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

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Abstract

Background

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.

Objectives

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

We used data on sociodemographic, lifestyle and clinical characteristics surveyed from an international cohort of people with MS at baseline and 2.5-year follow-up. Fatigue was defined by Fatigue Severity Scale (FSS>5), healthy lifestyle by the Healthy Lifestyle Index Score (HLIS) and the Smoking, Nutrition, Alcohol, 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

1,268 participants completed the FSS at both timepoints, approximately 62% had fatigue. Using doubly robust IPTW, high (>11/20) HLIS (OR=0.90, 95% 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, higher SNAP score

was associated with lower risk of fatigue (OR=0.89, 95% CI: 0.80-0.97) but that 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.

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 standardisation 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 IPW regression adjustment method, also known as doubly robust IPTW, which differ from standard IPTW in that the exposure and outcome variables have separate model components rather than each obliged to have the same. This gives a greater degree of confidence since it means only one of the models need be correctly specified in order to realise an unbiased measure of the exposure-outcome association[23].

We investigated the effect 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 2.5-year follow-up in the Health Outcomes and Lifestyle In a Sample of people with Multiple sclerosis (HOLISM) longitudinal cohort using IPTW.

2. Methods

2.1 Participants and recruitment

Participants were enrolled in the HOLISM study for which methodology 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 was ≥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 reidentifiable 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 George Jelinek or Tracey Weiland who can supply aggregate group data on request.

2.2 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 as 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 (DHQ)[29], querying aspects of food intake, as well as food selection and preparation, realising 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, categorised 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 estimated average daily grams of alcohol intake (the definition of a standard drink was provided for different alcoholic beverages and volumes).

Clinical measures

Clinically significant fatigue was assessed by 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 (PDDS) scale[32], from which disease duration-adjusted Patient-derived Multiple Sclerosis Severity Score (P-MSSS) was calculated[33]. Number of treated comorbidities were assessed at baseline using the Self-administered Comorbidity Questionnaire[34]. Prescription medication use was queried at each review, including immunomodulatory, antidepressant, and anti-fatigue medications.

Healthy lifestyle indices

Two lifestyle indices were used as primary exposure covariates. HLIS was estimated from lifestyle data, with score assignment based on quintiles for continuous DHQ, IPAQ, and BMI, and specified absolute terms for alcohol intake and smoking[35] (Supplemental Table 1). Scores were assigned to categories within variables with higher points corresponding to healthier lifestyle.

Five domain scores were summated realising a total HLIS score ranging 0-20, where 20 indicates healthiest behaviour. Since few participants scored below 3 (0=1, 1=0, 2=11) and above 18 (19=6, 20=0), total HLIS score was truncated to amalgamate scores 0-3 and 18-20, giving a total HLIS score ranging 3-18.

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 realise a total SNAP score ranging 0-5, 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 1-5.

2.4 Data analysis

Outcomes

Two outcomes were evaluated: (1) absolute risk of clinically significant fatigue (mean >5) at follow-up; (2) 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 dichotomised. For SNAP, 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 dichotomised composite scores, dichotomised 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 dichotomised as 0-3 vs 4. For SNAP, subdomains were already dichotomous terms of 0 or 1.

Characteristics by clinically significant fatigue

Analyses of between group difference for polychotomous 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.

IPTW regression analyses

We used an inverse probability weighting regression adjustment method; weighted regression coefficients were used to estimate probability of outcomes at each level of the treatment variable, from which risk ratios were estimated[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. We adopted the criterion of reducing the post-weighting standardised differences between groups to within an absolute value of 10%[21].

In addition, since IPTW is sensitive to misspecification of the propensity score model[37], further analyses were undertaken using doubly robust IPTW regression adjustment (IPTW-RA). In contrast to IPTW where both exposure and outcome variables have the same model covariates applied to each, in IPTW-RA, different model covariates can be applied to each variable.

