

Modifiable factors associated with depression and anxiety in multiple sclerosis

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1 **Modifiable factors associated with depression and anxiety in multiple sclerosis**

2 **Running Title:** Modifiable factors, depression and anxiety in MS

3

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20 Sclerosis Longitudinal Study for their support and willingness to complete the surveys.

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6 21 **ABSTRACT (225/250)**
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8
9 22 **Objectives:** Modifiable lifestyle factors are implicated in multiple sclerosis (MS) symptoms
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11 23 but their role in mood is unclear. This study aims to investigate associations between
12
13 24 lifestyle and depression and anxiety in Australian participants with MS.
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16 25 **Materials & Methods:** Self-reported data from the Australian Multiple Sclerosis
17
18 26 Longitudinal Study included the Hospital Anxiety and Depression Scale (HADS) and lifestyle
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20 27 measurements from 1,500 participants. SNAP score (range 0-5) was the sum of: non-
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22 28 smoking, sufficient fruit/vegetable intake, non-hazardous alcohol consumption, sufficient
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24 29 physical activity, and healthy BMI. Analyses by log-binomial and linear regression were
25
26 30 adjusted for confounding.
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30 31 **Results:** Depression and anxiety was prevalent in 27% and 40%, respectively; 20% had
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32 32 both. Mean SNAP score was 2.7/5; only 3% met all healthy lifestyle recommendations. Only
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34 33 10% reported adequate fruit/vegetable intake, and 22% reported a combination of
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36 34 unhealthy BMI, inadequate physical activity and inadequate nutrition. A healthier SNAP
37
38 35 score was associated with lower depression prevalence (adjusted prevalence ratio 0.83
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40 36 (95%CI 0.75, 0.92) per unit increase) and depression severity (adjusted β -0.44 (95%CI -
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42 37 0.64, -0.24)), but not with anxiety.
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47 38 **Conclusions:** Modifiable lifestyle factors are associated with lower frequency and severity
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49 39 of depression, but not anxiety, in Australian people with multiple sclerosis. The
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51 40 associations between a healthier SNAP score and lower depression are likely bi-directional.
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41 SNAP risk factor prevalence and co-occurrence, especially inadequate nutrition and low

42 physical activity, was high among Australians with MS.

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

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PROOF

46 INTRODUCTION

47 Clinically significant symptoms of anxiety or depression are observed in up to 40% of
48 people with multiple sclerosis (MS)¹, with prevalence estimates approximately twice that
49 of the general population². It is possible that anxiety and depression arise from
50 inflammation of the CNS and are hence considered symptoms of MS, yet they can also be
51 considered comorbidities, secondary to the disease³. Both mood states have been
52 associated with increased level of disability⁴ and fatigue⁵. Stress responses associated with
53 anxiety, as well as depressive symptoms, have been associated with increased
54 inflammation and with exacerbations of MS⁶.

55
56 Current pharmacological or psychological treatments for depression are proven to be
57 generally effective in reducing clinically significant symptoms⁷ in most people with MS.
58 However, the effectiveness of anxiety treatments for people with MS has not been
59 established⁷. Furthermore, only half of all people with MS suffering from anxiety or
60 depression receive treatment for their condition².

61
62 Modifiable lifestyle factors such as smoking status, nutrition, alcohol consumption, physical
63 activity level and body mass index (BMI) make up the 'SNAP' score, a construct used in
64 general practice⁸. These SNAP factors are major determinants of morbidity, mortality, and
65 functionality in the general population⁹. Growing evidence suggests that these same SNAP
66 factors also play a major role in brain and mental health⁹. Whether there is an additive

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5 67 effect from fulfilling more of these SNAP factors is unclear, given that few studies have
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8 68 explored SNAP score in ~~this population~~ people with MS.
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12 70 The current study uses a representative sample of people with MS in Australia to 1)
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14 71 describe the prevalence of SNAP risk factors and their co-occurrence; 2) investigate
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16 72 whether SNAP score is associated with the prevalence and severity of anxiety and
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18 73 depression.
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26 75 MATERIALS & METHODS

