A proinflammatory diet is associated with an increased likelihood of first clinical diagnosis of central nervous system demyelination in women

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Abstract

Background: While a number of studies have examined associations between dietary factors and risk of multiple sclerosis (MS), little is known about intakes of inflammation-modulating foods and nutrients and risk of MS.

Objectives: To test associations between the Dietary Inflammatory Index (DII®) and risk of a first clinical diagnosis of central nervous system (CNS) demyelination (FCD) (267 cases, 507 controls) using data from the Ausimmune Study.

Methods: The 2003-2006 Ausimmune Study was a multicentre, matched, case-control study examining environmental risk factors for an FCD, a common precursor to MS. The DII is a well-recognised tool that categorises individuals' diets on a continuum from maximally anti-inflammatory to maximally pro-inflammatory. The DII score was calculated from dietary intake data collected using a food frequency questionnaire. Conditional logistic regression models were used to estimate the association between DII and FCD separately for men and women.

Results: In women, a higher DII score was associated with increased likelihood of FCD, with a 17% increase in likelihood of FCD per one-unit increase in DII score (adjusted odds ratio 1.17, 95% confidence interval 1.04-1.33). There was no association between DII and FCD in men (adjusted odds ratio 0.88, 95% confidence interval 0.73-1.07).

Conclusions: These findings suggest that a pro-inflammatory diet is associated with an increased likelihood of FCD in women.

Key words: Ausimmune Study, multiple sclerosis, Dietary Inflammatory Index

Introduction

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system (CNS), with a complex aetiology involving environmental and genetic factors (Reich et al., 2018). It is a neurodegenerative condition, with autoimmune mechanisms (Lauer, 2010) and no known cure (Reich et al., 2018). The onset of MS is typically in early adulthood, often heralded by a first episode of neurological disability (a first demyelinating event, FDE). Onset is commonly between the ages of 20 to 40 years (Shivappa et al., 2016) and MS is more common in females than males (Reich et al., 2018; Riccio and Rossano, 2018). MS can cause a wide range of disabilities, including in balance, mobility, vision, cognition and sensation (Lauer, 2010). Environmental factors contributing to risk of MS include geographic location (higher latitude), history of infectious mononucleosis, smoking, low sun exposure and/or low vitamin D status (Lucas et al., 2007; Reich et al., 2018). A number of dietary factors also have been implicated in driving the risk of MS (Bjørnevik et al., 2017; Black, Baker, et al., 2019; Black, Bowe, et al., 2019; Black, Rowley, et al., 2019; Black, Zhao, et al., 2019; Cortese et al., 2015; Hoare et al., 2016; Jahromi et al., 2012; Sedaghat et al., 2016; Shivappa et al., 2016).

The Dietary Inflammatory Index (DII®) is a literature-derived, population-based index developed to assess the overall inflammatory effect of an individual's diet (Hébert et al., 2019). A pro-inflammatory diet (higher DII score) associates with higher risk of various chronic diseases (Hébert et al., 2019), including colorectal cancer (Shivappa, Godos, et al., 2017), cardiovascular disease (Garcia-Arellano et al., 2015; Georgousopoulou et al., 2016), dementia (Hayden et al., 2017), and with overall mortality (Shivappa, Hebert, et al., 2017). Two Iranian case-control studies associated a higher DII score with increased risk of MS (Abdollahpour et al., 2020; Shivappa et al., 2016). The first, a hospital-based case-control study (68 cases, 140 controls) found the likelihood of being a case more than doubled when

the DII score was above the median compared with DII score at or below the median (Shivappa et al., 2016). The second, a population-based study involving 547 incident MS cases and 1057 controls, found a positive dose-related association between DII score during adolescence and the likelihood of MS (Abdollahpour et al., 2020).

The 2003-2006 Ausimmune Study was a multicentre, population-based, matched, case-control study examining environmental risk factors for a first clinical diagnosis of central nervous system demyelination (FCD), a common precursor to MS. FCD includes those with an incident classic FDE, as well as those where subsequent history-taking revealed a past, undiagnosed demyelinating event. Using data from the Ausimmune Study, we have previously shown that a healthy dietary pattern, higher fish and unprocessed red meat consumption, and a Mediterranean diet including unprocessed red meat, were associated with a decreased likelihood of FCD (Black, Baker, et al., 2019; Black, Bowe, et al., 2019; Black, Rowley, et al., 2019; Black, Zhao, et al., 2019). To build on these findings, we estimated associations between the DII and likelihood of FCD using data from the Ausimmune Study.

