# A higher Mediterranean diet score, including unprocessed red meat, is associated with reduced risk of central nervous system demyelination in a case-control study of Australian adults

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**Abbreviations:**

25(OH)D: 25-hydroxyvitamin D

aMed: alternate Mediterranean diet score

aMED-Red: alternative Mediterranean diet score with unprocessed red meat

aOR: adjusted odds ratio

CNS: central nervous system

DQESv2: Cancer Council Victoria Dietary Questionnaire for Epidemiological Studies version 2

FCD: first clinical diagnosis of central nervous system demyelination

FDE: classic first demyelinating event

MS: multiple sclerosis

VLCn3PUFA: very long chain omega-3 PUFA

**Abstract**

**Background:** The evidence associating diet and risk of multiple sclerosis (MS) is inconclusive.

**Objectives:** We investigated associations between a Mediterranean diet and risk of a first clinical diagnosis of central nervous system demyelination (FCD), a common precursor to MS.

**Methods:** We used data from the 2003-2006 Ausimmune Study, an Australian multicenter, case-control study examining environmental risk factors for FCD, with participants matched on age, sex and study region (282 cases, 558 controls; 18-59 years old; 78% female). The alternate Mediterranean diet score (aMED) was calculated using data from a food frequency questionnaire. We created a modified version of the aMED (aMED-Red) where approximately one daily serving (65 g) of unprocessed red meat received one point. All other components remained the same as aMED. Conditional logistic regression (254 cases, 451 controls) was used to test associations between aMED and aMED-Red scores and categories and risk of FCD, adjusting for history of infectious mononucleosis, serum 25-hydroxyvitamin D concentrations, smoking, education, total energy intake and dietary under-reporting.

**Results:** There was no statistically significant association between aMED and risk of FCD (per one SD increase in aMED score: adjusted odds ratio (aOR):0.89; 95% confidence interval (CI):0.75,1.06; *P*=0.181). There was evidence of a non-linear relationship between aMED-Red and risk of FCD using a quadratic term (*P*=0.016). Compared with the lowest category of aMED-Red, higher categories were significantly associated with reduced risk of FCD, corresponding to a 37% (aOR:0.63; 95% CI:0.41,0.98; *P*=0.039), 52% (aOR:0.48; 95% CI:0.28,0.83; *P*=0.009) and 42%

(aOR:0.58; 95% CI:0.35,0.96; *P*=0.034) reduced risk of FCD in categories two, three and four, respectively.

**Conclusions:** A Mediterranean diet, including unprocessed red meat, was associated with reduced risk of FCD in this Australian adult population. The addition of unprocessed red meat to a Mediterranean diet may be beneficial for those at high risk of MS.

**Key Words:** Multiple sclerosis, Mediterranean diet, Ausimmune Study, nutrition and disease

## Introduction

Multiple sclerosis (MS) is a chronic inflammatory and neurodegenerative disease of the central nervous system (CNS) (1). The disease course typically begins with fully or partially reversible episodes of neurologic disability, developing after 10 to 20 years to progressive neurologic deterioration (1). MS is more common in females than males, and among those with an affected first-degree relative. The incidence of MS is increasing globally, with a suggested role for environmental risk factors, including low sun exposure, low vitamin D status, smoking and history of infectious mononucleosis (2). Poor diet may be a modifiable risk factor for MS onset; however, the evidence is inconclusive and many studies have assessed single foods or nutrients (3-16), rather than dietary patterns. The latter captures information about total diet, including the interactions that may occur between food components (17).

The traditional Mediterranean diet is known for its health benefits across a variety of chronic diseases. A recent umbrella review identified 29 meta-analyses investigating the association between adherence to a Mediterranean diet and 37 different health outcomes, which included neurodegenerative diseases but not specifically MS (18). The review supports the hypothesis that greater adherence to a Mediterranean diet reduces the risk of certain health outcomes, including overall mortality, cardiovascular diseases, diabetes, overall cancer incidence, Alzheimer's disease and dementia. To our knowledge, only one previous study has investigated the association between a Mediterranean diet and risk of MS. That study was conducted in Iran and reported that greater adherence was associated with reduced risk of MS, with a 77% reduced risk of

MS for those in the third tertile of the Mediterranean diet score compared with the first tertile (adjusted odds ratio (aOR):0.23; 95% CI:0.06,0.89; *P*-trend=0.04) (13).