Since IPTW and IPTW-RA models can only evaluate dichotomous or polychotomous terms, but not continuous terms, 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. First was using logistic regression, adjusted for ongoing symptoms from recent relapse. Second, a fully adjusted model was evaluated, further adjusted for baseline age, sex, MS type, number of treated comorbidities, P-MSSS, immunomodulatory medication use, and anti-fatigue medication use, these covariates included based on a priori review of literature and within-study associations with HLIS/SNAP and clinically significant fatigue. Third, the standard IPTW model was applied, as described above. Fourth, 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[38], 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 that 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, College Station, TX, USA).

3.0 Results

3.1 Cohort characteristics

Of 2,466 baseline participants, 1,268 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%), 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 39% having SNAP score >3. As would be expected, HLIS and SNAP score were strongly correlated (r=0.64, p<0.001).

-- Insert Table 1 About Here --

Comparing these characteristics by 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, though 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.

-- Insert Figure 1 About Here –

Baseline determinants of clinically significant fatigue risk at follow-up

Weighted standardised differences in model covariates were markedly reduced compared to unweighted scores for both HLIS and SNAP, falling well within the -10%-10% interval and generally lying close to 0%, indicative of balance between groups (Supplemental Figure 1).

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, though none reached statistical significance, non-smokers and higher physical activity showed robust associations by IPTW-RA, such that nonsmokers 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, while 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).

-- Insert Table 2. About Here –

Sensitivity analyses exploring dichotomised 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 (Supplementary Table 2).

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

Weighted standardised differences in model covariates were markedly reduced compared to the raw for both HLIS and SNAP, falling well within the -10%-10% interval and generally lying close to 0%, indicative of balance between groups (Supplementary Figure 2).

Baseline truncated continuous HLIS was associated with 7% lower change in clinically significant fatigue, though on adjustment this became non-significant (Table 3). HLIS >11 was associated with 36% lower change in clinically significant fatigue, and 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, 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 near significant.

-Insert Table 3 about here–

Sensitivity analyses for differing cut-points of dichotomised HLIS and SNAP showed inverse trends for HLIS 12 and SNAP≤3 (Supplementary Table 3).

4.0 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 comprehensively than standard multivariable regression, we found robust protective associations of higher healthy lifestyle scores with risk of clinically significant fatigue. In our cohort, higher HLIS was associated with 10% reduced risk of fatigue ($p=0.018$), while 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 benefits of healthy lifestyle, the value of lifestyle risk factor reduction in alleviating MS symptoms and/or disease course remains under-utilised, particularly when healthy lifestyle is conceptualised as a collection of behavioural choices. For heterogeneous conditions, such as MS, which likely[22] have several pathological processes driving disease, multimodal interventions offer potential to target different pathological mechanisms simultaneously[39].

Main findings

In our sample of adults with MS, baseline SNAP and HLIS were both associated with lower risk of fatigue at 2.5-year follow-up, even after controlling for confounders. For both composite scores, we demonstrated this effect using three methods: multivariable logistic regression, IPTW, and IPTW-RA. While HLIS>11 was associated with a 33% lower risk of subsequent fatigue using standard multivariable logistic regression, using the IPTW method the magnitude of effect reduced to a 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, though not reaching statistical significance, while for SNAP significant inverse associations were seen for all but the alcohol subdomain.

Despite the association observed for baseline SNAP and HLIS and lower risk of fatigue 2.5 post-baseline, the effects observed for change in fatigue over 2.5 years were less clear. Our analyses of differing cut-points of dichotomised SNAP and HLIS, produced conflicting results for HLIS and SNAP. Higher SNAP scores – the equivalent of adopting at least 4 of 5 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. Among subdomains, 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 lifestyles 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, 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 change in fatigue, despite both HLIS and SNAP showing similar magnitudes, that for HLIS was consistently weaker and less significant. We interpret this as a positive finding from a superior measure, concluding that the SNAP composite lifestyle score, and particularly the subdomains of smoking and diet, show a robust prospective association with fatigue and change thereof over 2.5 years' follow-up.