Methods

Study design

The Australian 2003-2006 Ausimmune Study was conducted in Brisbane city (27°S), Newcastle region (33°S), Geelong and the Western District of Victoria (37°S), and Tasmania (43°S) (Lucas et al., 2007). Case participants (n = 282) were aged between 18 and 59 years and were recruited as previously detailed (Lucas et al., 2007). For case participants, the date of onset and presenting symptoms suggestive of inflammatory CNS demyelination was confirmed by a neurologist following a full history and neurological examination (Lucas et al., 2007). Case participants had an incident FCD within the study period: classic FDE (n =

216) or primary progressive MS at neurological assessment on study entry (n = 18); or, a prior event highly suggestive of CNS demyelination that was neither recognised nor ascribed to demyelination (n = 48). The Australian Electoral Roll, for which citizens ≥18 years must register, was used to recruit control participants (n = 558). One to four control participants were matched to each case participant by age (± two years), sex and study region. Only participants who completed the Cancer Council Victoria Dietary Questionnaire for Epidemiological Studies version 2 (DQESv2) food frequency questionnaire (FFQ) (Cancer Council Victoria, 2009) and who had a total energy intake of 3000-20000 kJ/day were included in the current analysis (n = 774). The Human Research Ethics Committees of the participating institutions provided ethics approval (Lucas et al., 2007). All participants gave written informed consent. All participant information was anonymised and de-identified prior to analysis.

Dietary assessment

The DQESv2, which was designed for the ethnic-diversity of Australia's population (Ireland et al., 1994), was used to collect dietary intake data for the 12 months preceding the study interview. Frequencies of consumption were recorded on a scale from "never" to "three or more times per day" for foods from the following categories: cereals, sweets and snacks; dairy, meats and fish; fruit; vegetables. Portion size diagrams were used to aid estimation of respondents' average portion size of certain foods, and to adjust standard portion sizes accordingly (Cancer Council Victoria, 2009). Alcohol type and usual frequency of consumption were recorded as glasses consumed per day, and the maximum number of glasses of alcohol drunk in any 24 hours during the past year. Food and beverage consumption was recorded as grams per day for 101 items, and nutrient intakes were computed primarily using composition data from the Australian NUTTAB 95 database (Lewis et al., 1995).

Dietary Inflammation Index

The development of the DII has been described previously (Shivappa et al., 2014). In brief, peer-reviewed primary research articles were used to develop a scoring algorithm based on whether each of 45 dietary parameters (including foods, nutrients and other bioactive compounds) increased, decreased or had no effect on six inflammatory biomarkers: IL-1ß, IL-4, IL-6, IL-10, TNF-α and C-reactive protein. The DII uses dietary intake data (in this case, data from DQESv2) to score individuals' diets on a continuum from maximally anti-inflammatory to maximally pro-inflammatory. We calculated DII scores using intake data for 26 food/nutrient parameters (alcohol; beta-carotene; carbohydrate; cholesterol; total energy intake; total fat; fibre; folic acid, garlic; iron; magnesium; monounsaturated fatty acids, niacin; omega-3 polyunsaturated fatty acids; omega-6 polyunsaturated fatty acids; onion; protein; polyunsaturated fatty acids; riboflavin; saturated fat, thiamin; vitamins A, C and E; zinc; tea) (Supplementary Table 1).

Covariates

Education was recorded as the highest level attained at the time of the study and grouped as: up to year 10; year 11 or 12; Trade, Technical and Further Education (TAFE) or apprenticeship; and university. Smoking was coded to never smoked and smoked at any time. History of infectious mononucleosis was categorised as yes, no and don't know. Height and weight were measured by a health professional, and were used to estimate body mass index (BMI). The Harris and Benedict equation was used to calculate basal metabolic rate (BMR) (Harris and Benedict, 1918). The Goldberg cut-point of BMR x1.05 (Goldberg et al., 1991) was used to classify under-reporters, with a two-category variable created (under-reporter and normal/over-reporter). Most participants (94%) provided a blood sample: serum aliquots (1 mL) were stored at -80°C and analysed at study completion for 25-hydroxyvitamin D

(25(OH)D) concentrations using liquid chromatography tandem mass spectrometry (Lucas et al., 2011). Serum 25(OH)D concentrations for case participants were de-seasonalised using control serum 25(OH)D concentrations to account for blood samples being taken at different times of the year (Lucas et al., 2011).

Statistical analysis

For participant characteristics, we described categorical variables as frequency and percentage. Continuous variables with a normal distribution were described as mean and standard deviation (SD), while those with a non-normal distribution were described as median and interquartile range (IQR).

