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Author/s:
Gascoyne, CR;Simpson, S;Chen, J;van der Mei, I;Marck, CH

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MS. CLAUDIA ROSE GASCOYNE (Orcid ID : 0000-0002-1241-4062)

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Modifiable factors associated with depression and anxiety in multiple sclerosis

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Gascoyne, Claudia R MSc[1]; Simpson, Jr., Steve PhD[2,3]; Chen, Jing MD[3], van der Mei, Ingrid PhD[3]; Marck, Claudia H PhD[1,2];

[1]Disability and Health Unit, Melbourne School of Population and Global Health, The University of Melbourne

[2]Centre of Epidemiology and Biostatistics, Melbourne School of Population and Global Health, The University of Melbourne

[3]Menzies Institute for Medical Research, University of Tasmania.

Corresponding Author:

Claudia Gascoyne

Melbourne School of Population and Global Health

207 Bouverie St, The University of Melbourne, Victoria 3010, Australia

E-mail: claudiagascoyne@gmail.com

Telephone: +61 428 043 117

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ABSTRACT (225/250)

Objectives: Modifiable lifestyle factors are implicated in multiple sclerosis (MS) symptoms but their role in mood is unclear. This study aims to investigate associations between lifestyle and depression and anxiety in Australian participants with MS.

Materials & Methods: Self-reported data from the Australian Multiple Sclerosis Longitudinal Study included the Hospital Anxiety and Depression Scale (HADS) and lifestyle measurements from 1,500 participants. SNAP score (range 0-5) was the sum of: non-smoking, sufficient fruit/vegetable intake, non-hazardous alcohol consumption, sufficient physical activity, and healthy BMI. Analyses by log-binomial and linear regression were adjusted for confounding.

Results: Depression and anxiety was prevalent in 27% and 40%, respectively; 20% had both. Mean SNAP score was 2.7/5; only 3% met all healthy lifestyle recommendations. Only 10% reported adequate fruit/vegetable intake, and 22% reported a combination of unhealthy BMI, inadequate physical activity and inadequate nutrition. A healthier SNAP score was associated with lower depression prevalence (adjusted prevalence ratio 0.83 (95%CI 0.75, 0.92) per unit increase) and depression severity (adjusted β -0.44 (95%CI -0.64, -0.24)), but not with anxiety.

Conclusions: Modifiable lifestyle factors are associated with lower frequency and severity of depression, but not anxiety, in Australian people with multiple sclerosis. The associations between a healthier SNAP score and lower depression are likely bi-directional. SNAP risk factor prevalence and co-occurrence, especially inadequate nutrition and low physical activity, was high among Australians with MS.

Keywords: multiple sclerosis; anxiety; depression; lifestyle; health behaviours; SNAP

INTRODUCTION

Clinically significant symptoms of anxiety or depression are observed in up to 40% of people with multiple sclerosis (MS)[1], with prevalence estimates approximately twice that

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of the general population[2]. It is possible that anxiety and depression arise from inflammation of the CNS and are hence considered symptoms of MS, yet they can also be considered comorbidities, secondary to the disease[3]. Both mood states have been associated with increased level of disability[4] and fatigue[5]. Stress responses associated with anxiety, as well as depressive symptoms, have been associated with increased inflammation and with exacerbations of MS[6].

Current pharmacological or psychological treatments for depression are proven to be generally effective in reducing clinically significant symptoms[7] in most people with MS. However, the effectiveness of anxiety treatments for people with MS has not been established[7]. Furthermore, only half of all people with MS suffering from anxiety or depression receive treatment for their condition[2].

Modifiable lifestyle factors such as smoking status, nutrition, alcohol consumption, physical activity level and body mass index (BMI) make up the 'SNAP' score, a construct used in general practice[8]. These SNAP factors are major determinants of morbidity, mortality, and functionality in the general population[9]. Growing evidence suggests that these same SNAP factors also play a major role in brain and mental health[9]. Whether there is an additive effect from fulfilling more of these SNAP factors is unclear, given that few studies have explored SNAP score in people with MS.