A number of approaches have been proposed to define and measure adherence to a Mediterranean diet (19-24), all of which consider low intakes of red meat as beneficial. Indeed, the Mediterranean Diet Foundation suggests that meat/meat products be limited to <2 servings of red meat/week, <1 servings of processed meat/week and 2 servings of white meat/week, with serving sizes to be based on frugality and local habits (25). To put this in an Australian context, a standard serving of meat is defined as 65 g (26). Similarly, a recently proposed new Mediterranean Diet Italian Pyramid suggests a low intake of unprocessed and processed meat at 100 g/week and 50 g/week, respectively (27). However, a review of food intakes in 14 local Mediterranean populations (plus one study of Greek-Australian migrants living in Australia), spanning 46 years of data collection (1960-2006), showed that mean intake of meat/meat products was 105 g/day, (28), which is far higher than the aforementioned recommendations. Furthermore, median daily energy-adjusted meat consumption was approximately 100 g in elderly men and women resident in three Greek villages in 1990 (29), and meat consumption per capita in 2013 exceeded 100 g/day in the Mediterranean region (30). Hence, there is a discrepancy between actual meat intakes in the Mediterranean region and those recommended as part of the Mediterranean diet. The role of meat in the Mediterranean diet has recently been reviewed, with authors suggesting that up to one daily serving of unprocessed red meat should be considered part of the Mediterranean diet (31).

The Ausimmune Study was a multicenter, matched case-control study investigating environmental risk factors for a first clinical diagnosis of CNS demyelination (FCD), a common precursor to MS. It is one of the largest, most well-characterized samples of people with early MS worldwide. We previously found that higher intake of very long chain omega-3 PUFAs (VLCn3PUFAs) (12), higher unprocessed red meat consumption (16) and greater adherence to a healthy dietary pattern (15) were associated with reduced risk of FCD in the Ausimmune Study. To build on this evidence, we tested associations between a Mediterranean diet and risk of FCD using data from the Ausimmune Study. We tested the alternate Mediterranean diet score (aMED) (20), a commonly used measure of adherence to a Mediterranean diet. We also created a variation of the aMED (which we have named aMED-Red), and tested associations between aMED-Red and risk of FCD. The aMED-Red considers approximately one daily serving (65g) of unprocessed red meat to be a healthy component of a Mediterranean diet.

## Methods

*Study population*

The Ausimmune Study was conducted during 2003-2006 in four regions of Australia, namely Brisbane city (latitude 27° South), Newcastle region (33°S), Geelong and the Western districts of Victoria (37°S), and the island of Tasmania (43°S) (32). The study design and methodology are reported in detail elsewhere (32). In brief, participants aged between 18 and 59 years and presenting with a FCD (*n*=282) were notified to the study by a range of clinicians. The date of onset and presenting symptoms suggestive of inflammatory CNS demyelination were confirmed by a neurologist following a full

history and neurological examination (32). A total of 54% of case participants had >9 lesions at FCD; 46% had nine or fewer lesions (including 9% with no lesions). The date of the MRI scan preceding diagnosis was used as a proxy for date of the FCD, as these data were available for most participants. The median time lag from MRI scan to study interview was 103 days (IQR:153 days), with 116 cases having been interviewed within 90 days of the scan.

Case participants were diagnosed with CNS demyelination for the first time, within the study period. The diagnoses included: a classic first demyelinating event (FDE; defined as a single, first, episode of clinical symptoms suggestive of CNS demyelination; *n*=216); a first recognized event, but past history revealed a prior, undiagnosed event, that, on review was highly suggestive of CNS demyelination (*n*=48); first presentation of primary progressive MS (based on neurological assessment on study entry (*n*=18)). Control participants (*n*=558) were randomly selected from the general population via the Australian Electoral Roll and matched on sex, age (within 2 years) and study region (32). Up to four controls were matched to each case in order to maximize study power (32).

The study was conducted in accordance with the Declaration of Helsinki. Ethics approval was obtained from the nine Human Research Ethics Committees of the participating institutions (32). All participants gave written informed consent for the use of their data. All participant information was anonymized and de-identified prior to analysis.