For the univariate analyses, we tested statistical differences (by sex and between case/control) for the covariates using Pearson chi square, t-tests and Wilcoxon rank-sum as appropriate. Prior to multivariable analysis, missing values were confirmed as being missing completely at random (Little, 1988) in relation to FCD and DII. DII was established as linear in association to the outcome (Jann, 2008). We used DII with total energy intake as a covariate and compared the variance explained to that obtained when components of the DII were energy-adjusted (E-DII). Compared with the E-DII, the DII had greater explanatory power and was used for analysis (DII $r^2 = 0.0054$; E-DII $r^2 = 0.0002$). We tested multiplicative interactions between covariates and DII for case/control status. The interaction of DII and sex was statistically significant ($p = 0.039$, results not tabulated); therefore, we used conditional logistic models, stratified by sex, to test associations between DII and FCD (total n for cases and controls: men, n = 170; women, n=564). Original multivariable models included all covariates but the final models retained only covariates remaining significant at $p \leq 0.1$ (Harrell, 2001). We further tested associations in the subgroup of participants with a classic FDE presentation

(total n for cases and controls: men, n = 131; women, n = 423). Data were analysed using Stata 14 (StataCorp, 2015).

Results

Table 1 describes the characteristics of the sample. The median DII score was higher for women (n = 599) than men (n = 175) (median = 1.76 *vs*. 0.25; z = -8.07, p<0.0001). For women only, the median DII score for cases was statistically higher than for controls (women: case = 2.02 *vs*. control = 1.61, z = -2.46, p<0.01; men: case = 0.11 *vs*. control = 0.32, z = 0.904, p = 0.37). While total energy intake was significantly correlated with DII for both men and women in a simple univariate regression, when regressed against FCD, neither the main effects nor the interaction of total energy intake with DII remained statistically significantly related to FCD (DII OR = 1.17, p = 0.197; total energy intake OR = 1.00, p = 0.74; multiplicative interaction DII*total energy intake OR = 1.00, p = 0.35). In men, there was no association between DII and FCD nor between DII and FDE (Table 2). In women, a higher DII score was associated with increased likelihood of FCD and FDE, with an 17% increase in likelihood of FCD per one-unit increase in DII score.

Discussion

A more pro-inflammatory diet was associated with an increased likelihood of FCD in women. Total energy intake was not a statistically significant predictor of FCD, nor did it interact with DII and the effect of DII in association with FCD. Riccio and Rossano (Riccio and Rossano, 2015) have suggested two possible mechanisms to link dietary components and the chronic inflammatory state that is characteristic of MS. The first is a direct cellular pathway to inflammation through metabolism of pro-inflammatory foods that are typical of an energy-

dense, high-saturated fat and anabolism-promoting diet (Riccio and Rossano, 2015). The second is an indirect influence via the gut microbiome. In this scenario, a sustained energy-dense diet lacking in complex carbohydrates compromises the balance of the gut microbiota leading to a dysbiotic, inflamed gut and, in turn, systemic inflammation (Riccio and Rossano, 2015). Other studies have implicated diet in the regulation of chronic inflammation (Calder et al., 2009; Cavicchia et al., 2009; Cui et al., 2012; Rani et al., 2016; Shivappa et al., 2014), while the role of gut microbiota in neurodegeneration and neuro(auto)immunity is becoming a widely investigated topic (Mirza et al., 2020; Tremlett et al., 2017). As some dietary characteristics, such as energy density and high saturated fat intake, have the potential to influence the inflammatory state via either of these pathways, further research is needed to better understand how pro-inflammatory foods may increase the risk of FCD.

Our findings, in part, support two previous studies where a pro-inflammatory diet was associated with higher risk of MS (Abdollahpour et al., 2020; Shivappa et al., 2016). However, sex differences were not explored in those studies. It is not clear why we found an association between a more pro-inflammatory diet and higher likelihood of FCD in women only. Sex differences in diet are well documented (Ahmed et al., 2021; Australian Bureau of Statistics, 2015; Bennett et al.; Cowan et al., 2020; McKenzie et al., 2020) and associations between DII score and health outcomes have been shown to differ between men and women (Phillips et al., 2019). Similar to other studies (Gojanovic et al., 2021; Kim et al., 2019; Morimoto et al., 2019) we found that women had a more pro-inflammatory diet than men, according to the DII score. It is not clear which components specifically contributed to the higher DII score in women compared with men, although men had higher intakes of many anti-inflammatory DII parameters, including beta-carotene, magnesium, omega-3 fatty acids and vitamins A, C and E (Supplementary Table 1). Studies investigating other dietary

components and risk of MS have also noted sex differences. These include our previous analysis of the Ausimmune Study showing that higher consumption of unprocessed red meat was associated with lower risk of MS in women only (Black, Bowe, et al., 2019), and a Canadian case-control study showing that higher fish consumption was protective in women only (Ghadirian et al., 1998). Although we cannot explain why an association was not observed for men, it is plausible that an underlying effect exists but was not detectable due to the lower prevalence of FCD in men and the relatively small sample size in this study.