The current study uses a representative sample of people with MS in Australia to 1) describe the prevalence of SNAP risk factors and their co-occurrence; 2) investigate whether SNAP score is associated with the prevalence and severity of anxiety and depression.

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MATERIALS & METHODS

All data was sourced from the Australian Multiple Sclerosis Longitudinal Study (AMSLS). The sample is large, representative and generalisable to the Australian MS population[10]. To be eligible for the study, an individual must have a diagnosis of MS, be over 18 years of age, and live in any Australian state or territory. The study was approved by the Tasmanian Health and Medical Human Research Ethics Committee and all participants provided informed consent. The 2016 AMSLS Lifestyle survey was conducted from August to October 2016. Invitations were sent to all 3112 active participants (2182 online surveys and 930 paper surveys), and 1518 (48.78 %) participants responded to the survey (1067 online and 451 paper surveys). Non-response analyses showed no significant difference in sex ($p=0.101$) and education level ($p=0.113$) between the respondents and non-respondents, while the respondents were slightly older (+1.49 years, $p<0.01$) and had a slightly longer MS duration since diagnosis (+0.56 years, $p=0.04$). These differing factors were included in multivariable models.

SNAP Score

SNAP – comprised of smoking, nutrition, alcohol and physical activity – was first proposed as part of a policy framework tool by the Australian Government in 2001 for use in general practice[8]. SNAP has previously been used in a North American sample of people with MS to estimate prevalence of lifestyle risk factors[11]. The five factors comprising the SNAP score in our study were modelled on this study[11] and another more recent study[12] both using similar aggregate scores, with minor deviations to suit the Australian SNAP guidelines. Our aggregate SNAP score included smoking status, diet (assessed by the Diet History Questionnaire, DHQ[13]), alcohol consumption, physical activity level (assessed by the International Physical Activity Questionnaire, IPAQ[14]), and BMI (estimated from self-reported height and weight, as weight (kg)/height $(m)^2$), each coded as binary variables. To achieve a score for non-smoker, an individual had to report smoking less than one cigarette, cigar or pipe per day. A healthy diet was defined as consuming ≥5 serves of

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vegetables/day and ≥2 serves of fruit at least six days/week, as per the Australian Dietary Guidelines[15]. Non-hazardous alcohol consumption required consuming ≤2 standard alcoholic drinks/day, the national recommendation[16]. Adequate level of physical activity was defined as moderate/high (versus low) level of physical activity as scored per the IPAQ guidelines[14]. A healthy BMI was defined as within the healthy BMI range (18.5 kg/m^2 to 24.9 kg/m^2) as opposed to underweight (below 18.5 kg/m^2), overweight (25 kg/m^2 to 29.9 kg/m^2) or obese (30.0 kg/m^2 and above)[17].

Anxiety and Depression

The Hospital Anxiety and Depression Scale (HADS)[18] was used to measure cognitive and emotional symptoms of anxiety and depression. The HADS has been validated for use in people with MS to measure depression and generalised anxiety[19]. The two subscales of the HADS, anxiety and depression, each had a range of 0-21 and were evaluated to assess associations with depression/anxiety severity. The HADS threshold for mild symptoms (≥8) was used to determine whether an individual showed clinically significant symptoms of anxiety or depression[18].

Other data collected included age, sex, MS type, disability measured by the Patient-Determined Disease Steps (PDDS) scale[20], fatigue measured by the Fatigue Severity Scale (FSS)[21], disease duration since symptom onset, MS disease-modifying therapy use, treatment for depression or anxiety, number of previous or current comorbidities (including a list of 30 common chronic medical conditions and a “other” free text option), education level, employment status, remoteness, and socioeconomic status measured by the SEIFA Index of Relative Socioeconomic Advantage and Disadvantage (IRSAD)[22].