Our findings that never smoking and 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 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[40], or directly by affecting cellular metabolism oxidative stress, giving rise to immune dysregulation, chronic inflammation, modulation of glial function, and neurodegeneration[41]. The exact nature of the healthy diet which may improve MS progression is uncertain, though many diet programs have been proposed for people with MS, including lifestyle programs like the Wahls Elimination diets which was recently demonstrated to improve fatigue in people with MS[42, 43], as well as non-MS specific diets like the ketogenic diet which a single-arm pilot RCT suggested may improve fatigue[44]. Further research on this topic should be pursued.

These data are consistent with our previously reported observational data from this cohort at baseline[45], 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[46].

Increasingly, composite scores of lifestyle risk factors are being applied to data collected from observational studies people with MS[18, 19, 47, 48], including longitudinal cohorts. While such cohorts enable evaluation of causal inferences and permit long-term monitoring of conditions, residual confounding in multivariable modeling limits interpretation. The use of propensity weighting allows a superior regression methodology that more approximates, but 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, 49-51], 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 conceivable therefore that their health behaviors 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. While secondary email addresses were also queried, these were likely 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 program[52], which includes recommendations for sun exposure, physical activity, non-smoking, moderate alcohol consumption, supplement use, and healthy diet. While 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 generalisability 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. While 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[53], and so the absence of that here is a limitation.

Future Research

We used well established lifestyle composites derived from non-MS populations. 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 near 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.

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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				
Female	216 (17.3%)	85 (18.0%)	131 (16.8%)	
	1,035 (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				
2	55 (4.9%)	9 (2.1%)	46 (6.6%)	
3	219 (19.4%)	63 (14.4%)	156 (22.5%)	p=0.066
4	427 (37.8%)	141 (32.2%)	286 (41.3%)	**p=0.015**
5	343 (30.3%)	172 (39.3%)	171 (24.7%)	**p<0.001**
(Missing)	87 (7.7%)	53 (12.1%)	34 (4.9%)	**p<0.001**
	(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**
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. Abbreviations: HLIS = Healthy Lifestyle Index Score; P-MSSS = Participant-reported MS Severity Score; PPMS = Primary progressive MS; RRMS = relapsing-remitting MS; SNAP = Smoking, Nutrition, Alcohol Consumption, and Physical Activity; SPMS = secondary progressive MS.				

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 Female	131/216 (60.7%) 647/1,035 (62.5%)	 1.00 [Reference] 1.19 (0.87, 1.63) p=0.29	 1.00 [Reference] 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 SPMS PPMS Unsure/other	488/844 (57.8%) 105/133 (79.0%) 71/90 (78.9%) 101/168 (60.1%)	1.00 [Reference] **2.92 (1.85, 4.60)** **2.72 (1.55, 4.80)** 1.04 (0.73, 1.48)	1.00 [Reference] 1.53 (0.90, 2.59) 1.45 (0.74, 2.86) **-**		
P-MSSS		**1.33 (1.25, 1.41)** **p<0.001**	**1.26 (1.18, 1.35)** **p<0.001**		
Immunomodulatory					

medication use?					
No Yes	402/668 (60.2%) 376/583 (64.5%)	1.00 [Reference] 1.25 (0.98, 1.58) p= 0.070	1.00 [Reference] **1.37 (1.04, 1.82)** **p=0.026**		
Prescription antidepressant medication use?					
No Yes	614/1,046 (58.7%) 164/205 (80.0%)	1.00 [Reference] **2.81 (1.94, 4.08)** **p<0.001**	1.00 [Reference] 1.32 (0.85, 2.06) p= 0.22		
Prescription antifatigue medication use?					
No Yes	697/1,158 (60.2%) 81/93 (87.1%)	1.00 [Reference] **5.19 (2.72, 9.93)** **p<0.001**	1.00 [Reference] **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 >11	396/574 (69.0%) 273/518 (52.7%)	1.00 [Reference] **0.52 (0.40, 0.67)** **p<0.001**	1.00 [Reference] **0.67 (0.51, 0.89)** **p=0.005**	1.00 [Reference] **0.89 (0.80, 0.97)** **p=0.010**	1.00 [Reference] **0.90 (0.81, 0.98)** **p=0.018**

