A healthy dietary pattern associates with a lower risk of a first clinical diagnosis of central nervous system demyelination

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Abstract

Background: The evidence associating diet and risk of MS is inconclusive.

Objective: We investigated associations between dietary patterns and risk of a first clinical diagnosis of CNS demyelination (FCD), a common precursor to MS.

Methods: We used data from the 2003-2006 Ausimmune Study, a case-control study examining environmental risk factors for FCD, with participants matched on age, sex and study region. Using data from a food frequency questionnaire, dietary patterns were identified using principal component analysis. Conditional logistic regression models (*n*=698, 252 cases, 446 controls) were adjusted for history of infectious mononucleosis, serum 25-hydroxyvitamin D concentrations, smoking, race, education, BMI and dietary misreporting.

Results: We identified two major dietary patterns - healthy (high in poultry, fish, eggs, vegetables, legumes) and Western (high in meat, full fat dairy; low in wholegrains, nuts, fresh fruit, low fat dairy), explaining 9.3% and 7.5% of variability in diet, respectively. A one-standard deviation increase in the healthy pattern score was associated with a 25% reduced risk of FCD (Adjusted Odds Ratio 0.75; 95%CI 0.60,0.94; *P*=0.011). There was no statistically significant association between the Western dietary pattern and risk of FCD.

Conclusion: Following healthy eating guidelines may be beneficial for those at high risk of MS.

Introduction

There are a number of known environmental risk factors for MS, including low vitamin D status and low sun exposure [1], smoking [2] and a history of infectious mononucleosis [3]. Although diet may be a modifiable risk factor for MS, the current evidence focuses mainly on single foods and nutrients, with inconclusive results[4-7]. Dietary pattern analysis has advantages over the single food or single nutrient approach by capturing information about a person's total diet, including the interactions that may occur between food components [8]. To our knowledge, only two studies have investigated dietary patterns and risk of MS [9,10], both of which were case-control studies (n~70 cases) of Iranian people with established MS. In these studies, a Mediterranean diet was associated with reduced risk of MS [9], as were traditional Iranian, lacto-vegetarian and vegetarian dietary patterns [10].

This study uses dietary intake data from the Ausimmune Study, a multicentre, incident case-control study investigating the environmental risk factors for a first clinical diagnosis of CNS demyelination (FCD) [11]. Associating dietary factors close to the time of FCD, rather than in those with established MS, reduces the likelihood of reverse causation as participant responses are less likely to be biased by disease-related changes in behaviour [11]. This is important since dietary modification is common after a diagnosis of MS [11,12]. Previous analysis of the Ausimmune Study showed a lower risk of FCD with higher intake of long-chain omega-3 polyunsaturated fatty acids (PUFA) derived from fish [4]; we build on this work by testing associations between dietary patterns and risk of FCD.

Methods

Design

The 2003-2006 Ausimmune Study was a multicentre, case-control study conducted in four regions of Australia: Brisbane city (27°S), Newcastle region (33°S), Geelong and the Western districts of Victoria (37°S), and the island of Tasmania (43°S) [11]. Case participants (*n*=282, 18-59 years) were referred to the study as described previously, and the date of onset and presenting symptoms suggestive of inflammatory CNS demyelination were confirmed by a neurologist following a full history and neurological examination [11]. We used the date of the MRI scan preceding diagnosis as the date of FCD, as these data were available for most participants. The median (interquartile range (IQR)) time lag from the date of MRI scan by the neurologist (the date of the diagnosis which brought the participants into the study) to the study interview was 103 (153) days, with 116 case participants interviewed within 90 days of MRI scan.

Case participants had had an incident FCD within the study period, including a classic first demyelinating event (FDE; defined as a single, first, episode of clinical symptoms suggestive of CNS demyelination; *n*=216), and primary progressive MS on neurological assessment on study entry (*n*=18). A further 48 participants were found to have a prior event highly suggestive of CNS demyelination that had been unrecognised and not ascribed to demyelination and thus unlikely to have triggered any behavioural changes. Control participants (*n*=558) were randomly selected from the general population to be matched on age (within 2 years), sex and study region, via the Australian Electoral Roll (compulsory registration for citizens ≥18 years). Between one and four matched controls were matched to each case, to maximize the study power, with more controls per case in regions with a lower expected number of cases due to being either at higher latitude (and lower expected incidence) or a smaller source population. However, these ratios were altered during the course of the study for practical reasons: in 2006, all centres were recruiting two controls per

