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

Lucinda J Black[1*], Charlotte Rowley[1], Jill Sherriff[1], Gavin Pereira[1], Anne-Louise Ponsonby[2,3], Ausimmune Investigator Group, Robyn M Lucas[3, 4]

[1]School of Public Health, Curtin University, Perth, Australia
[2]Murdoch Children's Research Institute, University of Melbourne, Melbourne, Australia
[3]National Centre for Epidemiology and Population Health, Research School of Population Health, The Australian National University, Canberra, Australia
[4]Centre for Ophthalmology and Visual Science, University of Western Australia, Perth, Australia
*Correspondence:
Lucinda Black
School of Public Health, Curtin University
Kent Street, Bentley, Western Australia 6102
Australia
Phone: 08 9266 2523
lucinda.black@curtin.edu.au

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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 case. Ethics approval was obtained from the nine Human Research Ethics Committees of the participating institutions [11]. All participants gave written informed consent for the use of their data.

The current study included participants who provided complete data on dietary intake and all covariates, and who were part of at least a matched control pair. Of the 840 participants (282 cases, 558 controls) in the Ausimmune Study, 791 participants (272 cases, 519 controls) provided dietary intake data; 743 participants (259 cases, 484 controls) of these provided data for all covariates; and 698 participants (252 cases, 446 controls) of these were part of at least a matched pair and thus formed the study cohort for this analysis.

*Dietary assessment*

The Cancer Council Victoria Dietary Questionnaire for Epidemiological Studies version 2 (DQESv2) was used to collect information on habitual dietary intakes in the 12 months prior to the study interview. The DQES is a self-administered, semi-quantitative, food frequency questionnaire (FFQ) designed for use in the ethnically-diverse adult Australian population, the development of which has been outlined elsewhere [13]. The questionnaire has been validated relative to seven-day weighed food records in 63 women of child-bearing age, where it performed as well as other validated FFQs: mean intakes from the weighted food record and the DQES were within ±20% for 21 of 27 nutrients [14].

The frequencies of consumption of food items were recorded on a scale from 'never' to 'three or more times per day'. Portion size diagrams were used to determine respondents' average portion size factor. Consumption of alcohol was recorded as the total number of glasses 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*

We categorised the 101 food and beverage items into 34 food groups (Table 1), based on those used previously [18]. Each food group was energy-adjusted using the energy density method [19]. The food group data for control participants only were entered into the PCA procedure in Stata Statistical Software: Release 14 [20]. The factor solution was limited to those factors with an eigenvalue >1.0 and the number of factors to retain was based on the screeplot and also on the interpretability of the obtained patterns [21]. The identified factors were orthogonally rotated to improve their interpretability [22]. Food groups with a factor loading ≥0.2 were considered to contribute substantially to the pattern and were used to name each pattern. Standardised factor scores were computed using the PCA procedure in Stata 14 software [20], so that all participants were assigned a score for each dietary pattern, based on their FFQ intakes.

Nutrient intakes derived from the FFQ were energy adjusted using the energy-density method [19] and were described for the lowest and highest quintiles of each dietary pattern. Nutrient densities with Normal distributions were reported as mean and standard deviation (SD), and those with non-Normal distributions were reported as median and IQR. We compared nutrient intakes between the five quintiles of each dietary pattern using one-way ANOVA for nutrients with Normal distribution, and the Kruskal-Wallis test for nutrients with non-Normal distribution.

Characteristics of cases and controls ($n$=698, 252 cases, 446 controls) were described as frequency and percentage for categorical variables, mean and SD for continuous variables with a Normal distribution, and median and IQR for continuous variables with a non-Normal distribution. Characteristics of control participants who were included in the final model ($n$=446) were compared with those who were excluded from the final model due to missing data or missing matched case participant (*n*=112). Pearson's chi-square tests were used for categorical variables, independent samples t-tests for continuous variables with Normal distributions and Mann–Whitney U tests for continuous variables with non-Normal distributions.

We used conditional logistic regression models (participants matched on age, sex and study region) to estimate odds ratios (ORs), 95% confidence intervals (95% CI) and $p$ values for associations between dietary patterns and risk of FCD. Dietary pattern scores were analysed both as continuous variables (where a one-unit increase was equivalent to a one-SD increase in dietary pattern score) and as quintiles based on score thresholds for control participants.