Statistical Analyses

Associations with prevalent anxiety/depression were assessed using log-binomial regression, estimating a prevalence ratio. Associations with severity of anxiety and depression symptoms were assessed by linear regression. Polytomous independent

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variables were evaluated as predictors of outcomes using log-binomial regression, the stratum-specific values using an interaction-expansion operator. For ordinal polytomous independent variables, in addition to the stratum-specific estimates of association, the regression was also run without the interaction expansion operator, thus evaluating the categorical term as a continuous variable. The significance of this association denoted the test for trend. All models were adjusted for age, sex, disability, fatigue, depression/anxiety treatment, education, and socioeconomic status. These confounders were identified via a directed acyclic graph (DAG), which was created using relevant literature according to best practice epidemiological methods[23]. All analyses were complete case analyses, meaning only those with complete SNAP, anxiety and depression data were included in analyses. Analyses were conducted using STATA 13.0 (StataCorp, College Station, USA).

RESULTS

1500 participants completed enough data to be included in this study. The majority of participants were female (79.5%), unemployed (60.4%), used disease-modifying therapies (62.4%) and had relapsing-remitting MS (61.9%) (Table 1). Almost half of the sample had a mild level of disability as defined by PDDS<3 (47.6%). Comorbidities were experienced by the vast majority of participants (91.1%), with some reporting more than ten comorbidities. Those with complete data were similar to those with incomplete data, except that those with incomplete data were more likely to be severely disabled and receiving treatment for depression (Table 1). Over one-third of participants had clinically significant symptoms of anxiety and roughly one-quarter had clinically significant symptoms of depression; one-fifth had both anxiety and depression.

[Insert Table 1 here]

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SNAP Factors

Most participants did not smoke (89.6%) and reported alcohol consumption within recommended levels (82.9%; Table 2). Around 10% of the sample consumed the recommended daily intake of fruit and vegetables, with 33.1% meeting the fruit consumption targets and 17.0% meeting the vegetable consumption targets. Just over half of participants engaged in adequate physical activity (52.9%), while 39% had a healthy BMI.

[Insert Table 2 here]

SNAP Risk Factor Co-occurrence

The most common combination of SNAP risk factors was unhealthy BMI, inadequate physical activity and inadequate nutrition, observed in almost one-quarter of the participants (22.2%; Figure 1). Of those with just one SNAP risk factor, poor diet was the most common, with 14.0% meeting all other SNAP factor recommendations except for consumption of the recommended daily intake of fruit and vegetables.

[Insert Figure 1 here]

SNAP Protective Factor co-occurrence

Only 3.0% of the sample met all five SNAP protective factor recommendations, while 0.8% met none at all (Figure 1).

Anxiety and depression

Anxiety was less prevalent with increasing age, and more prevalent in females compared to males (Table 3). Participants with moderate or severe disability had a roughly 2-fold greater prevalence of depression, but for anxiety there was no consistent relationship with disability. Prevalent fatigue, however, was associated with a higher prevalence of anxiety and depression. Progressive-onset MS was associated with a greater prevalence of

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depression compared to relapse-onset MS. Those with more comorbidities were more likely to have anxiety and depression. Education, employment and socioeconomic status were associated with lower prevalence of depression, but none were significantly associated with anxiety. Participants reporting anxiety and/or depression treatment were more likely to have anxiety and depression.

[Insert Table 3 here]

SNAP Protective Factors and Anxiety & Depression

Non-smokers and those engaging in adequate physical activity had lower prevalence of depression and lower HADS-Depression scores (Table 4). Participants who met the recommendations for healthy diet had lower HADS-Depression scores. Those who reported non-hazardous consumption of alcohol had a lower prevalence of depression. Non-smoking status was associated with a lower anxiety severity, but none of the other individual SNAP factors were associated with anxiety severity or prevalence.

[Insert Table 4 here]

Higher SNAP score showed a significant and dose-dependent inverse relationship with depression prevalence and severity, such that those with a SNAP score of 4-5 had 43% lower prevalence of depression and 1.57-points lower HADS-Depression score compared to those with a SNAP score of 0-1. When analyzing the SNAP score as a continuous variable, every unit increase in SNAP score was associated with a 17% reduction in prevalent depression and a 0.44 unit lower actual HADS depression score. While there was some indication of an inverse relationship between SNAP score and anxiety severity, this was of poor dose-dependency and did not reach statistical significance.