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29 76 All data was sourced from the Australian Multiple Sclerosis Longitudinal Study (AMSLS).
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31 77 The sample is large, representative and generalisable to the Australian MS population¹⁰. To
32
33 78 be eligible for the study, an individual must have a diagnosis of MS, be over 18 years of
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35 79 age, and live in any Australian state or territory. The study was approved by the Tasmanian
36
37 80 Health and Medical Human Research Ethics Committee and all participants provided
38
39 81 informed consent. The 2016 AMSLS Lifestyle survey was conducted from August to October
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42 82 2016. Invitations were sent to all 3112 active participants (2182 online surveys and 930
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44 83 paper surveys), and 1518 (48.78 %) participants responded to the survey (1067 online and
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46 84 451 paper surveys). Non-response analyses showed no significant difference in sex
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49 85 (p=0.101) and education level (p=0.113) between the respondents and non-respondents,
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52 86 while the respondents were slightly older (+1.49 years, p<0.01) and had a slightly longer
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5 87 MS duration since diagnosis (+0.56 years, p=0.04). These differing factors were evaluated
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8 88 in multivariable models to control for the potential bias in participation.
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11 12 13 90 SNAP Score

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15 91 SNAP – comprised of smoking, nutrition, alcohol and physical activity – was first proposed
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18 92 as part of a policy framework tool by the Australian Government in 2001 for use in general
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20 93 practice⁸. SNAP has previously been used in a North American sample of people with MS to
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22 94 estimate prevalence of lifestyle risk factors¹¹. The five factors comprising the SNAP score in
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25 95 our study were modelled on from this study¹¹ and another more recent previous study¹²
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27
28 96 both using similar aggregate scores, ~~by~~¹¹ with minor deviations to suit the Australian SNAP
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30 97 guidelines. ~~and~~Our aggregate SNAP score included smoking status, diet (assessed by the
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32
33 98 Diet History Questionnaire, DHQ¹³), alcohol consumption, physical activity level (assessed
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35 99 by the International Physical Activity Questionnaire, IPAQ¹⁴), and BMI (estimated from self-
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37
38 100 reported height and weight, as weight (kg)/height (m)²), each coded as binary variables. To
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40 101 achieve a score for non-smoker, an individual had to report smoking less than one
41
42 102 cigarette, cigar or pipe per day. A healthy diet was defined as consuming ≥ 5 serves of
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44 103 vegetables/day and ≥ 2 serves of fruit at least six days/week, as per the Australian Dietary
45
46 104 Guidelines¹⁵. Non-hazardous alcohol consumption required consuming ≤ 2 standard
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48 105 alcoholic drinks/day, the national recommendation¹⁶. Adequate level of physical activity
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50 106 was defined as moderate/high (versus low) level of physical activity as scored per the IPAQ
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52 107 guidelines¹⁴. A healthy BMI was defined as within the healthy BMI range (18.5 kg/m² to
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5 108 24.9 kg/m²) as opposed to underweight (below 18.5 kg/m²), overweight (25 kg/m² to 29.9
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8 109 kg/m²) or obese (30.0 kg/m² and above)¹⁷.

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111 Anxiety and Depression

112 The Hospital Anxiety and Depression Scale (HADS)¹⁸ was used to measure cognitive and
113 emotional symptoms of anxiety and depression. ~~The HADS, and~~ has been validated for use
114 in people with MS ~~for to measure~~ depression and generalised anxiety¹⁹. The two subscales
115 ~~of the HADS, anxiety and depression, each ranged had a range of 0-21 and, which were~~
116 evaluated to assess associations with depression/anxiety severity. The HADS threshold for
117 mild symptoms (≥ 8) was used to determine whether an individual showed clinically
118 significant symptoms of anxiety or depression¹⁸.