HLIS Diet					
≤80% >80%	574/886 (64.8%) 173/323 (53.6%)	1.00 [Reference] **0.66 (0.51, 0.87)** **p=0.003**	1.00 [Reference] 0.85 (0.63, 1.13) p=0.26	1.00 [Reference] 0.95 (0.86, 1.04) p=0.31	1.00 [Reference] 0.97 (0.80, 1.06) p=0.55
HLIS physical activity					
≤80% >80%	663/1,064 (62.3%) 26/55 (47.3%)	1.00 [Reference] **0.55 (0.31, 0.96)** **p=0.034**	1.00 [Reference] 0.68 (0.38, 1.23) p=0.20	1.00 [Reference] 0.82 (0.60, 1.03) p=0.10	1.00 [Reference] 0.84 (0.65, 1.03) p=0.094
HLIS alcohol consumption					
≤80% >80%	431/741 (58.2%) 304/452 (67.3%)	1.00 [Reference] **1.44 (1.12, 1.85)** **p=0.005**	1.00 [Reference] 1.28 (0.97, 1.69) p=0.077	1.00 [Reference] 1.06 (0.96, 1.15) p=0.21	1.00 [Reference] 1.06 (0.97, 1.15) p=0.18
HLIS smoking					
≤80% >80%	370/559 (66.2%) 370/641 (57.7%)	1.00 [Reference] **0.69 (0.54, 0.88)** **p=0.003**	1.00 [Reference] **0.76 (0.58, 1.00)** **p=0.047**	1.00 [Reference] **0.92 (0.84, 1.00)** **p=0.048**	1.00 [Reference] 0.92 (0.84, 1.00) p=0.050
HLIS BMI					
≤80% >80%	533/826 (64.5%) 241/420 (57.4%)	1.00 [Reference] **0.77 (0.60, 0.99)**	1.00 [Reference] 0.91 (0.69, 1.20)	1.00 [Reference] 0.98 (0.89, 1.07)	1.00 [Reference] 0.97 (0.88, 1.06)

		p=0.039	p=0.50	p=0.66	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)**	**0.54 (0.41, 0.71)**	**0.81 (0.73, 0.89)**	**0.82 (0.74, 0.91)**
		p<0.001	**p<0.001**	**p<0.001**	**p<0.001**
SNAP diet domain					
Unhealthy	643/1,000 (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)**	**0.52 (0.36, 0.73)**	**0.81 (0.70, 0.91)**	**0.82 (0.72, 0.92)**
		p<0.001	**p<0.001**	**p<0.001**	**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)**	**0.65 (0.48, 0.90)**	**0.87 (0.79, 0.96)**	**0.86 (0.78, 0.95)**
		p<0.001	**p=0.008**	**p=0.007**	**p=0.003**
SNAP alcohol					

intake domain					
Unhealthy Healthy	117/204 (57.4%) 630/1,005 (62.7%)	1.00 [Reference] 1.25 (0.91, 1.72) p=0.16	1.00 [Reference] 1.10 (0.78, 1.56) p=0.59	1.00 [Reference] 1.00 (0.86, 1.13) p=0.97	1.00 [Reference] 1.00 (0.88, 1.13) p=0.95
SNAP smoking domain					
Unhealthy Healthy	82/100 (82.0%) 660/1,104 (59.8%)	1.00 [Reference] **0.35 (0.20, 0.61)** **p<0.001**	1.00 [Reference] **0.48 (0.27, 0.85)** **p=0.013**	1.00 [Reference] **0.82 (0.69, 0.95)** **p=0.022**	1.00 [Reference] **0.82 (0.69, 0.95)** **p=0.019**
SNAP BMI domain					
Unhealthy Healthy	375/537 (69.8%) 401/712 (56.3%)	1.00 [Reference] **0.55 (0.43, 0.70)** **p<0.001**	1.00 [Reference] **0.72 (0.55, 0.94)** **p=0.017**	1.00 [Reference] **0.90 (0.83, 0.98)** **p=0.022**	1.00 [Reference] **0.91 (0.83, 0.99)** **p=0.033**

Model 1 utilises logistic regression adjusted for whether participants were experiencing ongoing symptoms from recent relapse at either review.