73 case. Ethics approval was obtained from the nine Human Research Ethics Committees of the
74 participating institutions [11]. All participants gave written informed consent for the use of their
75 data.
76
77 The current study included participants who provided complete data on dietary intake and all
78 covariates, and who were part of at least a matched control pair. Of the 840 participants (282
79 cases, 558 controls) in the Ausimmune Study, 791 participants (272 cases, 519 controls)
80 provided dietary intake data; 743 participants (259 cases, 484 controls) of these provided data
81 for all covariates; and 698 participants (252 cases, 446 controls) of these were part of at least
82 a matched pair and thus formed the study cohort for this analysis.
83
84 *Dietary assessment*
85 The Cancer Council Victoria Dietary Questionnaire for Epidemiological Studies version 2
86 (DQESv2) was used to collect information on habitual dietary intakes in the 12 months prior
87 to the study interview. The DQES is a self-administered, semi-quantitative, food frequency
88 questionnaire (FFQ) designed for use in the ethnically-diverse adult Australian population, the
89 development of which has been outlined elsewhere [13]. The questionnaire has been validated
90 relative to seven-day weighed food records in 63 women of child-bearing age, where it
91 performed as well as other validated FFQs: mean intakes from the weighted food record and
92 the DQES were within ±20% for 21 of 27 nutrients [14].
93
94 The frequencies of consumption of food items were recorded on a scale from ‘never’ to ‘three
95 or more times per day’. Portion size diagrams were used to determine respondents’ average
96 portion size factor. Consumption of alcohol was recorded as the total number of glasses
97 usually drunk per day, and the maximum number of glasses drunk in any 24 hours. Intake of

101 food and beverage items was reported as grams per day, with nutrient intakes computed primarily using composition data from the Australian NUTTAB 95 database [15].

Covariates

Participants completed a self-administered questionnaire, with variables categorised as follows: race (Caucasian, other); history of infectious mononucleosis (yes, no, don't know); highest level of education (year 10 or less, year 12 and Technical and Further Education, university). Total number of years smoked was calculated minus any periods of abstinence. Most participants (94%) provided a blood sample: serum aliquots (1 mL) were stored at -80°C and analysed for 25-hydroxyvitamin D (25(OH)D) concentrations using liquid chromatography tandem mass spectrometry [1]. Since blood samples were taken at different times of the year, serum 25(OH)D concentrations for case participants were deseasonalised using the seasonal patterns of the control serum 25(OH)D concentrations [1]. The study nurse measured height and weight, and body mass index (BMI) was calculated as weight in kilograms divided by height in metres squared. Basal metabolic rate was calculated using the equations developed by Harris and Benedict [16]: males h=66.4730+13.7516W+5.0033S–6.7750A; females h=665.0955+9.5634W+1.8496S–4.6756A (where h=kcal day^{-1}; W=weight in kilograms; S=stature in centimeters; A=age in years). Under-reporters, plausible reporters and over-reporters were classified using Goldberg cut-off points as follows [17]: under-reporters, below BMRx1.05; plausible reporters between BMRx1.05 and BMRx2.28; over-reporters, above BMRx2.28. A three-category variable was created for dietary misreporting: under-reporter, plausible reporter, and over-reporter.

Statistical analysis

123 We categorised the 101 food and beverage items into 34 food groups (Table 1), based on
124 those used previously [18]. Each food group was energy-adjusted using the energy density
125 method [19]. The food group data for control participants only were entered into the PCA
126 procedure in Stata Statistical Software: Release 14 [20]. The factor solution was limited to those
127 factors with an eigenvalue >1.0 and the number of factors to retain was based on the screeplot
128 and also on the interpretability of the obtained patterns [21]. The identified factors were
129 orthogonally rotated to improve their interpretability [22]. Food groups with a factor loading
130 ≥0.2 were considered to contribute substantially to the pattern and were used to name each
131 pattern. Standardised factor scores were computed using the PCA procedure in Stata 14
132 software [20], so that all participants were assigned a score for each dietary pattern, based on
133 their FFQ intakes.
134
135 Nutrient intakes derived from the FFQ were energy adjusted using the energy-density method
136 [19] and were described for the lowest and highest quintiles of each dietary pattern. Nutrient
137 densities with Normal distributions were reported as mean and standard deviation (SD), and
138 those with non-Normal distributions were reported as median and IQR. We compared nutrient
139 intakes between the five quintiles of each dietary pattern using one-way ANOVA for nutrients
140 with Normal distribution, and the Kruskal-Wallis test for nutrients with non-Normal
141 distribution.
142
143 Characteristics of cases and controls (n=698, 252 cases, 446 controls) were described as
144 frequency and percentage for categorical variables, mean and SD for continuous variables
145 with a Normal distribution, and median and IQR for continuous variables with a non-Normal
146 distribution. Characteristics of control participants who were included in the final model
147 (n=446) were compared with those who were excluded from the final model due to missing

148 data or missing matched case participant (*n*=112). Pearson's chi-square tests were used for
149 categorical variables, independent samples t-tests for continuous variables with Normal
150 distributions and Mann–Whitney U tests for continuous variables with non-Normal
151 distributions.
152
153 We used conditional logistic regression models (participants matched on age, sex and study
154 region) to estimate odds ratios (ORs), 95% confidence intervals (95% CI) and *p* values for
155 associations between dietary patterns and risk of FCD. Dietary pattern scores were analysed
156 both as continuous variables (where a one-unit increase was equivalent to a one-SD increase
157 in dietary pattern score) and as quintiles based on score thresholds for control participants.
158
159 Potential confounders were selected on the basis of: 1) being a known risk factor for MS
160 (history of infectious mononucleosis, serum 25-hydroxyvitamin D concentrations, total years
161 of smoking); 2) being a possible risk factor for MS and/or having a potential influence on
162 dietary patterns (race, BMI and education); and 3) accounting for the well-documented under-
163 reporting of energy intake by self-reported dietary methods (dietary misreporting) [23]. The
164 impact of the dietary patterns on each other was investigated by including all dietary patterns
165 simultaneously in the final models [8]. Model 1 (*n*=698) was unadjusted; model 2 (*n*=698) was
166 adjusted for history of infectious mononucleosis, serum 25-hydroxyvitamin D concentration,
167 total years of smoking, race, education and dietary misreporting; model 3 (*n*=698) was
168 additionally adjusted for all dietary patterns; model 4 was additionally adjusted for BMI
169 (*n*=698). We tested for an interaction between the dietary pattern score and BMI using an
170 interaction term in the models. To test whether any associations differed by sex, we ran
171 models in males and females separately and examined differences in the effect estimates.
172