The current study included participants who provided complete data on dietary intake and all covariates, and who were part of at least a matched case-control pair. Of the 840 participants (282 cases, 558 controls) in the Ausimmune Study, 791 participants provided dietary intake data. Of these, 746 participants provided data for all covariates (missing data were serum 25-hydroxyvitamin D (25(OH)D) concentrations, *n*=38; history of infectious mononucleosis, *n*=1; eduation, *n*=1; smoking history, *n*=2; and dietary under-reporting, *n*=3). Of these, 705 (254 cases, 451 controls) participants 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 DQESv2 is a self-administered, semi-quantitative, FFQ designed for use in the ethnically-diverse adult Australian population; the development of the DQESv2 has been outlined elsewhere (33). 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 (34).

The DQESv2 included portion size diagrams and measured consumption of food items from four groups: 1) cereals, sweets and snacks; 2) dairy, meats and fish; 3) fruit; 4) vegetables. Consumption frequencies of food and drink items were recorded on a scale from ‘never’ to ‘three or more times a day’. Consumption of alcoholic beverages was recorded as the total number of glasses usually consumed per day, and the maximum

number of glasses drunk in any 24 hours. Intake of 101 food and beverage items were reported in grams per day. Nutrient intakes were computed primarily using composition data from the Australian NUTTAB 95 database (35).

*Score calculation*

We calculated the aMED, proposed by Fung and colleagues (20) as an adaptation of the nine-point Mediterranean diet score developed by Trichopoulou and colleagues (19). We created a variation of the aMED in order to include moderate consumption of unprocessed red meat (defined as beef, lamb, pork and veal) as a healthy component of a Mediterranean diet (aMED-Red). For the aMED, one point is assigned for intakes (g/day) of unprocessed and processed red meat (g/day) below the sex-specific median (20). For the aMED-Red, we modified the meat component of the aMED such that one point was assigned to intakes of approximately one daily serving (65 g) (26) of unprocessed red meat (between 0.5 and 1 servings/day; 32.5 and 97.5 g/day) (**Supplemental Table 1**). Other components remained the same as the aMED; hence, the scores for both the aMED and aMED-Red ranged between 0 and 9. Components, scoring criteria and scoring cut-off points (including sex-specific medians for control participants) for the aMED and the aMED-Red are described in Supplemental Table 1.

Some studies use energy-standardized component intakes in the computation of the aMED score (aMED-e) (36). Hence, we calculated energy-adjusted scores (aMED-e and aMED-Red-e) where component scores for fruit, vegetables, legumes, nuts, wholegrains, fish, and red and processed meat (aMED-e only) were based on intake

standardised to 2500 kcal/day in men and 2000 kcal/day in women, as previously described (36).

The total score for the aMED, aMED-Red, aMED-e and aMED-Red-e was calculated as the sum of all component scores and ranged between 0 and 9 (with 9 indicating the highest adherence to a Mediterranean diet). Four categories for the aMED, aMED-Red, aMED-e and aMED-Red-e were created as follows: category 1 (scores 0-2); category 2 (scores 3-4); category 3 (score 5); category 4 (scores 6-9).

*Covariates*

Self-report questionnaires were used to collect information on history of infectious mononucleosis, highest level of education and smoking history (total number of years smoked minus any periods of abstinence). The study nurse measured height and weight, and 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 (37). Under-reporters were classified using the Goldberg cut-off point of below basal metabolic rate x 1.05 (38). A two-category variable was created for dietary misreporting: under-reporter and plausible reporter.

Most participants (94%) provided a blood sample for measurement of serum 25(OH)D concentrations (since low vitamin D status is a known risk factor for MS (2)). Serum aliquots (1 mL) were stored at -80°C and analysed for serum 25(OH)D concentrations using liquid chromatography tandem mass spectrometry (39). To account for blood samples of cases and controls being taken at different times of the year, serum 25(OH)D

concentrations for control participants were statistically adjusted to match the date of the case blood draw, using region-specific seasonal patterns of 25(OH)D concentrations (39).

*Statistical analysis*

Characteristics of participants were described as percentage and frequency 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. For each of the nine components of the aMED and aMED-Red, we described the percentage of case and control participants scoring '1' for the component.

We used conditional logistic regression, with participants matched on age, sex and study region, to estimate OR, aOR, 95%CI and *P* for associations between aMED and aMED-Red categories and risk of FCD. We tested for non-linearity using a quadratic term for aMED and aMED-Red as the continuous variable divided by its standard deviation. Where linearity was indicated, we also reported associations for the continuous variable.