Model 2 utilises logistic regression adjusted for the covariates in Model 1, as well as age, sex, MS type, and P-MSSS, number of treated comorbidities, and prescription antifatigue medication use.

Model 3 utilises inverse probability treatment weighting adjusted for the covariates in Model 2.

Model 4 utilises inverse probability-weighted regression adjustment adjusted for the covariates in Models 2 & 3.

Abbreviations: BMI = Body mass index; HLIS = Healthy Lifestyle Index Score; 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;

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 Yes	553/949 (58.3%) 155/194 (79.9%)	1.00 [Reference] **1.85 (1.21, 2.84) p=0.005**	1.00 [Reference] 1.20 (0.74, 1.97) p=0.46		
Prescription antifatigue medication use?					
No Yes	631/1,054 (59.9%) 77/89 (86.5%)	1.00 [Reference] **2.64 (1.31, 5.30) p=0.006**	1.00 [Reference] **2.43 (1.17, 5.03) p=0.017**		
HLIS		**0.93 (0.89, 0.98) p=0.006**	0.96 (0.91, 1.01) p=0.088		
≤11 >11	378/550 (68.7%) 263/494 (53.2%)	1.00 [Reference] **0.64 (0.48, 0.87) p=0.004**	1.00 [Reference] **0.73 (0.53, 0.99) p=0.046**	1.00 [Reference] 0.92 (0.85, 1.00) p=0.068	1.00 [Reference] 0.93 (0.85, 1.01) p=0.080
HLIS Diet					
≤80% >80%	538/831 (64.7%) 170/312 (54.5%)	1.00 [Reference] 0.95 (0.69, 1.30)	1.00 [Reference] 1.04 (0.75, 1.45)	1.00 [Reference] 1.01 (0.92, 1.10)	1.00 [Reference] 1.02 (0.93, 1.11)

		p=0.74	p=0.81	p=0.84	p=0.66
HLIS physical activity					
≤80% >80%	636/1,018 (62.5%) 25/52 (48.1%)	1.00 [Reference] 0.59 (0.30, 1.14) p=0.12	1.00 [Reference] 0.66 (0.33, 1.30) p=0.23	1.00 [Reference] 0.83 (0.59, 1.08) p=0.19	1.00 [Reference] 0.88 (0.68, 1.07) p=0.22
HLIS alcohol consumption					
≤80% >80%	412/704 (58.5%) 284/423 (67.1%)	1.00 [Reference] 1.04 (0.77, 1.41) p=0.78	1.00 [Reference] 1.02 (0.74, 1.40) p=0.91	1.00 [Reference] 0.99 (0.90, 1.07) p=0.76	1.00 [Reference] 0.99 (0.91, 1.07) p=0.85
HLIS smoking					
Unhealthy Healthy	346/523 (66.2%) 355/611 (58.1%)	1.00 [Reference] **0.62 (0.46, 0.83)** **p=0.001**	1.00 [Reference] **0.67 (0.49, 0.91)** **p=0.009**	1.00 [Reference] **0.90 (0.83, 0.97)** **p=0.011**	1.00 [Reference] **0.90 (0.83, 0.97)** **p=0.011**
HLIS BMI					
Unhealthy Healthy	482/751 (64.2%) 222/388 (57.2%)	1.00 [Reference] 0.91 (0.67, 1.23) p=0.54	1.00 [Reference] 1.01 (0.74, 1.38) p=0.95	1.00 [Reference] 1.01 (0.92, 1.09) p=0.87	1.00 [Reference] 1.00 (0.91, 1.08) p=0.97
SNAP score					
0-1 2	43/52 (82.7%) 146/208 (70.2%)	1.47 (0.61, 3.51) 1.00 [Reference]	1.29 (0.53, 3.14) 1.00 [Reference]	0.78 (0.43, 1.14) 1.00 [Reference]	0.89 (0.73, 1.05) 1.00 [Reference]