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DISCUSSION

This study examined the association between an aggregate lifestyle score and depression & anxiety using data from a representative sample of people with MS in Australia. A healthier lifestyle, as measured by a higher SNAP score, was associated with a lower prevalence and severity of depression. No significant associations were observed with the prevalence and severity of anxiety.

Depression was common (27%) and associated with SNAP risk factors smoking, alcohol consumption and physical inactivity, while depression severity was associated with smoking, inadequate nutrition and physical inactivity. Every unit increase in SNAP score was associated with a 17% reduction in prevalent depression and a 0.44 unit lower actual HADS depression score. The findings are in line with previous work showing that smoking and poor diet were associated with increased risk of depression in people with MS[24]. Research into the mechanisms between diet and mood is still emerging, but evidence for this association is strong within the general population[25]. Observational studies in people with MS have consistently shown an association between physical inactivity and depression[26] as well as excessive alcohol use and depression[27], so our results here are in keeping with these prior findings. We did not find an association between BMI and depression prevalence or severity, however, which is inconsistent with previous studies[24,28]. This could reflect differences in study design or populations, however, this is mere speculation and more research is needed to clarify this.

The underlying mechanisms, and causality, of these associations cannot be disentangled from our data. On the one hand, research has shown that individuals experiencing clinically significant depression are more likely to engage in poor health behaviours[29] and may be less likely to have the motivation to engage in healthy lifestyle behaviours or be proactive about their health. Treating the depression may then also result in a reduction of modifiable risk factors, which may have flow-on effects for general health. However, on the other hand, a combination of lifestyle risk factors may also contribute to the risk for

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depression. Modifying these risk factors may then also see a decrease in depression. Both mechanisms may be at play simultaneously and it is likely that for those with depression a feedback loop exists, whereby the risk for depression is increased by poor health behaviours, while depressive symptoms increase the risk for poor health behaviours, and so on. Sophisticated feedback loops for depression including health behaviours have been described in the literature[30], and a further understanding of these may improve both depressive symptoms and health behaviours.

Anxiety was very common (40%) and anxiety symptom severity was associated with smoking, in line with a previous prospective study in people with MS[31]. However, no other associations were found between individual SNAP factors or SNAP score and anxiety prevalence or symptom severity. Far less is known about the association between anxiety and modifiable lifestyle factors in people with MS given that anxiety disorders are often overlooked and under-treated in this population[2]. One study found that people with MS who have a history of excessive alcohol consumption have a higher lifetime prevalence of anxiety[32] and another found that people with MS with obesity are more likely to have anxiety[28]. There is evidence that the SNAP protective factors are associated with anxiety in other populations, such as those with cardiovascular disease[33].

We found that SNAP risk factors were common, in line with previous studies in the United States[11,34]. The vast majority of people with MS are not consuming the recommended daily requirement of fruit and vegetables (90%), with proper vegetable intake being the most infrequent. The proportions of people with MS who were overweight or obese (58%), had hazardous consumption of alcohol (17%) or smoked (10%), were similar to those of previous studies[11]. Interestingly, however, physical activity levels in this sample were slightly higher compared to a previous study[11]. Inadequate nutrition, physical inactivity and unhealthy BMI was the most common combination of SNAP risk factors (22%)[11].

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Strengths and Limitations

This study benefits from a large sample size and broad and validated representativeness, both to the general Australian population and particularly to the MS population. Accordingly, the generalisability of these results is manifest. The comprehensive measurement of multiple demographic, clinical and lifestyle factors gives us great capacity to control for relevant confounding variables so as to assess the independence of the observed associations. A key limitation of the present analysis is its cross-sectional nature, thus precluding ascription of causal directionality. Likely there exists bi-directionality and further prospective cohort or randomised trial studies are needed to assess the causal direction of these associations, given that retrospective measures of modifiable lifestyle factors were not included as part of the current study.

The lack of association found between SNAP score and anxiety could be due to the fact that the HADS does not differentiate between different types of anxiety, but instead observes cognitive and emotional aspects of generalised anxiety[19]. The HADS measure may not have the specificity to detect other types of anxiety disorders, yet the association between SNAP score and anxiety and depression may differ between disorders.

