributed to the attrition at follow-up, due to a combination of changed email addresses, spam filtration, and other limitations of email contact methods. Whilst secondary email addresses were also queried, these were probably affected by the same limitations and so attrition was still appreciable.

Further to this, given the nature of recruitment, a sizeable proportion of our cohort was apt to engage in healthy lifestyle behaviours, particularly those derived from the Overcoming MS programme [51] which includes recommendations for sun exposure, physical activity, non-smoking, moderate alcohol consumption, supplement use, and healthy diet. Whilst the cohort has been demonstrated to be broadly representative of the general population as regards demographics and clinical characteristics [27], this bias to healthier lifestyle behaviours may limit the generalizability of these results to cohorts that are less apt to engage in healthy lifestyle to this extent.

Another potential limitation is the failure to assess sleep quality and sleep disorders as comorbid problems in this sample. Whilst fatigue in MS is neuropathic in nature and not remedied by rest, having a sleep disorder would add a further element of fatigue due to lack of effective sleep. It has been suggested that studies of fatigue in MS should assess sleep disorders [52] and so the absence of that here is a limitation.

Future research

Well established lifestyle composites derived from non-MS populations were used. The utility of a single score composite of lifestyle will be maximized for people with MS following the derivation of an empirically informed composite lifestyle index specific to this population.

Conclusions

Two different statistical methods used in a large diverse international population of people with MS derived nearly identical results, showing that a healthy lifestyle, specifically non-smoking and a healthy diet, has the potential to reduce fatigue in people with MS. Replication of these results in other cohorts is necessary but the potential of multimodal lifestyle interventions to improve fatigue in people with MS should be explored in RCTs.

ACKNOWLEDGEMENTS

The HOLISM study participants are thanked, and Mr Wal Pisciotta and anonymous donors who support the work of the Neuroepidemiology Unit at The University of Melbourne.

CONFLICT OF INTEREST

GAJ receives royalties for his books, Overcoming Multiple Sclerosis and Recovering from Multiple Sclerosis. GAJ and SLN received remuneration for conducting lifestyle educational workshops for people with MS.

AUTHOR CONTRIBUTIONS

Tracey J Weiland: Conceptualization (equal); data curation (supporting); formal analysis (supporting); funding acquisition (supporting); investigation (lead); methodology (equal); project administration (supporting); resources (supporting); supervision (equal); validation (supporting); visualization (supporting); writing—original draft (lead); writing—review and editing (equal). **Nupur Nag:** Supervision (supporting); writing—original draft (supporting); writing—review and editing (supporting). **George A Jelinek:** Funding acquisition (lead); investigation (equal); methodology (supporting); resources (equal); supervision (equal); validation (supporting); writing—review and editing (supporting). **William Bevens:** Data curation (equal); methodology (supporting); project administration (supporting); writing—review and editing (supporting). **Sandra L Neate:** Investigation (supporting);

methodology (supporting); supervision (supporting); writing—review and editing (supporting). **Steve Simpson-Yap:** Conceptualization (equal); data curation (lead); formal analysis (equal); investigation (equal); methodology (equal); software (equal); validation (lead); visualization (lead); writing—review and editing (equal).

DATA AVAILABILITY STATEMENT

The University of Melbourne Health Sciences Human Ethics Sub-Committee provided ethical approval (ID 1545102). Data may not be shared due to the conditions approved by this institutional ethics committee. All data are stored as re-identifiable information at the University of Melbourne in password-protected computer databases and only 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. Readers may contact Sandra Neate or Steve Simpson-Yap who can supply aggregate group data on request.