A major strength of our study is the use of one of the largest, most well-characterised samples of people with early MS worldwide, with an incident case-control design. The DII assesses an individual's diet as a whole, and is not limited to a specific population group, making it applicable across populations (Shivappa et al., 2014). We cannot rule out potential residual confounding by lifestyle characteristics that may be associated with a pro-inflammatory diet, but were not measured in our study. However, various lifestyle characteristics (e.g. BMI, physical activity and education) were not associated with risk of FCD in previous analysis of the Ausimmune Study (Ponsonby et al., 2013).

Although we used an established FFQ to collect habitual dietary intake data relating to the year prior to study interview, we cannot rule out the possibility that eating habits changed in case participants after diagnosis, because dietary modification is common post-diagnosis (Lucas et al., 2007; Russell et al., 2019). Our previous research shows that, after FCD, some of the participants made dietary changes that were more in line with an anti-inflammatory diet, such as increasing consumption of fish, fruit and vegetables (Russell et al., 2018). This suggests that any dietary changes made after FCD would likely lead to a decrease in DII score and the association between FCD and DII would attenuate.

The foods and nutrients used to calculate DII are those that have been shown to influence various inflammatory biomarkers. However, in studies using the DII, the score is calculated from FFQs that were not specifically designed to capture consumption of pro- or anti-inflammatory foods. Because the FFQ used in the Ausimmune Study was not designed for the calculation of the DII, intake data for some foods and nutrients which would otherwise have contributed to the DII score were not measured (e.g. green tea, ginger, rosemary, thyme, turmeric, saffron, pepper, polyphenols, caffeine, vitamin B12, vitamin B6 and selenium). Hence, it is difficult to compare our results with other studies that have used DII as a predictor variable, since the set of food and nutrient components used to calculate the DII depends on the specific food and beverage items included in the dietary assessment.

In conclusion, our results suggest that an anti-inflammatory diet may offer a protective effect against the likelihood of FCD in women. Longitudinal research is needed to explore whether an anti-inflammatory diet might also influence the disease progression of MS.

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Conflict of interest: Dr. James R. Hébert owns controlling interest in Connecting Health Innovations LLC (CHI), a company that has licensed the right to his invention of the Dietary Inflammatory Index (DII®) from the University of South Carolina in order to develop computer and smart phone applications for patient counselling and dietary intervention in clinical settings. Dr. Nitin Shivappa is an employee of CHI. The subject matter of this paper will not have any direct bearing on that work, nor has that activity exerted any influence on this project.

Authorship

Conceptualization: LJB; Writing - original draft: AM; Formal analysis: AD and GP; Writing - review and editing: FEL, ED, SH, NS, JS, RML, ALP, JRH, IvdM, LJB and the Ausimmune Investigator Group. All the authors read and approved the final version of the manuscript.

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Table 1. Characteristics of case and control participants from the Ausimmune Study with dietary intake data (n = 774), stratified by sex

	Men		Women	
	Case (n = 62)	**Control (n = 113)**	**Case (n = 205)**	**Control (n = 394)**
Age, year, mean [SD]	38.7 [9.4]	40.0 [9.6]	38.3 [9.9]	39.9 [9.7]
Study region, % (n)				
Brisbane (latitude 27°S)	21.5 (14)	23.5 (27)	37.2 (77)	37.9 (153)
Newcastle (latitude 33°S)	12.3 (8)	15.7 (18)	14.0 (29)	17.6 (71)
Geelong (latitude 37°S)	32.3 (21)	33.9 (39)	21.3 (44)	24.0 (97)
Tasmania (latitude 43°S)	33.9 (22)	27.0 (31)	27.5 (57)	20.5 (83)
Education, % (n)				
Year 10 or less	27.7 (18)	32.2 (37)	25.2 (52)	32.9 (133)
Year 11/12[1]	21.5 (14)	13.9 (16)	18.9 (39)	14.1 (57)
Trade/TAFE[2]/Apprenticeship	32.3 (21)	30.4 (35)	29.1 (60)	26.7 (108)
University	18.5 (12)	23.5 (27)	26.7 (55)	26.2 (106)
Smoking history, % (n)				
Never smoked	35.4 (23)	40.9 (47)	49.3 (199)	45.8 (280)
Smoked at any time	64.6 (42)	59.1 (68)	50.3 (203)	53.7 (328)
Body mass index, median [IQR]	27.0 [5.8]	26.4 [5.8]	24.7 [7.4]	25.6 [8.0]
History of infectious mononucleosis, % (n)				
No	66.2 (43)	80.9 (93)	79.2 (320)	74.8 (457)
Yes	24.6 (16)	16.3 (66)	16.3 (66)	20.1 (123)
Don't know	9.2 (6)	4.35 (5)	4.5 (18)	4.9 (30)
Serum 25(OH)D concentrations, nmol/L, mean [SD]	77.1 [28.0]	80.1 [27.8]	76.0 [30.4]	82.9 [31.1]
Total energy intake (kJ/day), median [IQR]	9623 [4412]	9900 [4351]	6450 [2907]	6731 [2929]
Dietary Inflammation Index, median [IQR]	0.11 [3.42]	0.32 (2.30)	2.02 [2.06]	1.61 [2.04]