All variables used in the analyses were self-reported, including all measures used for the SNAP score and the HADS. Due to the size of the study, it was not feasible to extract objective measures for every participant. This possibly introduced differential exposure measurement error, meaning that those with anxiety and/or depression may report their engagement in SNAP protective factors differently to those without anxiety and/or depression. Not enough is known about the direction of this bias to infer its effect on the association between SNAP protective factors and anxiety and depression. Selection bias may have resulted in an under-estimated prevalence of depression and/or anxiety, given that people with more severe symptoms of depression and/or anxiety may be less likely to participate in the survey. A recent relapse may have negatively impacted mood or engagement in modifiable lifestyle behaviours, however these data were not assessed. We

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included number of comorbidities as an aggregate covariable, ensuring a wide range of common chronic medical conditions were included. Analyses of each comorbidity type was beyond the scope of this study.

Implications of Findings

The high prevalence and co-occurrence of SNAP risk factors warrants increased health assessment and referrals by healthcare professionals, especially in people with MS and depression. It is likely that the presence of depressive symptoms will be accompanied by poor lifestyle behaviours, overweight or obesity. Anxiety and depression should be treated as separate and very unique constructs in this population, given their markedly different prevalence, as well as the diverse associations between SNAP score and anxiety and depression observed. Investigation of barriers faced by people with MS in improving health behaviours has identified fatigue, physical impairment and side effects of MS and associated medications[35] and these need to be assessed and addressed on an individual basis. The utility of the SNAP score may vary across the disease course. Longitudinal assessment of lifestyle modification among participants with greater and lesser degrees of disease severity would be informative.

Conclusion

We found that SNAP protective factors and a healthier SNAP score were associated with a lower depression prevalence and severity, while no associations were seen for anxiety. The present study is the first to provide evidence that there is a high prevalence of anxiety and depression in a representative sample of Australian people with MS and that many are not meeting health recommendations. Investigation of the co-occurrence of SNAP risk factors in this population showed that a combination of unhealthy BMI, poor diet and inadequate physical activity is common. Given that SNAP risk factors, anxiety and depression all contribute significantly to the morbidity of MS, efforts to improve the lifestyle and mental health outcomes for an individual with MS should be holistic and all-inclusive. Future prospective studies should elucidate the direction of association between depression and

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SNAP protective factors, alongside investigation of the viability of multi-modal lifestyle modification to treat depressive symptoms in this population.

DECLARATION OF CONFLICTING INTERESTS

The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are not publicly available unless on specific request to the study investigators. Availability is conditional on approval of data sharing from the institutional ethics committee.

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Table 1. Demographic characteristics of the 1,500 participants with multiple sclerosis included in the study.

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Characteristic	Total		Missing Outcome or Exposure Data		Outcome and Exposure Data Available		
	Mean	SD	Mean	SD	Mean	SD	*p*-value
Age, years	56.0	11.2	56.2	11.8	56.0	11.1	0.80
SNAP score	2.7	0.90	2.7	0.87	2.7	0.90	0.16
	Median	IQR	Median	IQR	Median	IQR	*p*-value
Years since symptoms onset	13.0	10.0	13.0	10.0	13.0	10.0	0.44
Comorbidity number	3.0	3.0	3.0	3.0	3.0	3.0	0.88
	N	%	N	%	N	%	*p*-value
Female sex	1,192	79.5%	274	83.0%	918	78.5%	0.07
PDDS							
Mild (1-3)	569	37.9%	20	6.1%	549	46.9%	[ref]