We conducted the following sensitivity analyses: a) excluding participants with implausible energy intakes (<3,000 or >20,000 kJ/day; *n*=4 cases, 9 controls)[22] (*n*=677, 247 cases, 430 controls); b) including only case participants who completed the study interview within 90 days from the date of MRI scan (*n*=321, 116 cases, 205 controls); and c) including only case participants with a classic FDE (*n*=528, 193 cases, 335 controls). Data were analysed using Stata 14 software [20].

Results

Participant characteristics

Table 2 shows the characteristics of case and control participants. Most participants (95%) were Caucasian. Case participants were more likely than controls to have a history of infectious mononucleosis, lower serum 25(OH)D concentrations, and to have completed education beyond year 10. There was no difference between the control participants who were included in the final model (*n*=446) and those who were excluded from the final model (*n*=112) with respect to the following characteristics: history of infectious mononucleosis (p=0.76), serum 25-hydroxyvitamin D concentration (p=0.11), total years of smoking (p=0.97), race (p=0.17), age (p=0.59), education (p=0.17), and BMI (p=0.49). Compared with those excluded from the final model, control participants included in the final model were more likely to be male (p=0.015) and to be from Brisbane or Tasmania (p<0.001).

Dietary patterns

PCA identified two major dietary patterns, explaining 9.3% and 7.5% of variability in diet (Table 3). The first (healthy) pattern was characterised by a higher intake of poultry, grilled and tinned fish, eggs, yellow and red vegetables, cruciferous vegetables, leafy green vegetables, other vegetables and legumes. The second (Western) pattern was characterised by

198 a higher intake of red meat, processed meat and full fat dairy, and was low in wholegrains,
199 nuts, fresh fruit and low fat dairy.
200
201 Compared with those in the lowest quintile of the healthy pattern, participants in the highest
202 quintile had: lower intakes of total energy; lower energy-adjusted intakes of total fat, saturated
203 fat and monounsaturated fat; and higher energy-adjusted intakes of long-chain omega-3
204 PUFA, protein, dietary fibre, and various vitamins and minerals (Table 4). Compared with
205 those in the lowest quintile of the Western pattern, participants in the highest quintile had:
206 higher intakes of total energy; higher energy-adjusted intakes of total fat, saturated fat and
207 monounsaturated fat; and lower energy-adjusted intakes of PUFA, long-chain omega-3
208 PUFA, carbohydrate, dietary fibre, and various vitamins and minerals.
209
210 *Dietary patterns and risk of FCD*
211 In the unadjusted model (Model 1), a one-SD increase in the healthy pattern score was
212 associated with a 17% (Adjusted Odds Ratio (AOR) 0.83; 95% CI 0.69, 0.99) reduced risk of
213 FCD (Table 5). A one-SD increase in the healthy pattern score was associated with a 24%
214 (AOR 0.76; 95% CI 0.62, 0.94) reduced risk of FCD when adjusted for potential confounders
215 (Model 2), and a 25% (AOR 0.75; 95% CI 0.60, 0.94) reduced risk of FCD when further
216 adjusted for the Western dietary pattern (Model 3) and BMI (Model 4). Compared with the
217 lowest quintile of the healthy dietary pattern score, the risk of FCD was 47% (AOR 0.53; 95%
218 CI 0.29, 0.96) lower in the fourth quintile and 55% (AOR 0.45; 95% CI 0.24, 0.83) lower in
219 the highest quintile in the fully adjusted model (Model 4). There was no statistically
220 significant interaction between the healthy dietary pattern score and BMI in the model using
221 the dietary pattern score as a continuous variable (p=0.09) and as quintiles. We found no
222 evidence of a statistically significant association between a Western dietary pattern and risk of

FCD, nor was there a statistically significant interaction between the Western dietary pattern score and BMI in the model using the dietary pattern score as a continuous variable (p=0.11) and as quintiles.

Similar findings were observed in the sensitivity analyses of those with plausible energy intakes (Table 6a) and those who completed the study interview within 90 days from the date of MRI scan (Table 6b). In the classic FDE group, the findings were similar but with wider confidence intervals (Table 6c).