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120 Other data collected included age, sex, MS type, disability measured by the Patient-
121 Determined Disease Steps (PDDS) scale²⁰, fatigue measured by the Fatigue Severity Scale
122 (FSS)²¹, disease duration ~~since~~ symptom onset, MS disease-modifying therapy use,
123 treatment for depression or anxiety, number of ~~previous or current~~ comorbidities
124 ~~(including a list of 30 common chronic medical conditions and a "other" free text option),~~
125 education level, employment status, remoteness, and socioeconomic status measured by
126 the SEIFA Index of Relative Socioeconomic Advantage and Disadvantage (IRSAD)²².

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128 Statistical Analyses

129 Associations with prevalent anxiety/depression were assessed using log-binomial
130 regression, estimating a prevalence ratio. Associations with severity of anxiety and
131 depression symptoms were assessed by linear regression. Polytomous independent
132 variables were evaluated as predictors of outcomes using log-binomial regression, the
133 stratum-specific values using an interaction-expansion operator. For ordinal polytomous
134 independent variables, in addition to the stratum-specific estimates of association, the
135 regression was also run without the interaction expansion operator, thus evaluating the
136 categorical term as a continuous variable. The significance of this association denoted the
137 test for trend. All models were adjusted for age, sex, disability, fatigue, depression/anxiety
138 treatment, education, and socioeconomic status. These confounders were identified via a
139 directed acyclic graph (DAG), which was created using relevant literature according to best
140 practice epidemiological methods²³ factors selected based on literature review. All analyses
141 were complete case analysisanalyses, meaning; that is, only those with complete SNAP,
142 anxiety and depression data were included in analyses. Analyses wereis was conducted
143 using STATA 13.0 (StataCorp, College Station, USA).

144

145 RESULTS

146 1500 participants completed enough data to be included in this study. The majority of
147 participants were female (79.5%), unemployed (60.4%), used disease-modifying therapies
148 (62.4%) and had relapsing-remitting MS (61.9%) (Table 1). Almost half of the sample had a

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5 149 mild level of disability as defined by PDDS<3 (47.6%). Comorbidities were experienced by
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8 150 the vast majority of participants (91.1%), with some reporting more than ten
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10 151 comorbidities. Those with complete ~~SNAP, anxiety and depression~~ data were similar to
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12 152 those with incomplete data, except that those ~~lacking with in~~ complete data were more
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15 153 likely to be severely disabled and receiving treatment for depression (Table 1). Over one-
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18 154 third of participants had clinically significant symptoms of anxiety and roughly one-quarter
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20 155 had clinically significant symptoms of depression; one-fifth had both anxiety and
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22 156 depression.
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27 158 [Insert Table 1 here]
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31 32 160 SNAP Factors

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35 161 Most participants did not smoke (89.6%) and reported alcohol consumption within
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37 162 recommended levels (82.9%; Table 2). Around 10% of the sample consumed the
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40 163 recommended daily intake of fruit and vegetables, with 33.1% meeting the fruit
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42 164 consumption targets and 17.0% meeting the vegetable consumption targets. Just over half
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45 165 of participants engaged in adequate physical activity (52.9%), while 39% had a healthy BMI.
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169 SNAP Risk Factor Co-occurrence

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

175

176 [Insert Figure 1 here]

177

178 SNAP Protective Factor co-occurrence

179 Only 3.0% of the sample met all five SNAP protective factor recommendations, while 0.8%
180 met none at all (Table 3)

181

182 [~~Insert Table 3 here~~Figure 1).