Potential confounders were selected on the basis of: 1) being a known risk factor for MS (history of infectious mononucleosis, serum 25-hydroxyvitamin D concentrations, total years of smoking); 2) being a possible risk factor for MS and/or having a potential influence on dietary patterns (race, BMI and education); and 3) accounting for the well-documented under-reporting of energy intake by self-reported dietary methods (dietary misreporting) [23]. The impact of the dietary patterns on each other was investigated by including all dietary patterns simultaneously in the final models [8]. Model 1 (*n*=698) was unadjusted; model 2 (*n*=698) was adjusted for history of infectious mononucleosis, serum 25-hydroxyvitamin D concentration, total years of smoking, race, education and dietary misreporting; model 3 (*n*=698) was additionally adjusted for all dietary patterns; model 4 was additionally adjusted for BMI (*n*=698). We tested for an interaction between the dietary pattern score and BMI using an interaction term in the models. To test whether any associations differed by sex, we ran models in males and females separately and examined differences in the effect estimates.

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 a higher intake of red meat, processed meat and full fat dairy, and was low in wholegrains, nuts, fresh fruit and low fat dairy.

Compared with those in the lowest quintile of the healthy pattern, participants in the highest quintile had: lower intakes of total energy; lower energy-adjusted intakes of total fat, saturated fat and monounsaturated fat; and higher energy-adjusted intakes of long-chain omega-3 PUFA, protein, dietary fibre, and various vitamins and minerals (Table 4). Compared with those in the lowest quintile of the Western pattern, participants in the highest quintile had: higher intakes of total energy; higher energy-adjusted intakes of total fat, saturated fat and monounsaturated fat; and lower energy-adjusted intakes of PUFA, long-chain omega-3 PUFA, carbohydrate, dietary fibre, and various vitamins and minerals.

*Dietary patterns and risk of FCD*

In the unadjusted model (Model 1), a one-SD increase in the healthy pattern score was associated with a 17% (Adjusted Odds Ratio (AOR) 0.83; 95% CI 0.69, 0.99) reduced risk of FCD (Table 5). A one-SD increase in the healthy pattern score was associated with a 24% (AOR 0.76; 95% CI 0.62, 0.94) reduced risk of FCD when adjusted for potential confounders (Model 2), and a 25% (AOR 0.75; 95% CI 0.60, 0.94) reduced risk of FCD when further adjusted for the Western dietary pattern (Model 3) and BMI (Model 4). Compared with the lowest quintile of the healthy dietary pattern score, the risk of FCD was 47% (AOR 0.53; 95% CI 0.29, 0.96) lower in the fourth quintile and 55% (AOR 0.45; 95% CI 0.24, 0.83) lower in the highest quintile in the fully adjusted model (Model 4). There was no statistically significant interaction between the healthy dietary pattern score and BMI in the model using the dietary pattern score as a continuous variable (p=0.09) and as quintiles. We found no 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 suggests that the lack of statistical association for men was possibly due to the lower sample size for men due to the female case excess. We did not observe any statistically significant associations between a Western dietary pattern and risk of FCD. The two major dietary patterns we identified were similar to the ‘healthy’ and ‘Western’ patterns identified in other studies of adults, as reviewed previously [24]. Although the small amount of total variability in diet explained by the dietary patterns is a limitation, this is similar to other studies of dietary patterns derived by PCA [25,26].

Our findings are similar to the study by Sedaghat and colleagues [9] which showed that, in a hospital-based case-control study of people with MS in Iran (*n*=70 cases, 142 controls), a high quality Mediterranean diet was associated with reduced risk of MS. In that study, the Mediterranean diet (high in vegetables, legumes, fruits, nuts, fish and a high ratio of unsaturated to saturated fatty acids; and low in dairy, meat and meat products and refined grains) was assessed using a modified version of the 9-Unit dietary score [24]. Our results support these findings since a healthy dietary pattern - high in vegetables, legumes and fish - is similar to a Mediterranean diet.

Jahromi and colleagues [10] used factor analysis to identify dietary patterns in a case-control study of women with relapsing/remitting MS (*n*=77 cases, 75 controls). Three dietary patterns were inversely associated with risk of MS: 1) traditional (high in low-fat dairy products, red meat, vegetable oil, onion, wholegrain, soy, refined grains, organ meats, coffee and legumes); 2) lacto-vegetarian (high in nuts, fruits, French fries, coffee, sweets and desserts, vegetables and high-fat dairy products); and 3) vegetarian (high in green leafy vegetables, hydrogenated fats, tomato, yellow vegetables, fruit juices, onion and other vegetables). A Western dietary 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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Prof Alan Coulthard, Royal Brisbane and Women's Hospital and the University of Queensland, Brisbane, Queensland, Australia
Prof Keith Dear, School of Public Health, University of Adelaide, South Australia, Australia
Prof Terry Dwyer, Murdoch Childrens Research Institute, University of Melbourne, Melbourne, Victoria, Australia
Prof Trevor Kilpatrick, Centre for Neuroscience, University of Melbourne, Melbourne, Australia
Prof Robyn Lucas, National Centre for Epidemiology and Population Health, The Australian National University, Canberra, Australian Capital Territory, Australia
Prof Tony McMichael (dec), National Centre for Epidemiology and Population Health, The Australian National University, Canberra, Australian Capital Territory, Australia
Prof Michael P Pender, Royal Brisbane and Women's Hospital and the University of Queensland, Brisbane, Queensland, Australia
Prof Anne-Louise Ponsonby, Murdoch Childrens Research Institute, University of Melbourne, Melbourne, Victoria, Australia
Prof Bruce Taylor, Menzies Research Institute Tasmania, University of Tasmania, Hobart, Tasmania, Australia