Models were run unadjusted and adjusted for history of infectious mononucleosis, serum 25-hydroxyvitamin D concentration, total years of smoking, education, total energy intake, and dietary misreporting. Adjustment variables were selected on the basis of: 1) being a known risk factor for MS (history of infectious mononucleosis, serum 25-hydroxyvitamin D concentrations, smoking); 2) being a possible risk factor for MS (education); and 3) accounting for the well-documented under-reporting of energy

intake by self-reported dietary methods (dietary misreporting) (40); and 4) accounting for total energy intake. We investigated possible interactions between sex and diet scores using a multiplicative term in adjusted models with a likelihood ratio test.

We investigated the importance of individual components of aMED and aMED-Red by further conducting conditional logistic regression models including all individual components in the same model (unadjusted and adjusted as above). For statistically significant components, we performed additional models with the individual component only (unadjusted and adjusted as above).

We conducted the following sensitivity analyses: a) excluding participants with implausible energy intakes (<3,000 or >20,000 kJ/day) (41) ($n$=684, 249 cases, 435 controls) and b) including only case participants with a classic FDE ($n$=535, 195 cases, 340 controls). To investigate any differences between raw and energy-adjusted components in associations with risk of FCD, we ran additional conditional logistic regression models using aMED-e and aMED-Red-e as per the main models (although models were not adjusted for total energy intake), and we tested for non-linearity and possible interactions between sex and diet scores. Data were analyzed using Stata 14 software (42). Statistical significance was defined as $P < 0.05$.

**Results**

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 (**Table 1**). The majority of participants scored between 2 and 6 on both

aMED and aMED-Red (**Figure 1**). Compared with control participants, there was a lower percentage of case participants with a score of 1 *vs*. 0 on healthy components of vegetables, legumes, wholegrains, fish and MUFA:SFA, and a higher percentage scoring 1 on fruit (**Supplemental Table 2**). Compared with control participants, there was a lower percentage of case participants scoring 1 for unprocessed red meat (where 1=approximately one daily serving of 65 g), and a higher percentage of case participants scoring 1 for red meat (unprocessed and processed) below the sex-specific median of control participants.

Quadratic terms indicated no evidence of a non-linear relationship between aMED and risk of FCD, but evidence of a non-linear relationship between aMED-Red and risk of FCD ($P$=0.016). Hence, we did not run models with aMED-Red as the continuous variable. There were no statistically significant associations between aMED and risk of FCD (**Supplemental Table 3**). Compared with the lowest category of aMED-Red, higher categories were statistically significantly associated with reduced risk of FCD, corresponding to a 37% (aOR:0.63, 95% CI:0.41,0.98; $P$=0.039), 52% (aOR:0.48, 95% CI:0.28,0.83; $P$=0.009) and 42% (aOR:0.58; 95% CI:0.35,0.96; $P$=0.034) reduced risk of FCD in categories two, three and four, respectively (**Figure 2**). For both aMED and aMED-Red, there was no evidence of an interaction with sex ($P$-interaction > 0.1). Similar findings were observed in the sensitivity analyses of those with plausible energy intakes and in the classic FDE group (**Supplemental Table 4**), and when using energy-adjusted components (**Supplemental Table 5**).

When included together in a single model, no individual components of aMED were statistically significantly associated with risk of FCD (**Table 2**). However, of the aMED-Red components, a score of 1 compared with a score of 0 for unprocessed red meat was significantly associated with reduced risk of FCD in models adjusted for all other components and potential confounders (Table 2). In a model adjusted for potential confounders, but excluding the other aMED-Red components, the odds ratio for a score of 1 compared with a score of 0 for the unprocessed red meat component and risk of FCD was similar, albeit of borderline statistical significance (aOR:0.72; 95% CI:0.52,1.00; *P*=0.053).