ORCID

Tracey J. Weiland https://orcid.org/0000-0002-4053-5507
Steve Simpson-Yap https://orcid.org/0000-0001-6521-3056

REFERENCES

1. van der Mei IA, Simpson S Jr, Stankovich J, Taylor BV. Individual and joint action of environmental factors and risk of MS. *Neurol Clin*. 2011;29:233-255.
2. Feinstein A. *The Clinical Neuropsychiatry of Multiple Sclerosis*. Cambridge, UK: Cambridge University Press; 1999.
3. Freal JE, Kraft GH, Coryell JK. Symptomatic fatigue in multiple sclerosis. *Arch Phys Med Rehabil*. 1984;65:135-138.
4. Lerdal A, Celius EG, Krupp L, Dahl AA. A prospective study of patterns of fatigue in multiple sclerosis. *Eur J Neurol*. 2007;14:1338-1343.
5. Krupp L. Fatigue is intrinsic to multiple sclerosis (MS) and is the most commonly reported symptom of the disease. *Mult Scler*. 2006;12:367-368.
6. Smith MM, Arnett PA. Factors related to employment status changes in individuals with multiple sclerosis. *Mult Scler*. 2005;11:602-609.
7. Salter A, Fox RJ, Tyry T, Cutter G, Marrie RA. The association of fatigue and social participation in multiple sclerosis as assessed using two different instruments. *Mult Scler Relat Disord*. 2019;31:165-172.
8. Janardhan V, Bakshi R. Quality of life in patients with multiple sclerosis: the impact of fatigue and depression. *J Neurol Sci*. 2002;205:51-58.
9. Members of the MS in the 21st Century Steering Group, Rieckmann P, Centonze D, et al. Unmet needs, burden of treatment, and patient engagement in multiple sclerosis: a combined perspective from the MS in the 21st Century Steering Group. *Mult Scler Relat Disord*. 2018;19:153-160.
10. Multiple Sclerosis Research Australia; 2020. https://msra.org.au/wp-content/uploads/2017/04/ms-research-priorities-survey-full-report.pdf. Accessed 28 January 2020.
11. Penner IK, Paul F. Fatigue as a symptom or comorbidity of neurological diseases. *Nat Rev Neurol*. 2017;13:662-675.
12. World Health Organisation. World Health Report. Reducing risks, promoting healthy life. Geneva; 2002.
13. Poortinga W. The prevalence and clustering of four major lifestyle risk factors in an English adult population. *Prev Med*. 2007;44:124-128.
14. Coyle PK. Symptom management and lifestyle modifications in multiple sclerosis. *Continuum (Minneap Minn)*. 2016;22:815-836.
15. Swank RL, Bourdillon RB. Multiple sclerosis: assessment of treatment with a modified low-fat diet. *J Nerv Ment Dis*. 1960;131:468-488.
16. Swank RL. Treatment of multiple sclerosis with a low-fat diet. *J Am Diet Assoc*. 1960;36:322-325.
17. Strober LB, Becker A, Randolph JJ. Role of positive lifestyle activities on mood, cognition, well-being, and disease characteristics in multiple sclerosis. *Appl Neuropsychol Adult*. 2018;25:304-311.
18. Fitzgerald KC, Tyry T, Salter A, et al. Diet quality is associated with disability and symptom severity in multiple sclerosis. *Neurology*. 2018;90:e1-e11.
19. Marck CH, De Livera AM, Brown CR, et al. Health outcomes and adherence to a healthy lifestyle after a multimodal intervention in people with multiple sclerosis: three year follow-up. *PLoS One*. 2018;13:e0197759.
20. Moss BP, Rensel MR, Hersh CM. Wellness and the role of comorbidities in multiple sclerosis. *Neurotherapeutics*. 2017;14:999-1017.
21. Austin PC, Stuart EA. Moving towards best practice when using inverse probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies. *Stat Med*. 2015;34:3661-3679.
22. Ali MS, Groenwold RHH, Klungel OH. Best (but oft-forgotten) practices: propensity score methods in clinical nutrition research. *Am J Clin Nutr*. 2016;104:247-258.
23. Funk MJ, Westreich D, Wiesen C, Stürmer T, Brookhart MA, Davidian M. Doubly robust estimation of causal effects. *Am J Epidemiol*. 2011;173:761-767.
24. McKenzie F, Ferrari P, Freisling H, et al. Healthy lifestyle and risk of breast cancer among postmenopausal women in the European Prospective Investigation into Cancer and Nutrition cohort study. *Int J Cancer*. 2015;136:2640-2648.
25. The Royal Australian College of General Practitioners. *Smoking, Nutrition, Alcohol, Physical activity (SNAP): A Population Health Guide to Behavioural Risk Factors in General Practice*, 2nd ed. Melbourne, VIC: RACGP; 2015.
26. Hadgkiss EJ, Jelinek GA, Weiland TJ, Pereira NG, Marck CH, van der Meer DM. Methodology of an international study of people with multiple sclerosis recruited through Web 2.0 platforms: demographics, lifestyle, and disease characteristics. *Neurol Res Int*. 2013;2013:580596.
27. Weiland TJ, De Livera AM, Brown CR, et al. Health outcomes and lifestyle in a sample of people with multiple sclerosis (HOLISM): longitudinal and validation cohorts. *Front Neurol*. 2018;9:1074.
28. Craig CL, Marshall AL, Sjostrom M, et al. International physical activity questionnaire: 12-country reliability and validity. *Med Sci Sports Exerc*. 2003;35:1381-1395.
29. McKellar S, Horsley P, Chambers R, et al. Development of the diet habits questionnaire for use in cardiac rehabilitation. *Australian J Prim Health*. 2008;14:43-47.
30. Krupp LB, LaRocca NG, Muir-Nash J, Steinberg AD. The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. *Arch Neurol*. 1989;46:1121-1123.
31. Smedal T, Beiske AG, Glad SB, et al. Fatigue in multiple sclerosis: associations with health-related quality of life and physical performance. *Eur J Neurol*. 2011;18:114-120.
32. Hohol MJ, Orav EJ, Weiner HL. Disease steps in multiple sclerosis: a simple approach to evaluate disease progression. *Neurology*. 1995;45:251-255.
33. Kister I, Chamot E, Salter AR, Cutter GR, Bacon TE, Herbert J. Disability in multiple sclerosis: a reference for patients and clinicians. *Neurology*. 2013;80:1018-1024.
34. Sangha O, Stucki G, Liang MH, Fossel AH, Katz JN. The Self-Administered Comorbidity Questionnaire: a new method to assess comorbidity for clinical and health services research. *Arthritis Rheum*. 2003;49:156-163.
35. Cattaneo MD. Efficient semiparametric estimation of multi-valued treatment effects under ignorability. *J Econom*. 2010;155:138-154.