When stratified by sex, a one-SD increase in the healthy pattern score was associated with a 28% reduced risk of FCD in women in the fully adjusted model (AOR 0.72; 95% CI 0.56, 0.93; *P*=0.011; *n*=189 cases, 339 controls). There was an 9% reduced risk of FCD in men but this association was statistically non-significant (AOR 0.91; 95% CI 0.43, 1.93; *P*=0.808; (*n*=63 cases, 107 controls). Supplementary Figure 1 shows histograms of the healthy dietary pattern score for cases and controls, stratified by sex. There was no statistically significant association between a Western dietary pattern and risk of FCD in models stratified by sex (women: AOR 0.93; 95% CI 0.75, 1.16; *P*=0.512; men: AOR 1.19; 95% CI 0.73, 1.94; *P*=0.495).

Discussion

Our results suggest a protective effect of a healthy dietary pattern (high in poultry, fish, eggs, vegetables and legumes) on risk of FCD. The association was independent of history of infectious mononucleosis, serum 25-hydroxyvitamin D concentration, total years of smoking, race, education, BMI, dietary misreporting and Western dietary pattern score. The association was stronger in women than in men; however, the large overlap in the interval estimates

248 suggests that the lack of statistical association for men was possibly due to the lower sample
249 size for men due to the female case excess. We did not observe any statistically significant
250 associations between a Western dietary pattern and risk of FCD. The two major dietary
251 patterns we identified were similar to the 'healthy' and 'Western' patterns identified in other
252 studies of adults, as reviewed previously [24]. Although the small amount of total variability in
253 diet explained by the dietary patterns is a limitation, this is similar to other studies of dietary
254 patterns derived by PCA [25,26].
255
256 Our findings are similar to the study by Sedaghat and colleagues [9] which showed that, in a
257 hospital-based case-control study of people with MS in Iran (n=70 cases, 142 controls), a
258 high quality Mediterranean diet was associated with reduced risk of MS. In that study, the
259 Mediterranean diet (high in vegetables, legumes, fruits, nuts, fish and a high ratio of
260 unsaturated to saturated fatty acids; and low in dairy, meat and meat products and refined
261 grains) was assessed using a modified version of the 9-Unit dietary score [24]. Our results
262 support these findings since a healthy dietary pattern - high in vegetables, legumes and fish -
263 is similar to a Mediterranean diet.
264
265 Jahromi and colleagues [10] used factor analysis to identify dietary patterns in a case-control
266 study of women with relapsing/remitting MS (n=77 cases, 75 controls). Three dietary patterns
267 were inversely associated with risk of MS: 1) traditional (high in low-fat dairy products, red
268 meat, vegetable oil, onion, wholegrain, soy, refined grains, organ meats, coffee and legumes);
269 2) lacto-vegetarian (high in nuts, fruits, French fries, coffee, sweets and desserts, vegetables
270 and high-fat dairy products); and 3) vegetarian (high in green leafy vegetables, hydrogenated
271 fats, tomato, yellow vegetables, fruit juices, onion and other vegetables). A Western dietary
272 pattern (high in animal fats, potato, meat products, sugars and hydrogenated fats, and low in

wholegrains) was positively associated with risk of MS. A limitation of the study was that case participants had been diagnosed with the disease up to three years previously and some changes in dietary habits occurred in a number of case participants after the onset of the disease.

A major strength of the Ausimmune Study was its incident case-control design, where collection of dietary data was soon after the FCD, rather than in people with established MS. Most of the limited dietary research in relation to MS has been conducted in individuals who have established MS. The proportion of people making dietary changes after a diagnosis of MS ranges from 17% [27] to 42% [12], making reverse causation (i.e. that the diagnosis has led to behaviour changes in dietary intake) an important consideration. By recruiting participants with FCD, rather than MS, the possibility of reverse causation is reduced, since the participants did not have a medical diagnosis of MS and minimal time had passed since they were initially assessed by a medical specialist. However, there is some evidence to suggest the existence of a multiple sclerosis prodrome, with degenerative processes and symptoms, including fatigue and depression, possibly starting years prior to clinical manifestation of demyelination [28-30]. Prodromal symptoms, such as fatigue and depression, may lead to differences in eating prior to a FCD; therefore, we cannot rule out the possibility of reverse causation.

A further limitation of our study is the widely acknowledged under-reporting of energy intake from self-reported dietary assessment methods [23]. It is well-known that energy under-reporting of foods is selective, with unhealthy and snack foods more likely to be forgotten during dietary reporting [31,32]. Although this may potentially bias the analysis of dietary patterns, it is likely that recall error in our study was similar for case and control participants.

Similarly, although portion size photos in self-administered FFQs have limited value for ranking individuals correctly according to their actual portion sizes [33], recall error was likely to be similar for case and control participants.

Other limitations of our study include potential residual confounding and lack of generalisability. We cannot rule out residual confounding, whereby those following a healthy dietary pattern have other unmeasured lifestyle characteristics that reduce the risk of FCD. However, with the exception of smoking, most lifestyle characteristics - including BMI, alcohol intake and physical activity - were not associated with risk of FCD in previous analysis of the Ausimmune Study [34]. Lastly, these results may not be generalisable to other populations – the dietary patterns were derived specifically from this group of participants who were living in Australia and were predominantly Caucasian; the diets of people of other races and those living in other countries are likely to be different from the diets followed by our participants.