## Discussion

Our results support an association between greater adherence to a Mediterranean diet that includes unprocessed red meat and reduced risk of FCD. Compared with the lowest category, the three higher categories were associated with reduced risk of FCD, although the association was non-linear, with the lowest odds ratio seen in category three compared with category one. Our results suggest that scoring between one and two (category one) on the aMED-Red should be avoided if these estimates represent causal effects, with insufficient evidence to differentiate the benefits of being in the higher categories. Using a common scoring system for the Mediterranean diet (aMED), which emphasizes low red meat (unprocessed and processed) consumption, we did not observe any statistically significant associations with risk of FCD. Indeed, the unprocessed red meat consumption component of the aMED-Red was the only component to associate independently with risk of FCD. This supports our recent findings that higher consumption of unprocessed red meat was associated with reduced

296 risk of FCD in the Ausimmune Study (16). The new findings presented here highlight
297 the importance of unprocessed red meat as part of a healthy Mediterranean diet and
298 association with reduced risk of FCD.
299
300 Our findings support previous studies investigating dietary patterns and risk of MS (13,
301 14). A hospital-based case control study in Iran showed that a higher Mediterranean diet
302 score was associated with reduced risk of MS (13). Similar to our study, the score used
303 to measure adherence to a Mediterranean diet in that study did not emphasize low red
304 meat consumption; rather, a lower ratio of red meat to white meat was considered
305 beneficial. The typical Iranian diet is characterized in part by high red meat and organ
306 meat consumption (14); hence, overall red meat consumption was likely to be high in
307 that population. Indeed, a further study in the Iranian population showed that higher
308 adherence to a traditional Iranian dietary pattern (high in low-fat dairy products, red
309 meat, vegetable oil, onion, whole grain, soy, refined grains, organ meats, coffee, and
310 legumes) was associated with reduced risk of MS (14).
311
312 Red meat contains important macro- and micronutrients, including protein, iron, zinc,
313 selenium, potassium, vitamin D (43), a range of B-vitamins and, for grass-fed beef,
314 VLCn3PUFAs (44-46). Many of these nutrients are important for healthy neurological
315 function, and low levels of vitamin D (2, 39), VLCn3PUFAs (12, 47) and iron (48) have
316 been associated with increased risk and/or progression of MS. Indeed, in previous
317 analysis of the Ausimmune Study, we found that higher intake of VLCn3PUFAs, such
318 as those found in fish and meat, was associated with reduced risk of FCD, but not
319 higher intake of alpha-linolenic acid, found in some plant-based foods (12). It has also

320 been suggested that iron sufficiency may be important in preventing MS since iron is
321 involved in the synthesis, maintenance and repair of myelin, may be critical to
322 oligodendrocyte activity and integrity, and plays an integral role in mitochondrial
323 energy production (49). Unprocessed red meat is high in heme iron (50), which is more
324 bioavailable than the plant form of iron (non-heme) (51). A study in older Australian
325 adults showed that restricting red meat was one of the most difficult aspects of adhering
326 to a Mediterranean diet over a six-month dietary intervention (52), which may affect the
327 long-term sustainability of the diet (53). Hence, encouraging restriction of red meat to
328 <3 servings/week (as suggested by the Mediterranean Diet Foundation (25)) may be
329 unnecessary and difficult to follow and, according to our findings, may be detrimental
330 to those at high risk of FCD.
331
332 A recent randomized, crossover, controlled feeding trial showed that adopting a
333 Mediterranean-style diet, with or without reduction in red meat intake, improved
334 multiple cardiometabolic risk factors in overweight or moderately obese adults (54).
335 Authors concluded that adults who are overweight or obese can consume approximately
336 70 g/day of lean, unprocessed red meat without adversely affecting cardiometabolic
337 health. A further randomized controlled trial is underway to assess the inclusion of pork
338 in the Mediterranean diet and subsequent effects on cardiovascular risk and cognitive
339 function, with authors hypothesizing that pork may be an appropriate addition to the
340 Mediterranean diet (53). In light of the current interest in unprocessed red meat as part
341 of the Mediterranean diet, the aMED-Red score may be worthy of investigation in
342 epidemiological analysis of other health outcomes beyond MS.
343

Other epidemiologic research in relation to diet and risk of MS has been conducted in individuals who have established MS, making reverse causation (i.e. that the diagnosis led to behavior changes in dietary intake) a potential limitation of those studies. A major strength of the Ausimmune Study was that collection of dietary data was soon after the FCD, rather than in people with established MS. However, we acknowledge that prodromal symptoms, such as fatigue and depression (55-57), may lead to differences in eating habits in the years prior to FCD; therefore, we cannot rule out the possibility of reverse causation.