36. Robins JM. Association, causation, and marginal structural models. *Synthese*. 1999;121:151-179.
37. Achiron A, Givon U, Magalashvili D, et al. Effect of alfacalcidol on multiple sclerosis-related fatigue: a randomized, double-blind placebo-controlled study. *Mult Scler*. 2015;21:767-775.
38. National Academies of Sciences, Engineering and Medicine. *Developing Multimodal Therapies for Brain Disorders: Proceedings of a Workshop*. Washington, DC: The National Academies Press; 2017.
39. Arroyo Hornero R, Hamad I, Corte-Real B, Kleinewietfeld M. The impact of dietary components on regulatory T cells and disease. *Front Immunol*. 2020;11:253.
40. Langley MR, Triplet EM, Scarisbrick IA. Dietary influence on central nervous system myelin production, injury, and regeneration. *Biochim Biophys Acta Mol Basis Dis*. 2020;1866:165779.
41. Wahls T, Scott MO, Alshare Z, et al. Dietary approaches to treat MS-related fatigue: comparing the modified Paleolithic (Wahls Elimination) and low saturated fat (Swank) diets on perceived fatigue in persons with relapsing–remitting multiple sclerosis: study protocol for a randomized controlled trial. *Trials*. 2018;19:309.
42. Wahls T, Watson K, Turpin R, Tsuyuki R. P0208—effects of Wahls elimination and Swank dietary patterns on multiple sclerosis related fatigue, quality of life, processing speed and waking distance. MSVirtual 2020, 2020.
43. Brenton JN, Banwell B, Bergqvist AGC, et al. Pilot study of a ketogenic diet in relapsing–remitting MS. *Neurol Neuroimmunol Neuroinflamm*. 2019;6:e565.
44. Weiland TJ, Jelinek GA, Marck CH, et al. Clinically significant fatigue: prevalence and associated factors in an international sample of adults with multiple sclerosis recruited via the internet. *PLoS One*. 2015;10:e0115541.
45. Razazian N, Kazeminia M, Moayedi H, et al. The impact of physical exercise on the fatigue symptoms in patients with multiple sclerosis: a systematic review and meta-analysis. *BMC Neurol*. 2020;20:93.
46. Balto JM, Ensari I, Hubbard EA, Khan N, Barnes JL, Motl RW. Individual and co-occurring SNAP risk factors: smoking, nutrition, alcohol consumption, and physical activity in people with multiple sclerosis. *Int J MS Care*. 2016;18:298-304.
47. Leong TI, Weiland TJ, Jelinek GA, et al. Longitudinal associations of the healthy lifestyle index score with quality of life in people with multiple sclerosis: a prospective cohort study. *Front Neurol*. 2018;9:874.
48. Fisk JD, Pontefract A, Ritvo PG, Archibald CJ, Murray TJ. The impact of fatigue on patients with multiple sclerosis. *Can J Neurol Sci*. 1994;21:9-14.
49. Krupp LB, Alvarez LA, LaRocca NG, Scheinberg LC. Fatigue in multiple sclerosis. *Arch Neurol*. 1988;45:435-437.
50. Minden SL, Frankel D, Hadden L, Perloffp J, Srinath KP, Hoaglin DC. The Sonya Slifka Longitudinal Multiple Sclerosis Study: methods and sample characteristics. *Mult Scler*. 2006;12:24-38.
51. Jelinek GA. *Overcoming Multiple Sclerosis: The Evidence-based 7 Step Recovery Program*, 2nd ed. Crows Nest, NSW: Allen & Unwin; 2016.
52. Veauthier C, Hasselmann H, Gold SM, Paul F. The Berlin Treatment Algorithm: recommendations for tailored innovative therapeutic strategies for multiple sclerosis-related fatigue. *EPMA J*. 2016;7:25.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Weiland TJ, Nag N, De Livera A, et al. Two healthy lifestyle scores are associated with lower subsequent fatigue risk using inverse probability weighting in an international longitudinal cohort of people with multiple sclerosis. *Eur J Neurol*. 2021;28:2952–2964. https://doi.org/10.1111/ene.14956