In summary, our results suggest that following a healthy diet characterised by poultry, fish, eggs, vegetables and legumes may lower the risk of FCD. Such a diet is in line with recommendations for the general population, including the Australian Dietary Guidelines [35]. In the absence of convincing evidence to the contrary, healthy eating guidelines designed for the general population are currently the best available dietary recommendations for people at high risk of MS. Given that less than 4% of the Australian population follow the Australian Dietary Guidelines [35], improved nutrition education for people at high risk of MS onset may be beneficial in helping them follow a healthy diet, and may subsequently reduce their risk of FCD, or of MS.

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Table 1: Categorisation of 101 foods into 34 food groups

	Food group	Foods
1	Red meat	Beef, veal, lamb, pork
2	Processed meat	Bacon, ham, salami, sausage
3	Poultry	Chicken
4	Take away	Meat pie, pizza, hamburger
5	Grilled/tinned fish	Grilled fish, tinned fish
6	Fried fish	Fried fish
7	Eggs	Eggs
8	Wholegrains	Rye bread, multigrain bread, wholegrain bread, high fibre bread, All-bran, bran flakes, Weetbix, porridge, muesli
9	Refined grains	Crackers, pasta, rice, cornflakes, white bread
10	Yellow and red vegetables	Pepper, carrot, pumpkin, tomato
11	Cruciferous vegetable	Cabbage, cauliflower, broccoli
12	Leafy green vegetables	Lettuce, spinach
13	Potato	Potato
14	Fried potato	Chips
15	Other vegetables	Cucumber, celery, beetroot, onion, garlic, mushroom, zucchini, sprouts
16	Legumes	Peas, green beans, baked beans, other beans, tofu
17	Nuts	Nuts
18	Fresh fruit	Orange, apple, pear, banana, melon, pineapple, strawberry, apricot, peach, avocado, mango
19	Tinned fruit	Tinned fruit
20	Juice	Fruit juice
21	Low fat dairy	Reduced fat milk, skim milk, soya milk, low fat cheese, ricotta cheese
22	Full fat dairy	Full fat milk, cream cheese, soft cheese, firm cheese, hard cheese, yoghurt
23	Sweetened dairy	Flavoured milk, ice cream
24	Sauces	Tomato sauce
25	Crisps	Crisps

26	Confectionary	Chocolate
27	Cakes biscuits & sweet pastries	Sweet biscuits, cakes
28	Added sugar	Jam, sugar
29	Saturated spreads	Butter, margarine, margarine blends
30	Unsaturated spreads	Polyunsaturated margarine, monounsaturated margarine
31	Other spreads	Peanut butter, vegemite
32	Wine	Red wine, white wine, fortified wine
33	Spirits	Spirits
34	Beer	Low strength beer, full strength beer

Table 2. Characteristics of participants (n=698; 252 cases, 226 controls) included in the current study

	Case	Control
Sex, % (*n*)[a]		
Male	25.0 (*63*)	24.0 (*107*)
Female	75.0 (*189*)	76.0 (*339*)
Age, year, mean (SD)[a]	38.7 (9.7)	40.0 (9.6)
Study region, % (*n*)[a]		
Brisbane (27°S)	34.1 (*86*)	37.4 (*167*)
Newcastle (33°S)	12.3 (*31*)	14.4 (*64*)
Geelong (37°S)	23.8 (*60*)	24.7 (*110*)
Tasmania (43°S)	29.8 (*75*)	23.5 (*105*)
Race, % (*n*)		
Caucasian	96.4 (*243*)	94.0 (*419*)
Other	3.6 (*9*)	6.0 (*27*)
History of infectious mononucleosis, % (*n*)		
No	65.1 (*164*)	79.2 (*353*)
Yes	27.8 (*70*)	16.1 (*72*)
Don't know	7.1 (*18*)	4.7 (*21*)
Serum 25(OH)D concentrations, mean (SD)	76.8 (29.7)	81.8 (30.7)
Total years of smoking, median (IQR)	5.4 (18.7)	2.0 (15.0)
Education, % (*n*)		
Year 10 or less	24.6 (*62*)	33.2 (*148*)
Year 12 and TAFE	49.6 (*125*)	41.7 (*186*)
University	25.8 (*65*)	25.1 (*112*)
Body mass index, median (IQR)	25.9 (7.6)	25.5 (7.4)
Dietary misreporting, % (*n*)		
Under-reporter	42.5 (*107*)	40.4 (*180*)
Plausible reporter	55.6 (*140*)	57.2 (*255*)
Over-reporter	2.0 (*5*)	2.5 (*11*)

[a] Case and control participants were matched on sex, age (within two years) and study region FCD, first clinical diagnosis of central nervous system demyelination; SD, standard deviation; IQR, interquartile range; 25(OH)D, 25-hydroxyvitamin D; TAFE, Technical And Further Education

Table 3. Factor loadings of the food groups in the two major dietary patterns identified with principal component analysis