183

184 Anxiety and depression

185 Anxiety was less prevalent with increasing age, and more prevalent in females compared to
186 males (Table 43). Participants with moderate or severe disability had a roughly 2-fold
187 greater prevalence of depression, but for anxiety there was no consistent relationship with
188 disability. Prevalent fatigue, however, was associated with a higher prevalence of anxiety
189 and depression. Progressive-onset MS was associated with a greater prevalence of

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5 190 depression compared to relapse-onset MS. Those with more comorbidities were more
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8 191 likely to have anxiety and depression. Education, employment and socioeconomic status
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10 192 were associated with lower prevalence of depression, but none were significantly
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12 193 associated with anxiety. Participants reporting anxiety and/or depression treatment were
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15 194 more likely to have anxiety and depression.
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20 196 [Insert Table 4-3 here]
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23 24 25 198 SNAP Protective Factors and Anxiety & Depression

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27 199 Non-smokers and those engaging in adequate physical activity had lower prevalence of
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30 200 depression and lower HADS-Depression scores (Table 5-4). Participants who met the
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32 201 recommendations for healthy diet had lower HADS-Depression scores. Those who reported
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35 202 non-hazardous consumption of alcohol had a lower prevalence of depression. Non-
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37 203 smoking status was associated with a lower anxiety severity, but none of the other
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39 204 individual SNAP protective factors were significantly associated with, but no other lifestyle
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42 205 factors were significantly associated with an anxiety severity or prevalence.
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52 209 Higher SNAP score showed a significant and dose-dependent inverse relationship with
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54 210 depression prevalence and severity, such that those with a SNAP score of 4-5 had 43%
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57 211 lower prevalence of depression and 1.57-points lower HADS-Depression score compared to
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5 212 those with a SNAP score of 0-1. When analyzing the SNAP score as a continuous variable,
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8 213 every unit increase in SNAP score was associated with a 17% reduction in prevalent
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10 214 depression and a 0.44 unit lower actual HADS depression score. While there was some
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12 215 indication of an inverse relationship between SNAP score and anxiety severity, this was of
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15 216 poor dose-dependency and did not reach statistical significance.
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218 DISCUSSION

219 ~~This is the first study examining~~This study examined the association between an aggregate
220 lifestyle score and depression & anxiety using data from a representative sample of people
221 with MS in Australia. A healthier lifestyle, as measured by a higher SNAP score, was
222 associated with a lower prevalence and severity of depression. No significant associations
223 were observed with the prevalence and severity of anxiety.
224

225 Depression was common (27%) and associated with SNAP risk factors smoking, alcohol
226 consumption and physical inactivity, while depression severity was associated with
227 smoking, inadequate nutrition and physical inactivity. ~~The associations persisted after~~
228 ~~adjustment for age, sex, disability, treatment for depression, education level and~~
229 ~~socioeconomic status.~~ Every unit increase in SNAP score was associated with a 17%
230 reduction in prevalent depression and a 0.44 unit lower actual HADS depression score. The
231 findings are in line with previous work showing that smoking and poor diet were associated
232 with increased risk of depression in people with MS²⁴. Research into the mechanisms

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5 233 between diet and mood is still emerging, but evidence for this association is strong within
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8 234 the general population²⁵. Observational studies in people with MS have consistently shown
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10 235 an association between physical inactivity and depression²⁶ as well as excessive alcohol use
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12 236 and depression²⁷, so our results here are in keeping with these prior findings. We did not
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15 237 find an association between BMI and depression prevalence or severity, however, which is
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17 238 inconsistent with previous studies^{24,28}. ~~Potentially, this could reflect the self-reported~~
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20 239 ~~nature of the height/weight, with errors potentially affecting these associations~~
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22 240 ~~differences in study design or populations, however, this is mere speculation and more research is~~
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25 241 ~~needed to clarify this.~~

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30 243 The underlying mechanisms, and causality, of these associations cannot be disentangled
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32 244 from our data. On the one hand, research has shown that individuals experiencing clinically
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34 245 significant depression are more likely to engage in poor health behaviours²⁹ and may be
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36 246 less likely to have the motivation to engage in healthy lifestyle behaviours or be proactive
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38 247 about their health. Treating the depression may then also result in a reduction of
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41 248 modifiable risk factors, which may have flow-on effects for general health. ~~This mechanism~~
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44 249 ~~likely accounts for some of the association we observed between SNAP score and~~
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46 250 ~~depression.~~ However, on the other hand, a combination of lifestyle risk factors may also
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49 251 contribute to the risk for depression. Modifying these risk factors may then also see a
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51 252 decrease in depression. ~~Indeed, exercise has been shown to be effective in treating~~
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54 253 ~~depression in people with MS~~³⁰. Both mechanisms may be at play simultaneously and it is
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56 254 likely that for those with depression a feedback loop exists, whereby the risk for depression