As with all studies using self-reported dietary assessment methods, a limitation of our study is the widely acknowledged under-reporting of energy intake (40). We attempted to account for dietary under-reporting by including a misreporting variable in adjusted models. Cases may be more likely to recall exposure to risk factors than controls (58). However, we believe this bias to be minimal in our study since diet is not commonly considered a cause of CNS demyelination. Moreover, if the recall of unhealthy food intake and portion sizes for the FCD cases was systematically greater than for controls, this would imply that FCD cases would recall a greater intake and portion sizes of unprocessed red meat, since red meat is often considered part of a "Western" (unhealthy) diet. Such recall bias would likely result in attenuation of the OR for the association between unprocessed red meat and FCD. Therefore, our results provide a conservative estimate of the association between aMED-Red and risk of FCD. Typical of any epidemiological analysis, we cannot rule out the potential of residual confounding where other unmeasured lifestyle characteristics may influence the relationship between dietary intake and 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 analyses of data from the Ausimmune Study (59). Finally, our study population was predominantly female and Caucasian, with participants likely to be consuming a typical Australian diet. Investigating associations between a Mediterranean diet and risk of FCD or MS in a multi-ethnic population would allow greater generalizability of results.

Limitations notwithstanding, our results show that a Mediterranean diet that includes approximately one daily serving of unprocessed red meat (where one serving=65 g) is associated with lower risk of FCD. Given that the maximum number of weekly servings of lean red meat recommended for Australian adults is seven (26), such a diet is in line with recommendations for the general population. The intake of unprocessed red meat in the Australian adult population is considerably higher than this recommendation - current median intake for Australian adults aged >18 years is 150 g/day (60). In general, young Australian women are advised to eat more red meat, while Australian adult males need to eat less red meat (61). Healthy eating guidelines designed for the general population are currently the best available dietary recommendations for people at high risk of MS; however, less than 4% of the Australian population follow the Australian Dietary Guidelines (26). Hence, improved nutrition education for people at high risk of MS may be beneficial for their general health as well as reducing their risk of FCD, or of MS.

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Table 1. Characteristics of participants with FCD and matched controls

| | Case (*n*=254) | Control (*n*=451) |
|---|---|---|
| Sex[2] | | |
| Male | *64* (25.2) | *109* (24.2) |
| Female | *190* (74.8) | *342* (75.8) |
| Age, years[2] | 38.6 ± 9.7 | 40.0 ± 9.6 |
| Study region[2] | | |
| Brisbane (27°S) | *86* (33.9) | 167 (37.0) |
| Newcastle (33°S) | *32* (12.6) | *66* (14.6) |
| Geelong (37°S) | *60* (23.6) | *111* (24.6) |
| Tasmania (43°S) | *76* (29.9) | *107* (23.7) |
| History of infectious mononucleosis | | |
| No | *166* (65.4) | *356* (78.9) |
| Yes | *70* (27.6) | *73* (16.2) |
| Don't know | *18* (7.1) | *22* (4.9) |
| Serum 25(OH)D concentrations (nmol/L) | 75.7 ± 29.6 | 81.9 ± 30.6 |
| Total years of smoking | 5.4 [18.6] | 2.0 [15.0] |
| Education | | |
| Year 10 or less | *63* (24.8) | *150* (33.3) |
| Year 12 and TAFE | *126* (49.6) | *188* (41.7) |
| University | *65* (25.6) | *113* (25.1) |
| Dietary misreporting | | |
| Under-reporter | *107* (42.1) | *182* (40.4) |
| Plausible/over-reporter | *147* (57.9) | *269* (59.6) |
| Total energy intake (kcal/day) | 1673 [905] | 1730 [883] |
| aMED category | | |
| Category 1 (scores 0-2) | *61* (24.0) | *90* (20.0) |
| Category 2 (scores 3-4) | *87* (34.3) | *165* (36.6) |
| Category 3 (score 5) | *52* (20.5) | *82* (18.2) |
| Category 4 (scores 6-9) | *54* (21.3) | *114* (25.3) |
| aMED-Red category | | |
| Category 1 (scores 0-2) | *75* (29.5) | *87* (19.3) |
| Category 2 (scores 3-4) | *81* (31.9) | *156* (34.6) |
| Category 3 (score 5) | *43* (16.9) | *96* (21.3) |
| Category 4 (scores 6-9) | *55* (21.7) | *112* (24.8) |