Food group	Healthy	Western
Red meat	0.14	0.30[a]
Processed meat	0.12	0.34[a]
Poultry	0.21[a]	0.18
Take away	-0.03	0.19
Grilled/tinned fish	0.30[a]	-0.03
Fried fish	0.05	0.16
Eggs	0.35[a]	0.12
Wholegrains	-0.01	-0.42[a]
Refined grains	-0.11	0.12
Yellow and red vegetables	0.23[a]	-0.08
Cruciferous vegetable	0.25[a]	0.07
Leafy green vegetables	0.40[a]	0.01
Potato	-0.12	0.04
Fried potato	-0.11	0.18
Other vegetables	0.43[a]	-0.04
Legumes	0.20[a]	-0.01
Nuts	0.13	-0.26[a]
Fresh fruit	0.17	-0.29[a]
Canned fruit	-0.02	-0.10
Juice	-0.12	-0.14
Low fat dairy	0.01	-0.40[a]
Full fat dairy	-0.05	0.23[a]
Sweetened dairy	-0.02	0.10
Sauces	-0.12	0.02
Crisps	-0.18	0.04
Confectionary	0.01	0.10
Cakes biscuits & sweet pastries	-0.13	0.01
Added sugar	-0.07	0.07
Saturated spreads	-0.12	0.002
Unsaturated spreads	-0.04	-0.04
Other spreads	-0.09	-0.002
Wine	0.06	-0.15
Spirits	-0.002	0.05
Beer	-0.09	0.04
Variance explained (%)	9.3	7.5

[a] Food groups with a factor loading ≥0.2 (higher intake) were considered characteristic of the dietary pattern

Table 4. Nutrient intakes (as energy density) for the lowest and highest quintiles of the two dietary pattern scores

	Healthy pattern			Western pattern		
	Lowest quintile	Highest quintile	*P*	Lowest quintile	Highest quintile	*P*
Total energy intake (kJ)[a]	8938.8 (5701.2)	5492.7 (2202.8)	<0.001	6211.9 (2818.1)	8644.7 (5150.8)	<0.001
Total fat density (g/MJ/d)[b]	41.7 (6.0)	37.6 (7.0)	<0.001	34.4 (6.5)	44.4 (4.5)	<0.001
Saturated fat density (g/MJ/d)[b]	18.5 (3.7)	14.3 (3.8)	<0.001	12.5 (3.0)	19.8 (3.0)	<0.001
Monounsaturated fat density (g/MJ/d)[b]	14.3 (2.3)	13.8 (3.0)	0.028	12.3 (2.8)	15.7 (1.9)	<0.001
Polyunsaturated fat density (g/MJ/d)[a]	5.2 (2.5)	5.3 (2.6)	0.313	5.8 (3.7)	4.9 (1.6)	0.013
Long-chain omega 3 fatty acid density (mg/MJ/d)[a]	84.9 (109.4)	296.7 (300.8)	<0.001	221 (247.9)	120.1 (147.1)	<0.001
Protein density (g/MJ/d)[b]	41.6 (6.1)	53.0 (8.8)	<0.001	47.6 (7.4)	48.1 (8.8)	0.585
Carbohydrate density (g/MJ/d)[b]	102.1 (16.0)	102.0 (15.9)	0.538	113.6 (18.5)	91.9 (14.8)	<0.001
Dietary fibre density (g/MJ/d)[b]	8.8 (2.3)	14.4 (3.8)	<0.001	14.6 (3.4)	8.4 (2.2)	<0.001
Calcium density (mg/MJ/d)[b]	456.2 (145.4)	566.5 (183.3)	<0.001	627.2 (195.0)	430.5 (138.4)	<0.001
Magnesium density (mg/MJ/d)[b]	131.8 (20.1)	184.5 (31.5)	<0.001	192.5 (26.0)	127.3 (17.0)	<0.001
Zinc density (mg/MJ/d)[b]	5.3 (1.0)	6.8 (1.3)	<0.001	6.1 (1.0)	6.3 (1.4)	0.368
Iron density (mg/MJ/d)[a]	5.6 (1.5)	7.4 (2.0)	<0.001	7.3 (2.1)	5.8 (1.5)	<0.001
Beta-carotene density (mcg/MJ/d)[a]	934.0 (783.3)	2139.8 (947.6)	<0.001	1785.7 (1037.6)	1132.1 (1033.7)	<0.001
Thiamin density (mg/MJ/d)[b]	0.76 (0.24)	0.83 (0.21)	0.026	0.9 (0.2)	0.7 (0.2)	<0.001
Riboflavin density (mg/MJ/d)[b]	1.2 (0.3)	1.4 (0.3)	<0.001	1.5 (0.4)	1.1 (0.3)	<0.001
Niacin equivalents density (mg/MJ/d)[b]	18.1 (2.8)	22.6 (3.3)	<0.001	21.0 (3.2)	20.0 (3.4)	0.115
Folate density (mcg/MJ/d)[b]	124.4 (30.8)	179.0 (42.0)	<0.001	179.9 (39.7)	122.4 (28.6)	<0.001
Vitamin C density (mg/MJ/d)[a]	45.4 (33.8)	83.0 (41.2)	<0.001	80.4 (53.2)	48.2 (31.5)	<0.001
Vitamin E density (mg/MJ/d)[b]	3.0 (0.6)	4.0 (1.3)	<0.001	4.0 (1.2)	2.9 (0.6)	<0.001