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Moderate (4-6)	412	27.5%	9	2.7%	403	34.4%	0.23
Severe (7-9)	214	14.3%	15	4.6%	199	17.0%	**0.04**
(missing)	305	20.3%	286	86.7%	19	1.6%	**<0.001**
Type of MS at onset							
Relapse-onset MS	858	57.2%	28	8.5%	830	70.9%	[ref]
Progressive-onset MS	119	7.9%	6	1.8%	113	9.7%	0.33
(missing)	523	34.9%	296	89.7%	227	19.4%	**<0.001**
Type of MS now							
Primary-progressive MS	97	8.7%	5	12.2%	92	8.6%	0.37
Relapsing-remitting MS	691	61.9%	23	56.1%	668	62.1%	[ref]
Secondary-progressive MS	167	15.0%	5	12.2%	162	15.1%	0.83
Progressive-relapsing MS	22	2.0%	1	2.4%	21	2.0%	0.76
Unsure	139	12.5%	7	17.1%	132	12.3%	0.33
Prevalent anxiety (HADS-A ≥ 8)	483	39.8%	20	44.4%	463	39.6%	0.51
Prevalent depression (HADS-D ≥ 8)	332	27.3%	10	22.2%	322	27.5%	0.43
Anxiety and depression	237	19.5%	6	13.3%	231	19.7%	0.29
Employed	479	39.6%	12	26.1%	467	40.1%	0.06
DMT use	756	62.4%	23	53.5%	733	62.8%	0.22

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Prevalent fatigue (FSS ≥ 5)	502	41.3%	23	48.9%	479	40.9%	0.28
Socioeconomic status							
Low	428	28.5%	102	30.9%	326	27.9%	0.14
Medium	413	27.5%	96	29.1%	317	27.1%	0.21
High	659	43.9%	132	40.0%	527	45.0%	[ref]
Depression treatment	353	23.5%	96	29.1%	257	22.0%	**0.01**
Anxiety treatment	204	13.6%	49	14.9%	155	13.3%	0.45

Abbreviations: DMT=Disease modifying therapies; IQR=Inter-quartile range; PDDS=Patient Determined Disease Steps; SD=Standard deviation.

Differences in normally distributed continuous variables assessed by Student's t-test, while skewed continuous variables were assessed using Kruskal-Wallis rank sum test. Differences in categorical variables assessed by multinomial logistic regression.

Results in boldface denote statistical significance.

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Table 2. SNAP factor prevalence.

SNAP factor	N	%
Smoking		
At least one cigar/cigarette/pipe per day	156	10.4%
Less than one cigar/cigarette/pipe per day	1,344	89.6%
Diet		
Insufficient fruit and vegetable intake	1,340	89.9%
Sufficient fruit and vegetable intake	151	10.1%
Consumption of alcohol		
More than two standard drinks per day	256	17.1%
Two or less standard drinks per day	1,244	82.9%
Level of physical activity		
Low in the last week	707	47.1%
Moderate or high in the last week	793	52.9%
Body Mass Index		
Underweight, overweight or obese	883	61.0%
Healthy	564	39.0%

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Table 3. Prevalence ratios of prevalent anxiety and depression (HADS ≥ 8).

	Prevalence Ratio (95% Confidence Interval)	
	Anxiety	Depression
Age (years)		
0-49	1.00 [ref]	1.00 [ref]
50-59	**0.80 (0.67, 0.94)**	1.19 (0.94, 1.51)
60-64	0.86 (0.71, 1.05)	1.27 (0.97, 1.67)
65+	**0.67 (0.55, 0.82)**	0.93 (0.70, 1.22)
P-trend	**<0.001**	0.68
Sex (female)	**1.32 (1.09, 1.61)**	0.94 (0.76, 1.18)
Type of MS at onset		
Remitting-onset MS	1.00 [ref]	1.00 [ref]
Progressive-onset MS	1.17 (0.95, 1.45)	**1.34 (1.02, 1.75)**
Type of MS now		
Primary-progressive MS	1.00 [ref]	1.00 [ref]
Relapsing-remitting MS	0.94 (0.74, 1.21)	**0.70 (0.51, 0.95)**
Secondary-progressive MS	0.88 (0.65, 1.19)	1.09 (0.78, 1.53)
Progressive-relapsing MS	**1.51 (1.02, 2.23)**	1.20 (0.68, 2.13)
Unsure	0.73 (0.52, 1.03)	0.80 (0.55, 1.18)