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5 255 is increased by poor health behaviours, while depressive symptoms increase the risk for
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8 256 poor health behaviours, and so on. Sophisticated feedback loops for depression including
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10 257 health behaviours have been described in the literature³⁰, and a further understanding of
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13 258 these may improve both depressive symptoms and health behaviours.
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17 260 Anxiety was very common (40%) and anxiety symptom severity was associated with
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20 261 smoking, in line with a previous prospective study in people with MS³¹, ~~though an inverse~~
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22 262 ~~association with anxiety prevalence did not reach significance~~. However, no other
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25 263 associations were found between individual SNAP ~~protective~~ factors or SNAP score and
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27 264 anxiety prevalence or symptom severity. ~~In contrast to the results for depression, we did~~
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30 265 ~~not find an association between SNAP score and anxiety prevalence or symptom severity.~~
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32 266 Far less is known about the association between anxiety and modifiable lifestyle factors in
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35 267 people with MS given that anxiety disorders are often overlooked and under-treated in this
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37 268 population². One study found that people with MS who have a history of excessive alcohol
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40 269 consumption have a higher lifetime prevalence of anxiety³² and another found that people
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42 270 with MS with obesity are more likely to have anxiety²⁸. There is evidence that the SNAP
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45 271 protective factors are associated with anxiety in other populations, such as those with
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47 272 cardiovascular disease³³. ~~Health anxiety, or anxiety about one's health, overlaps with~~
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49 273 ~~generalised anxiety in symptomology and has a much greater prevalence in people with~~
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52 274 ~~MS compared to the general population³⁵, which may suggest that participants may be~~
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54 275 ~~anxious about their health and therefore proactive in achieving the recommended~~
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57 276 ~~requirements for the SNAP protective factors.~~
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278 We found that SNAP risk factors were common, in line with previous studies in the United
279 States^{11,34}. The vast majority of people with MS are not consuming the recommended daily
280 requirement of fruit and vegetables (90%), with proper vegetable intake being the most
281 infrequent. The proportions of people with MS who were overweight or obese (58%), had
282 hazardous consumption of alcohol (17%) or smoked (10%), were similar to those of
283 previous studies¹¹. Interestingly, however, physical activity levels in this sample were
284 slightly higher compared to a previous study¹¹. Inadequate nutrition, physical inactivity
285 and unhealthy BMI was the most common combination of SNAP risk factors (22%)¹¹.

286

287 Strengths and Limitations

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

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5 299 The lack of association found between SNAP score and anxiety could be due to the fact
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8 300 that the HADS does not differentiate between different types of anxiety, but instead
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10 301 observes cognitive and emotional aspects of generalised anxiety¹⁹. The HADS measure may
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12 302 not have the specificity to detect other types of anxiety disorders, yet the association
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14 303 between SNAP score and anxiety and depression may differ between disorders.
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20 305 All variables used in the analyses were self-reported, including all measures used for the
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22 306 SNAP score and the HADS. Due to the size of the study, it was not feasible to extract
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24 307 objective measures for every participant. This possibly introduced differential exposure
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26 308 measurement error, meaning that those with anxiety and/or depression may report their
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28 309 engagement in SNAP protective factors differently to those without anxiety and/or
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30 310 depression. Not enough is known about the direction of this bias to infer its effect on the
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32 311 association between SNAP protective factors and anxiety and depression. Selection bias
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34 312 may have resulted in an under-estimated prevalence of depression and/or anxiety, given
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36 313 that people with more severe symptoms of depression and/or anxiety may be less likely to
37
38 314 participate in the survey. Distance from relapse may have negatively impacted mood or
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40 315 engagement in modifiable lifestyle behaviours, however these data were not assessed. We
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42 316 included number of comorbidities as an aggregate covariable, created using Australian
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44 317 National Healthy Survey data to ensure a wide range of common chronic medical
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46 318 conditions were included³⁵. Analyses of each comorbidity type was beyond the scope of
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48 319 this study.
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321 Implications of Findings