[a] Median (interquartile range), *P*-values derived from Kruskal-Wallis test; [b] Mean (standard deviation), *P*-values derived from one-way Anova

Table 5. Associations between dietary patterns (healthy and Western) and risk of FCD in participants of the Ausimmune Study

	Model 1: unadjusted		**Model 2[a]: partially adjusted**		**Model 3[b]: partially adjusted**		**Model 4[c]: fully adjusted**	
	OR (95% CI)	***P***	**AOR (95% CI)**	***P***	**AOR (95% CI)**	***P***	**AOR (95% CI)**	***P***
n (cases, controls)	*698 (252, 446)*		*698 (252, 446)*		*698 (252, 446)*		*698 (252, 446)*	
Healthy (per SD)	0.83 (0.69, 0.99)	0.042	0.76 (0.62, 0.94)	0.013	0.75 (0.60, 0.94)	0.011	0.75 (0.60, 0.94)	0.011
Quintile 1	Reference		Reference		Reference		Reference	
Quintile 2	0.80 (0.49, 1.31)	0.377	0.77 (0.46, 1.31)	0.342	0.75 (0.44, 1.29)	0.300	0.75 (0.44, 1.29)	0.300
Quintile 3	0.91 (0.56, 1.49)	0.714	0.75 (0.44, 1.27)	0.282	0.72 (0.42, 1.23)	0.226	0.72 (0.42, 1.23)	0.226
Quintile 4	0.66 (0.40, 1.11)	0.199	0.56 (0.31, 0.99)	0.046	0.53 (0.29, 0.96)	0.035	0.53 (0.29, 0.96)	0.035
Quintile 5	0.59 (0.35, 1.01)	0.056	0.48 (0.26, 0.86)	0.014	0.45 (0.24, 0.83)	0.011	0.45 (0.24, 0.83)	0.011
P (trend)		0.047		0.009		0.007		0.007
Western (per SD)	0.97 (0.82, 1.14)	0.676	1.00 (0.84, 1.20)	0.971	0.94 (0.77, 1.13)	0.504	0.94 (0.77, 1.13)	0.506
Quintile 1	Reference		Reference		Reference		Reference	
Quintile 2	0.99 (0.61, 1.60)	0.962	1.06 (0.64, 1.76)	0.830	0.91 (0.54, 1.55)	0.738	0.91 (0.54, 1.55)	0.738
Quintile 3	0.97 (0.60, 1.57)	0.907	1.03 (0.62, 1.70)	0.918	0.88 (0.52, 1.48)	0.621	0.88 (0.52, 1.48)	0.621
Quintile 4	0.67 (0.39, 1.14)	0.137	0.75 (0.42, 1.32)	0.317	0.65 (0.36, 1.17)	0.146	0.65 (0.36, 1.17)	0.147
Quintile 5	0.91 (0.55, 1.50)	0.701	0.99 (0.57, 1.72)	0.966	0.80 (0.44, 1.44)	0.451	0.80 (0.44, 1.44)	0.451
P (trend)		0.324		0.601		0.247		0.248

[a] Adjusted for history of infectious mononucleosis, serum 25-hydroxyvitamin D concentrations, total years of smoking, race, education and dietary misreporting; [b] As previous and additionally adjusted for the alternate dietary pattern (both patterns included in the model); [c] As previous and additionally adjusted for body mass index