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PDDS		
Mild disability	1.00 [ref]	1.00 [ref]
Moderate disability	**1.39 (1.20, 1.62)**	**2.07 (1.66, 2.59)**
Severe disability	1.01 (0.81, 1.24)	**2.28 (1.78, 2.91)**
P-trend	0.16	**<0.001**
Prevalent fatigue	**1.80 (1.56, 2.06)**	**3.22 (2.63, 3.95)**
Years since symptom onset		
0-9	1.00 [ref]	1.00 [ref]
10-14	0.91 (0.76, 1.08)	1.01 (0.78, 1.30)
15-19	0.89 (0.73, 1.08)	1.17 (0.90, 1.53)
20+	0.71 (0.58, 0.88)	1.10 (0.85, 1.42)
P-trend	**0.002**	0.30
DMT use	1.07 (0.93, 1.24)	0.91 (0.76, 1.10)
Anxiety treatment	**2.05 (1.81, 2.33)**	**1.71 (1.39, 2.11)**
Depression treatment	**1.55 (1.35, 1.78)**	**2.06 (1.72, 2.46)**
Comorbidities		
0-2	1.00 [ref]	1.00 [ref]
3-5	**1.59 (1.33, 1.90)**	**1.65 (1.31, 2.09)**
6+	**2.07 (1.71, 2.50)**	**2.38 (1.85, 3.05)**
P-trend	**<0.001**	**<0.001**

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Highest education level		
Primary School	1.00 [ref]	1.00 [ref]
Secondary School	1.46 (0.45, 4.75)	1.01 (0.31, 3.29)
Certificate or Diploma	1.46 (0.45, 4.74)	1.13 (0.35, 3.68)
Bachelor's Degree	1.31 (0.40, 4.26)	0.85 (0.26, 2.79)
Postgraduate Degree	1.24 (0.38, 4.08)	0.62 (0.18, 2.09)
P-trend	0.13	**0.002**
Employed	1.04 (0.91, 1.20)	**0.66 (0.54, 0.81)**
Socioeconomic status		
Low	1.00 [ref]	1.00 [ref]
Medium	0.96 (0.81, 1.15)	0.85 (0.67, 1.07)
High	0.87 (0.74, 1.03)	**0.72 (0.58, 0.89)**
P-trend	0.097	**0.003**
Rurality		
Major city	1.00 [ref]	1.00 [ref]
Regional	0.98 (0.85, 1.14)	1.14 (0.94, 1.37)
Remote	0.50 (0.14, 1.72)	0.76 (0.22, 2.64)

Abbreviations: DMT=Disease Modifying Therapies; MS=Multiple sclerosis; PDDS=Patient Determined Disease Steps; ref=Reference category.

Prevalence ratios estimated using log-binomial regression and are unadjusted.

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Boldface values denote statistical significance ($p<0.05$).

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Table 4. Association between SNAP protective factors & SNAP score and occurrence and severity of anxiety & depression.

	N	%	Anxiety		Depression	
			Prevalence Ratio	Symptom Severity (Adjusted β_1)	Prevalence Ratio	Symptom Severity (Adjusted β_1)
Non-smoker	1,344	89.6%	0.83 (0.68, 1.00)	**-1.33 (-2.10, -0.55)**	**0.75 (0.59, 0.94)**	**-1.12 (-1.76, -0.48)**
Healthy diet	151	10.1%	0.92 (0.72, 1.18)	-0.38 (-1.13, 0.36)	0.80 (0.57, 1.11)	**-0.81 (-1.42, -0.20)**
Non-hazardous consumption of alcohol	1,244	82.9%	1.01 (0.84, 1.22)	-0.19 (-0.80, 0.42)	**0.79 (0.63, 0.99)**	-0.32 (-0.82, 0.19)
Adequate physical activity	793	52.9%	0.98 (0.85, 1.14)	-0.13 (-0.62, 0.37)	**0.70 (0.57, 0.87)**	**-0.85 (-1.25, -0.44)**
Healthy BMI	564	39.0%	1.03 (0.89, 1.18)	0.03 (-0.44, 0.49)	0.94 (0.78, 1.14)	-0.16 (-0.54, 0.23)
SNAP score						
0/1	115	8.0%	1.00 [ref]	1.00 [ref]	1.00 [ref]	1.00 [ref]
2	490	34.0%	1.01 (0.79, 1.28)	-0.43 (-1.31, 0.46)	0.79 (0.62, 1.01)	**-0.81 (-1.53, -0.09)**
3	515	35.8%	1.03 (0.80, 1.31)	-0.37 (-1.25, 0.51)	**0.64 (0.49, 0.83)**	**-1.26 (-1.98, -0.54)**
4/5	320	22.2%	0.94 (0.71, 1.25)	-0.81 (-1.76, 0.13)	**0.57 (0.40, 0.81)**	**-1.57 (-2.34, -0.80)**
SNAP score (continuous)			0.98 (0.91, 1.06)	-0.20 (-0.45, 0.04)	**0.83 (0.75, 0.92)**	**-0.44 (-0.64, -0.24)**