3 4 5 Trend:	278/413 (67.3%) 166/328 (50.6%) 31/79 (39.2%)	1.15 (0.75, 1.75) **0.64 (0.42, 0.99)** 0.63 (0.33, 1.18) **p=0.003**	1.23 (0.79, 1.90) 0.78 (0.50, 1.23) 0.66 (0.34, 1.27) **p=0.038**	1.05 (0.92, 1.17) 0.90 (0.78, 1.03) 1.02 (0.84, 1.21)	1.04 (0.92, 1.17) 0.90 (0.78, 1.03) 0.96 (0.78, 1.14)
0-3 >3	467/673 (69.4%) 197/407 (48.4%)	1.00 [Reference] **0.57 (0.42, 0.77)** **p<0.001**	1.00 [Reference] **0.65 (0.47, 0.89)** **p=0.007**	1.00 [Reference] **0.88 (0.80, 0.97)** **p=0.008**	1.00 [Reference] **0.89 (0.80, 0.97)** **p=0.011**
SNAP diet domain					
Unhealthy Healthy	612/952 (64.3%) 91/184 (49.5%)	1.00 [Reference] **0.66 (0.45, 0.98)** **p=0.037**	1.00 [Reference] **0.63 (0.42, 0.94)** **p=0.024**	1.00 [Reference] **0.88 (0.78, 0.99)** **p=0.036**	1.00 [Reference] **0.88 (0.77, 0.98)** **p=0.022**
SNAP physical activity domain					
Unhealthy Healthy	273/361 (75.6%) 402/732 (54.9%)	1.00 [Reference] **0.65 (0.47, 0.91)** **p=0.012**	1.00 [Reference] 0.84 (0.59, 1.19) p=0.32	1.00 [Reference] 0.96 (0.87, 1.06) p=0.46	1.00 [Reference] 0.96 (0.87, 1.05) p=0.36
SNAP alcohol intake domain					
Unhealthy Healthy	110/195 (56.4%) 598/948 (63.1%)	1.00 [Reference] 1.20 (0.82, 1.74) p=0.36	1.00 [Reference] 1.11 (0.75, 1.65) p=0.60	1.00 [Reference] 0.99 (0.87, 1.12) p=0.89	1.00 [Reference] 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	626/1,043 (60.0%)	**0.49 (0.27, 0.91)**	0.57 (0.31, 1.06)	**0.84 (0.70, 0.99)**	0.86 (0.72, 1.00)
		p=0.023	p=0.075	**p=0.048**	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)	0.88 (0.64, 1.19)	0.97 (0.89, 1.05)	0.97 (0.89, 1.05)
		p=0.096	p=0.40	p=0.44	p=0.47

Model 1 utilises logistic regression adjusted for baseline fatigue and whether participants were experiencing ongoing symptoms from recent relapse at either review.

Model 2 utilises logistic regression adjusted for the covariates in Model 1, as well as age, sex, MS type, and P-MSSS, number of treated comorbidities, and prescription antifatigue medication use.

Model 3 utilises inverse probability treatment weighting adjusted for the covariates in Model 2.

Model 4 utilises inverse probability-weighted regression adjustment adjusted for the covariates in Models 2 & 3.

Abbreviations: BMI = Body mass index; HLIS = Healthy Lifestyle Index Score; 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.