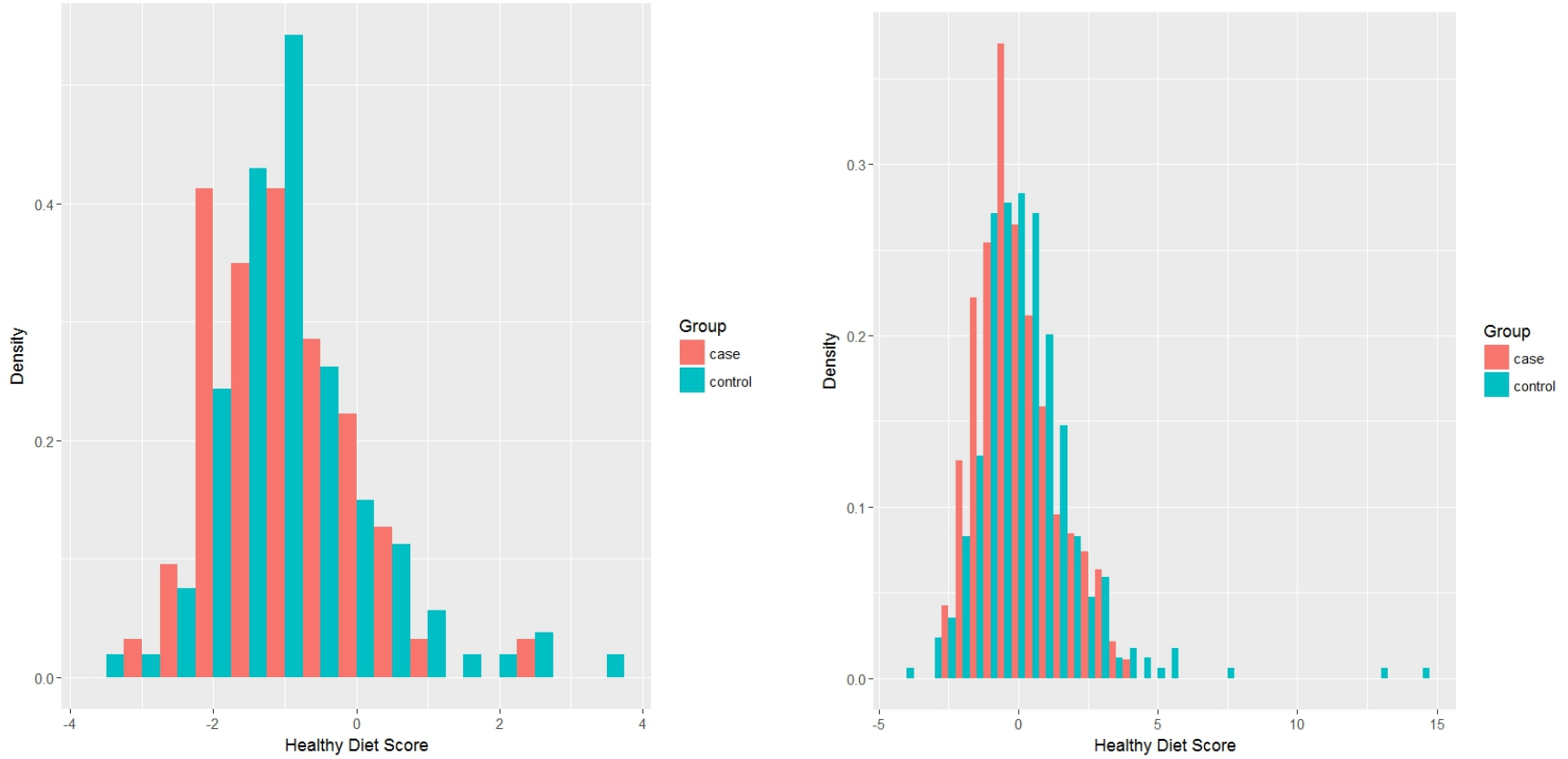
FCD, first clinical diagnosis of central nervous system demyelination

Table 6. Associations between dietary patterns (healthy and Western) and (a) risk of FCD excluding participants with implausible energy intakes (<3,000 or >20,000 kJ/day), (b) risk of FCD in case participants who completed the study interview within 90 days from the date of MRI scan, and (c) risk of FDE

	Model 1: unadjusted		**Model 2[a]: partially adjusted**		**Model 3[b]: partially adjusted**		**Model 4[c]: fully adjusted**	
	OR (95% CI)	***P***	**AOR (95% CI)**	***P***	**AOR (95% CI)**	***P***	**AOR (95% CI)**	***P***
a) risk of FCD excluding participants with implausible energy intakes								
n (cases, controls)	*677 (247, 430)*		*677 (247, 430)*		*677 (247, 430)*		*677 (247, 430)*	
Healthy (per SD)	0.86 (0.71, 1.04)	0.127	0.78 (0.62, 0.98)	0.030	0.76 (0.60, 0.96)	0.024	0.76 (0.60, 0.97)	0.025
Western (per SD)	0.96 (0.81, 1.13)	0.598	1.00 (0.84, 1.20)	0.965	0.93 (0.77, 1.13)	0.489	0.93 (0.77, 1.13)	0.475
b) risk of FCD in case participants who completed the study interview within 90 days from the date of MRI scan								
n (cases, controls)	*321 (116, 205)*		*321 (116, 205)*		*321 (116, 205)*		*321 (116, 205)*	
Healthy (per SD)	0.78 (0.59, 1.04)	0.106	0.67 (0.46, 0.96)	0.029	0.65 (0.44, 0.95)	0.027	0.62 (0.42, 0.91)	0.015
Western (per SD)	0.97 (0.76, 1.25)	0.552	1.00 (0.75, 1.32)	0.972	0.91 (0.67, 1.23)	0.545	0.88 (0.65, 1.17)	0.372
c) risk of FDE								
n (cases, controls)	*528 (193, 335)*		*528 (193, 335)*		*528 (193, 335)*		*528 (193, 335)*	
Healthy (per SD)	0.83 (0.67, 1.02)	0.082	0.81 (0.63, 1.04)	0.099	0.78 (0.60, 1.02)	0.071	0.79 (0.61, 1.03)	0.085
Western (per SD)	0.96 (0.80, 1.15)	0.670	0.96 (0.78, 1.18)	0.675	0.90 (0.72, 1.13)	0.363	0.90 (0.72, 1.12)	0.336

[a] Adjusted for history of infectious mononucleosis, serum 25-hydroxyvitamin D concentrations, total years of smoking, race, education and dietary misreporting; [b] As previous and additionally adjusted for the alternate dietary pattern (both patterns included in the model); [c] As previous and additionally adjusted for body mass index

FCD, first clinical diagnosis of central nervous system demyelination; FDE, incident classic first demyelinating event



a) b)

Supplementary Figure 1. Histograms of the healthy dietary pattern score for case and control participants of the Ausimmune Study for a) men (*n*=63 cases, 107 controls) and b) women (*n*=189 cases, 339 controls)