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P Trend	*0.62*	*0.10*	***<0.001***	***<0.001***

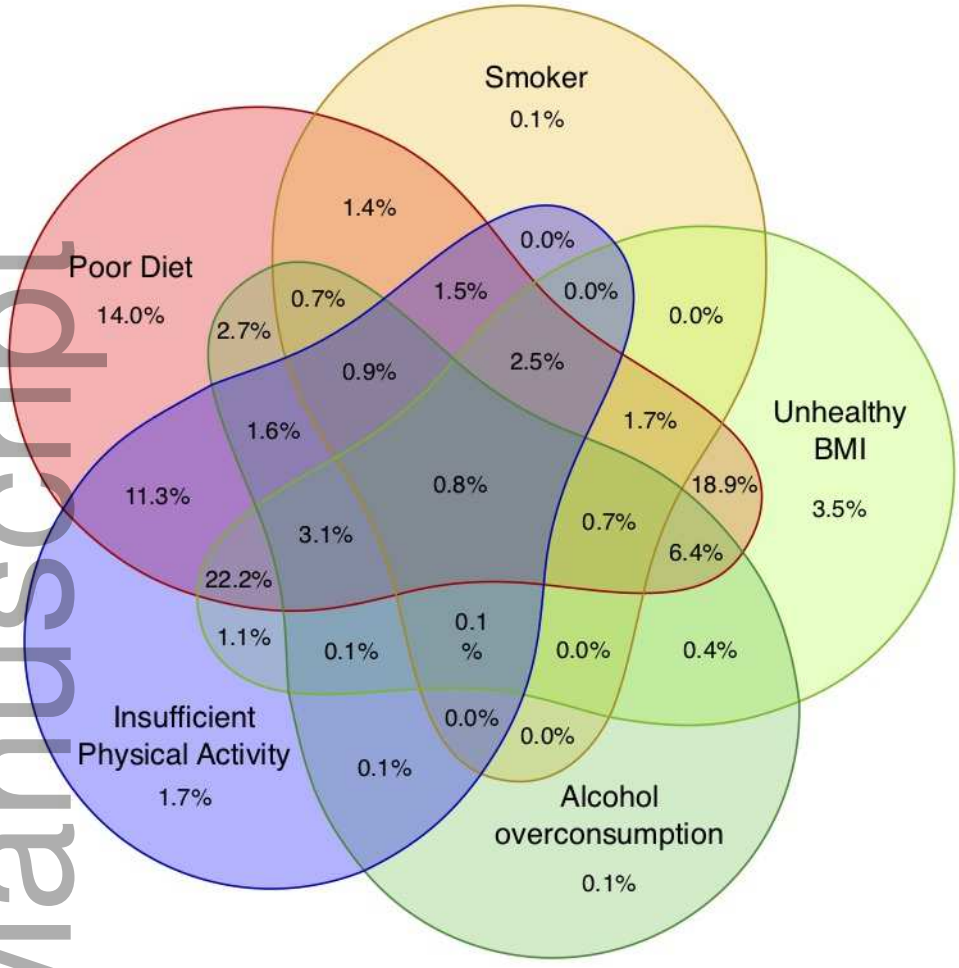
All models adjusted for age, sex, Patient-Determined Disease Steps score, depression or anxiety treatment, fatigue level, education level and socioeconomic status.

Boldface values denote statistical significance (p<0.05).

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