322 The high prevalence and co-occurrence of SNAP risk factors ~~in this study was high,~~
323 ~~consistent with previous studies, and~~ warrants increased health assessment and referrals
324 by healthcare professionals, especially in people with MS and depression. It is likely that
325 the presence of depressive symptoms will be accompanied by poor lifestyle behaviours,
326 overweight or obesity. Anxiety and depression ~~are common and often co-occur. However,~~
327 ~~these~~ should be treated as separate and very unique constructs in this population, given
328 their markedly different prevalence, as well as the diverse associations between SNAP
329 score and anxiety and depression observed. Investigation of barriers faced by people with
330 MS in improving health behaviours has identified fatigue, physical impairment and side
331 effects of MS and associated medications³⁶ and these need to be assessed and addressed
332 on an individual basis. The utility of the SNAP score may vary across the disease course.
333 Longitudinal assessment of lifestyle modification among participants with greater and
334 lesser degrees of disease severity would be informative.

335

336 Conclusion

337 We found that SNAP protective factors and a healthier SNAP score were associated with a
338 lower depression prevalence and severity, while no associations were seen for anxiety. The
339 present study is the first to provide evidence that there is a high prevalence of anxiety and
340 depression in a representative sample of Australian people with MS and that many are not
341 meeting health recommendations. Investigation of the co-occurrence of SNAP risk factors
342 in this population showed that a combination of unhealthy BMI, poor diet and inadequate

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5 343 physical activity is common. Given that SNAP risk factors, anxiety and depression all
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7 344 contribute significantly to the morbidity of MS, efforts to improve the lifestyle and mental
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9 345 health outcomes for an individual with MS should be holistic and all-inclusive. Future
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11 346 prospective studies should elucidate the direction of association between depression and
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13 347 SNAP protective factors, alongside investigation of the viability of multi-modal lifestyle
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15 348 modification to treat depressive symptoms in this population.
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PROOF

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5 350 **DECLARATION OF CONFLICTING INTERESTS**

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8 351 The authors declared no potential conflicts of interest with respect to the research,
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10 352 authorship and/or publication of this article.

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27
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33 361 **DATA AVAILABILITY STATEMENT**

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36 362 The data that support the findings of this study are available from Multiple Sclerosis

37
38 363 Research Australia. Restrictions apply to the availability of these data, which were used

39
40 364 under license for this study. Data are available from the authors with the permission of

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43 365 Multiple Sclerosis Research Australia.
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Table 1. Demographic characteristics of the 1,500 participants with multiple sclerosis included in the study.

Characteristic	Total		Missing Outcome or Exposure Data		Outcome and Exposure Data Available		<i>p</i> -value
	Mean	SD	Mean	SD	Mean	SD	
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	<i>p</i> -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	%	<i>p</i> -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]
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							