A/Prof Patricia Valery, Menzies School of Health Research, Brisbane, Queensland, Australia

A/Prof Ingrid van der Mei, Menzies Research Institute Tasmania, University of Tasmania, Hobart, Tasmania, Australia

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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

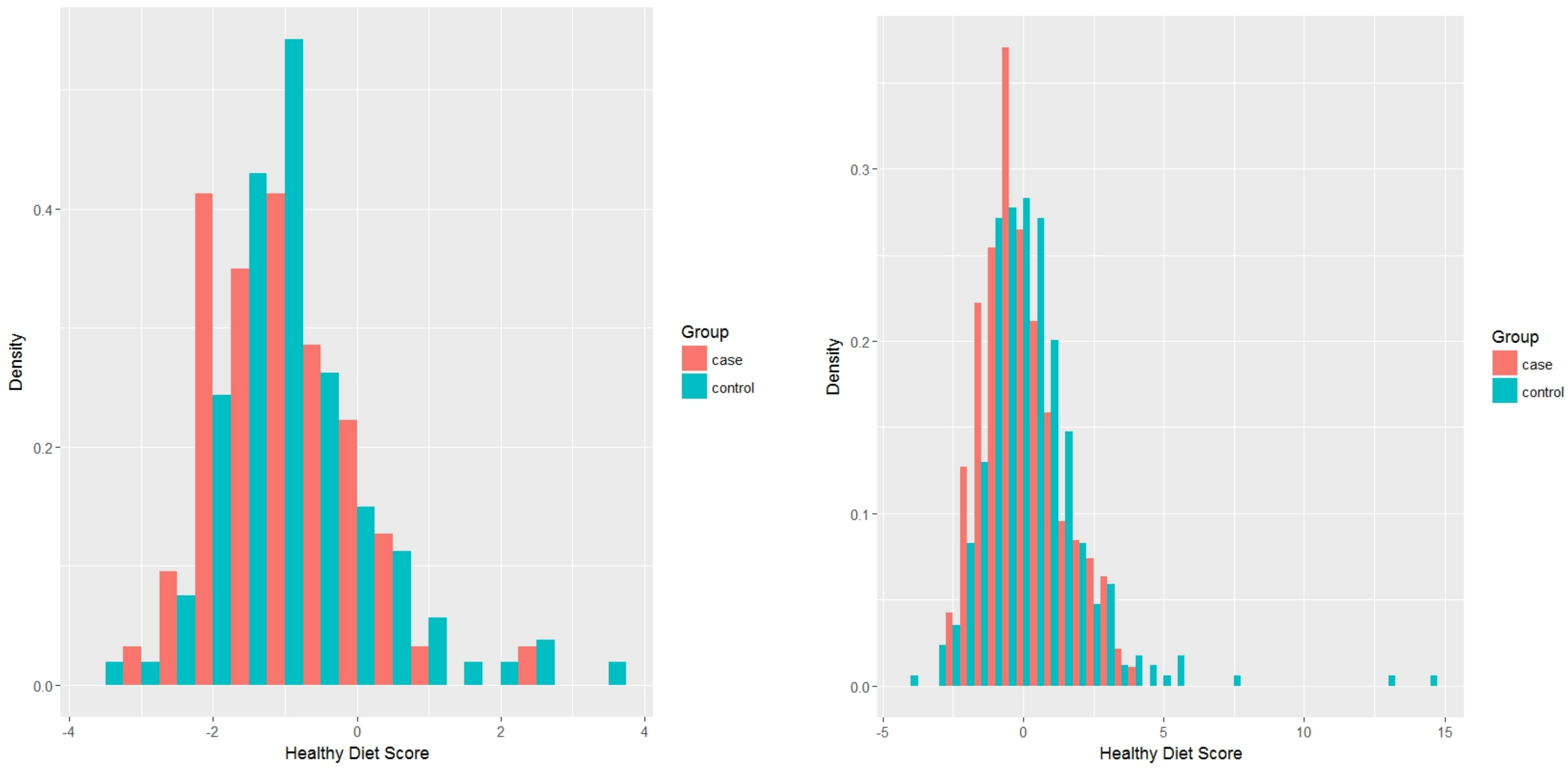
FCD, first clinical diagnosis of central nervous system demyelination

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




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)