[1]Values are frequencies (percentages), means ± SDs, or medians [IQRs]
[2]Case and control participants were matched for sex, age (within 2 years) and study region
25(OH)D, 25-hydroxyvitamin D; aMED, alternate Mediterranean diet score; aMED-Red, alternative Mediterranean diet score with unprocessed red meat; FCD, first clinical

diagnosis of central nervous system demyelination; TAFE, Technical And Further Education

Table 2. aORs, 95% CIs and *P* for components of the aMED and aMED-Red (for scoring 1 *vs*. 0 on the component) and risk of FCD (254 cases, 451 controls)

| | **Unadjusted for covariates[1]** | | **Adjusted for covariates[2]** | |
|---|---|---|---|---|
| | **aOR (95% CI)** | ***P*** | **aOR (95% CI)** | ***P*** |
| aMED | | | | |
| Fruit | 1.36 (0.95, 1.95) | 0.09 | 1.41 (0.96, 2.06) | 0.08 |
| Vegetables | 0.86 (0.61, 1.19) | 0.36 | 0.88 (0.61, 1.25) | 0.47 |
| Legumes | 0.77 (0.55, 1.07) | 0.12 | 0.72 (0.50, 1.02) | 0.07 |
| Nuts | 1.13 (0.79, 1.60) | 0.51 | 1.18 (0.81, 1.70) | 0.39 |
| Wholegrains | 0.77 (0.54, 1.08) | 0.13 | 0.73 (0.50, 1.05) | 0.09 |
| Fish | 0.78 (0.56, 1.08) | 0.13 | 0.74 (0.52, 1.05) | 0.09 |
| Red and processed meat | 1.31 (0.96, 1.81) | 0.09 | 1.38 (0.93, 2.02) | 0.11 |
| MUFA:SFA | 0.91 (0.66, 1.26) | 0.58 | 0.86 (0.61, 1.23) | 0.41 |
| Alcohol | 1.03 (0.69, 1.54) | 0.89 | 1.01 (0.66, 1.55) | 0.96 |
| aMED-Red | | | | |
| Fruit | 1.35 (0.94, 1.93) | 0.10 | 1.40 (0.96, 2.06) | 0.08 |
| Vegetables | 0.81 (0.58, 1.13) | 0.21 | 0.86 (0.60, 1.24) | 0.42 |
| Legumes | 0.76 (0.54, 1.06) | 0.11 | 0.71 (0.50, 1.01) | 0.06 |
| Nuts | 1.16 (0.82, 1.66) | 0.40 | 1.23 (0.85, 1.78) | 0.28 |
| Wholegrains | 0.77 (0.55, 1.09) | 0.15 | 0.74 (0.51, 1.07) | 0.11 |
| Fish | 0.76 (0.54, 1.05) | 0.10 | 0.75 (0.53, 1.07) | 0.11 |
| Unprocessed red meat | 0.67 (0.49, 0.93) | 0.02 | 0.70 (0.50, 0.97) | 0.03 |
| MUFA:SFA | 0.92 (0.66, 1.29) | 0.63 | 0.85 (0.59, 1.21) | 0.36 |
| Alcohol | 1.07 (0.71, 1.60) | 0.76 | 1.01 (0.66, 1.55) | 0.96 |

[1]All components included in one model for aMED and one model for aMED-Red, not adjusted for covariates; [2]All components included in one model for aMED and one model for aMED-Red, and further adjusted for history of infectious mononucleosis, serum 25-hydroxyvitamin D concentrations, total years of smoking, education, total energy intake and dietary under-reporting
aMED, alternate Mediterranean diet score; aMED-Red, alternative Mediterranean diet score with unprocessed red meat; aOR, adjusted odds ratio; FCD, first clinical diagnosis of central nervous system demyelination

Figure 1. Distribution of aMED (A) and aMED-Red scores (B) in adults with FCD (*n*=254) and matched controls (*n*=451)
aMED, alternate Mediterranean diet score; aMED-Red, alternate Mediterranean diet score with unprocessed red meat; FCD, first clinical diagnosis of central nervous system demyelination

Figure 2. OR, aOR[1] and 95% CI of categories of aMED-Red and risk of FCD (254 cases, 451 controls)
[1]Adjusted for history of infectious mononucleosis, serum 25-hydroxyvitamin D concentrations, total years of smoking, education, total energy intake and dietary under-reporting
aMED-Red, alternate Mediterranean diet score with unprocessed red meat; aOR, adjusted odds ratio; FCD, first clinical diagnosis of central nervous system demyelination