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5	Primary-progressive MS	97	8.7%	5	12.2%	92	8.6%	0.37
6	Relapsing-remitting MS	691	61.9%	23	56.1%	668	62.1%	[ref]
7	Secondary-progressive MS	167	15.0%	5	12.2%	162	15.1%	0.83
8	Progressive-relapsing MS	22	2.0%	1	2.4%	21	2.0%	0.76
9	Unsure	139	12.5%	7	17.1%	132	12.3%	0.33
10	Prevalent anxiety (HADS-A \geq 8)	483	39.8%	20	44.4%	463	39.6%	0.51
11	Prevalent depression (HADS-D \geq 8)	332	27.3%	10	22.2%	322	27.5%	0.43
12	Anxiety and depression	237	19.5%	6	13.3%	231	19.7%	0.29
13	Employed	479	39.6%	12	26.1%	467	40.1%	0.06
14	DMT use	756	62.4%	23	53.5%	733	62.8%	0.22
15	Prevalent fatigue (FSS \geq 5)	502	41.3%	23	48.9%	479	40.9%	0.28
16	Socioeconomic status							
17	Low	428	28.5%	102	30.9%	326	27.9%	0.14
18	Medium	413	27.5%	96	29.1%	317	27.1%	0.21
19	High	659	43.9%	132	40.0%	527	45.0%	[ref]
20	Depression treatment	353	23.5%	96	29.1%	257	22.0%	0.01
21	Anxiety treatment	204	13.6%	49	14.9%	155	13.3%	0.45
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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.

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%

Table 3. Prevalence ratios of prevalent anxiety and depression (HADS \geq 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)
<i>P-trend</i>	<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)
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)
<i>P-trend</i>	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)

1	20+	0.71 (0.58, 0.88)	1.10 (0.85, 1.42)
2			
3	<i>P-trend</i>	0.002	0.30
4	DMT use	1.07 (0.93, 1.24)	0.91 (0.76, 1.10)
5	Anxiety treatment	2.05 (1.81, 2.33)	1.71 (1.39, 2.11)
6	Depression treatment	1.55 (1.35, 1.78)	2.06 (1.72, 2.46)
7	Comorbidities		
8			
9	0-2	1.00 [ref]	1.00 [ref]
10	3-5	1.59 (1.33, 1.90)	1.65 (1.31, 2.09)
11	6+	2.07 (1.71, 2.50)	2.38 (1.85, 3.05)
12			
13	<i>P-trend</i>	<0.001	<0.001
14	Highest education level		
15	Primary School	1.00 [ref]	1.00 [ref]
16	Secondary School	1.46 (0.45, 4.75)	1.01 (0.31, 3.29)
17	Certificate or Diploma	1.46 (0.45, 4.74)	1.13 (0.35, 3.68)
18	Bachelor's Degree	1.31 (0.40, 4.26)	0.85 (0.26, 2.79)
19	Postgraduate Degree	1.24 (0.38, 4.08)	0.62 (0.18, 2.09)
20			
21	<i>P-trend</i>	0.13	0.002
22	Employed	1.04 (0.91, 1.20)	0.66 (0.54, 0.81)
23	Socioeconomic status		
24			
25	Low	1.00 [ref]	1.00 [ref]
26	Medium	0.96 (0.81, 1.15)	0.85 (0.67, 1.07)
27	High	0.87 (0.74, 1.03)	0.72 (0.58, 0.89)
28			
29	<i>P-trend</i>	0.097	0.003
30	Rurality		
31	Major city	1.00 [ref]	1.00 [ref]
32	Regional	0.98 (0.85, 1.14)	1.14 (0.94, 1.37)
33	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.

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

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)
<i>P Trend</i>			<i>0.62</i>	<i>0.10</i>	<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 ($p < 0.05$).