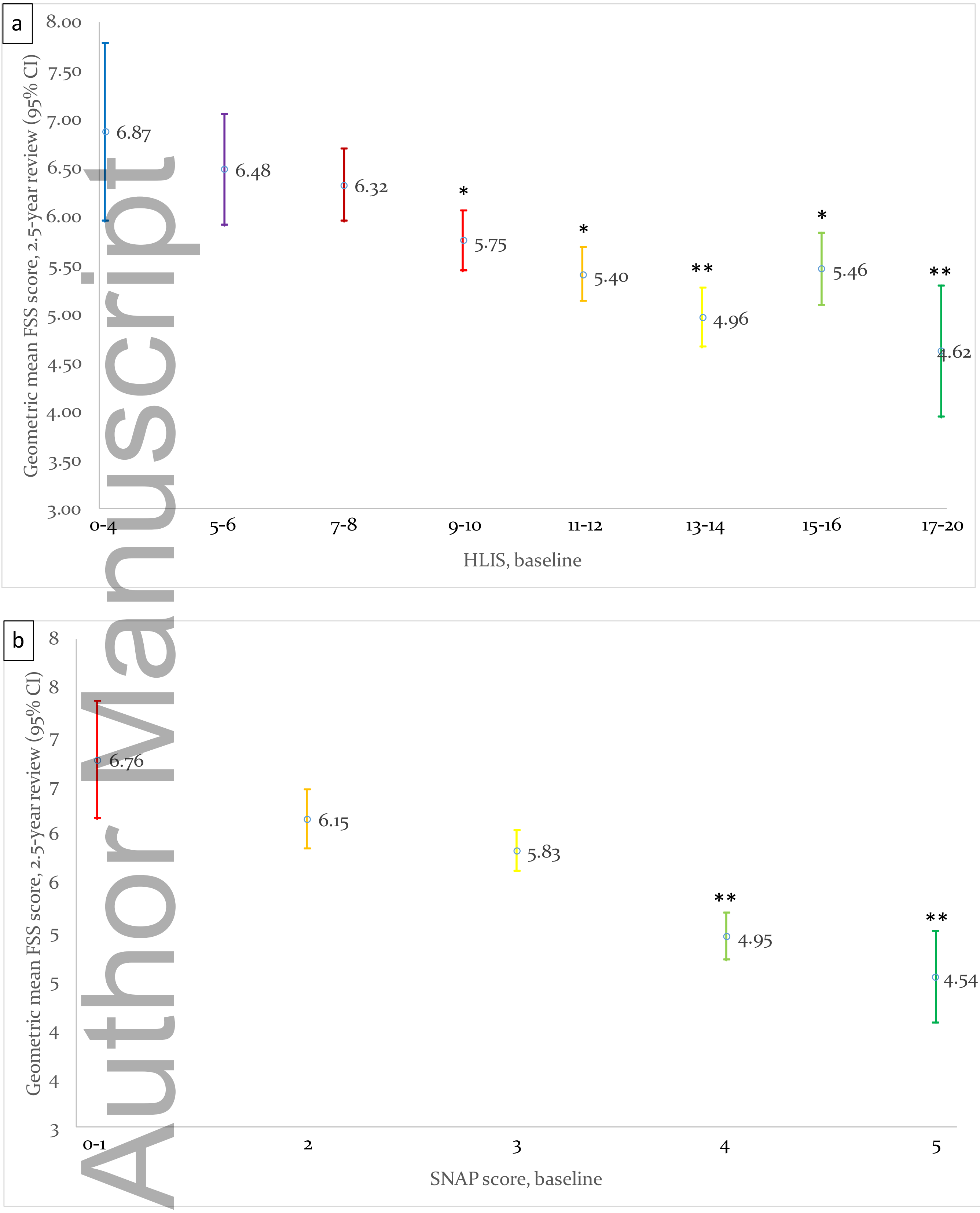

Figure 1: Fatigue Severity Score sum at follow-up against (a) HLIS and (b) SNAP at baseline. The plots show geometric mean follow-up FSS (95% CI) by level of baseline HLIS (a) and SNAP (b) scores, adjusted for ongoing symptoms from recent relapse. *=p<0.05. **=p<0.001.