*"It all started with shortness of breath while scuba diving..."**

Solving a 27-year-long diagnostic dilemma in a patient with unexplained progressive respiratory and muscle weakness

Would you recognise the red flags of Pompe disease?

Pompe disease is a rare but treatable neuromuscular disease with a wide spectrum of symptoms.[1]

Join Professor Merrilee Needham—co-author of the publication *Is it Pompe Disease? Australian Diagnostic Considerations*—in the latest series of the Hereditary Diseases Pod.

Over the course of three episodes, she uses real-world Australian case studies to address Pompe disease red flags and diagnostic challenges.

Listen to *Is it Pompe disease? Exploring Australian cases* with

Professor Merrilee Needham
Neurologist, Fiona Stanley Hospital and Perron Institute, Perth

Case 1: Delayed diagnosis in a patient with limb-girdle weakness

Case 2: Diagnostic work-up of a patient with hyperCKaemia

Case 3: Diagnostic journey of a patient with respiratory involvement

Scan the QR code below to download the latest episode of *Is it Pompe disease*?

Listen on Apple Podcasts

Listen on Spotify

*Adapted from a case study presented in episode 3 of *Is it Pompe disease? Exploring Australian cases*.
Image ©JoshWells/www.joshwellsphotography.com

References: 1. Tchan M et al. Neuromuscul Disord 2020;30:389–99.

sanofi-aventis australia pty ltd trading as Sanofi Genzyme ABN 31 008 558 807.
12–24 Talavera Road, Macquarie Park, NSW 2113.
MAT-AU-2100514. POM0064. Prepared March 2021

Proudly supported by Sanofi

SANOFI GENZYME