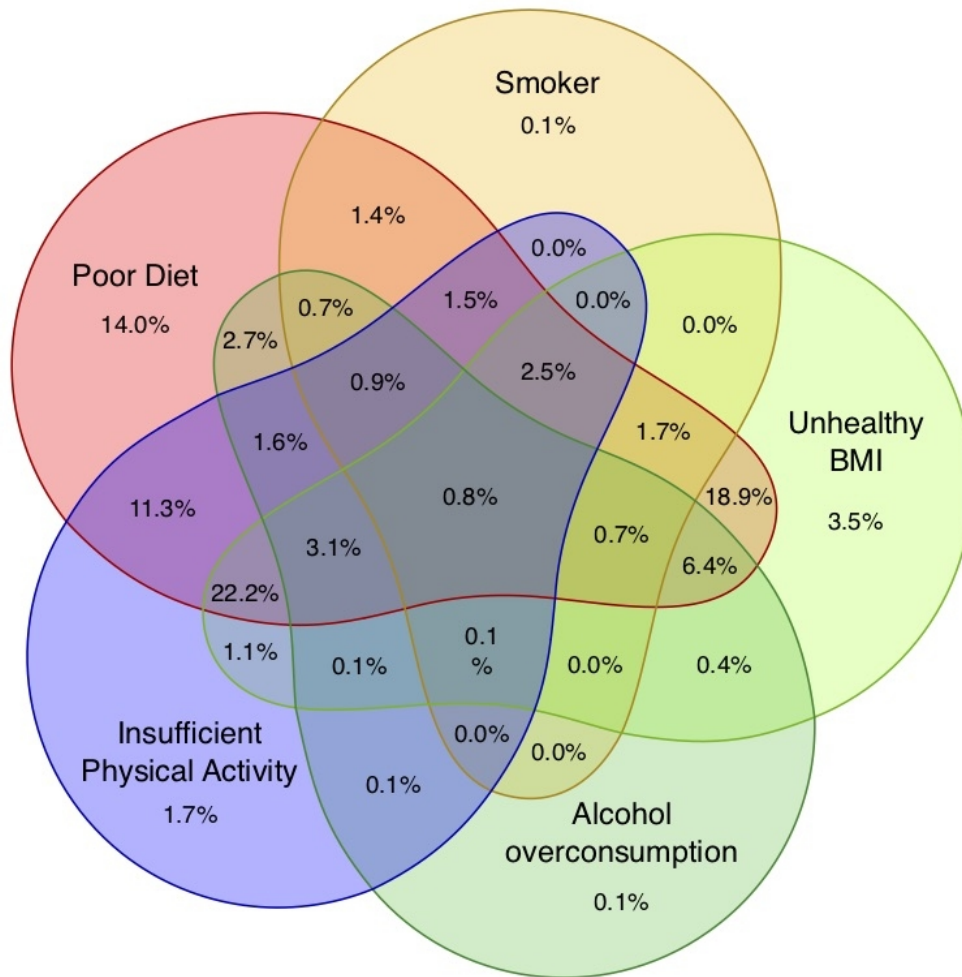


Figure 1. Venn diagram showing the co-occurrence of lifestyle risk factors.

130x129mm (150 x 150 DPI)

Supplementary Table 1. Prevalence and co-occurrence of SNAP protective factors.

SNAP score	SNAP score prevalence		Pattern prevalence		Non-Smoker	Healthy diet	Non-hazardous alcohol consumption	Adequate physical activity	Healthy BMI
	N	%	N	%					
0	11	0.8%							
1			44	42.3%	✓				
1			1	1.0%		✓			
1	104	7.2%	36	34.6%			✓		
1			10	9.6%				✓	
1			13	12.5%					✓
2			1	0.2%	✓	✓			
2			319	65.1%	✓		✓		
2			92	18.8%	✓			✓	
2			23	4.7%	✓				✓
2	490	34.0%	0	0.0%		✓	✓		
2			0	0.0%		✓		✓	
2			0	0.0%		✓			✓
2			24	4.9%			✓	✓	
2			21	4.3%			✓		✓
2			10	2.0%				✓	✓
3			20	3.9%			✓	✓	✓
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3	515	35.8%	39	7.6%	✓			✓	✓
3			162	31.5%	✓		✓		✓
3			272	52.8%	✓		✓	✓	
3			1	0.2%	✓	✓			✓
3			5	1.0%	✓	✓		✓	
3			16	3.1%	✓	✓	✓		
4			2	0.7%		✓	✓	✓	✓
4			201	72.3%	✓		✓	✓	✓
4	278	19.3%	1	0.4%	✓	✓		✓	✓
4			24	8.6%	✓	✓	✓		✓
4			50	18.0%	✓	✓	✓	✓	
5	42	2.9%			✓	✓	✓	✓	✓

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