Table based on data from participants whose total energy intake was between 3000 and 20000 kJ/day. The following variables had missing data: education (1 case); smoking (1 case, 2 controls); serum 25(OH)D concentrations (7 cases, 28 controls); body mass index (1 case, 3 controls); history of infectious mononucleosis (1 case).

SD, standard deviation; TAFE, Technical and Further Education; IQR, interquartile range; 25(OH)D; 25-hydroxyvitamin D

Table 2. Adjusted odds ratios associated with Dietary Inflammation Index, stratified by sex, for participants with an FCD and the subgroup of those with a classic FDE at presentation

	Men		Women	
	aOR (95% CI)	*p*	aOR (95% CI)	*p*
	FCD			
Dietary Inflammation Index	0.88 (0.73, 1.07)	0.210	1.17 (1.04, 1.33)	0.012
History of infectious mononucleosis				
No	Reference			
Yes	3.19 (1.27, 8.01)	0.014	2.09 (1.34, 3.25)	0.001
Don't know	4.73 (0.95, 23.53)	0.057	2.19 (1.00, 4.79)	0.049
Smoking history				
Never smoked	Reference			
Smoked at any time	0.99 (0.53, 1.86)	0.972	1.51 (1.06, 2.15)	0.022
	FDE			
Dietary Inflammation Index	0.83 (0.67, 1.03)	0.083	1.18 (1.02, 1.37)	0.026
History of infectious mononucleosis				
No	Reference			
Yes	2.73 (0.98, 7.61)	0.055	1.92 (1.17, 3.15)	0.010
Don't know	1.69 (0.31, 9.05)	0.541	2.09 (0.84, 5.21)	0.114
Smoking history				
Never smoked	Reference			
Smoked at any time	1.32 (0.62, 2.80)	0.469	1.46 (0.97, 2.21)	0.068

Table based on data from participants whose total energy intake was between 3000 and 20000 kJ/day. Initial models for men and women adjusted for education, total energy intake, body mass index, dietary misreporting, smoking history, serum 25-hydroxyvitamin D concentrations, history of infectious mononucleosis. The final models retained only covariates remaining statistically significant at $p \leq 0.1$ for either men or women (history of infectious mononucleosis and smoking history).

FCD, first clinical diagnosis of central nervous system demyelination; aOR, adjusted odds ratio; CI, confidence interval; FDE, first demyelinating event

Supplementary Table 1. Overall inflammatory effect scores of parameters used to calculate the Dietary Inflammatory Index®, including mean (standard deviation) daily intakes for the study population, stratified by sex

		Men (n = 175)		Women (n = 599)	
Food parameter	Overall inflammatory effect score[1]	Mean daily intake	Standard deviation	Mean daily intake	Standard deviation
Alcohol (g)	–0.278	18.4	21.5	9.4	15.0
Beta-carotene (µg)	–0.584	3008.3	1501.1	2702.2	1482.3
Carbohydrate (g)	0.097	246.1	85.7	176.0	61.6
Cholesterol (mg)	0.110	353.2	156.9	251.8	110.2
Total energy (kcal)	0.180	2425.2	822.5	1694.0	564.0
Total fat (g)	0.298	98.3	39.5	67.5	27.9
Fibre (g)	–0.663	23.8	9.4	19.0	7.4
Folic acid (µg)	–0.190	322.3	121.6	248.3	88.9
Garlic (g)	–0.412	0.5	0.5	0.5	0.4
Iron (mg)	0.032	15.1	5.9	11.4	4.6
Magnesium (mg)	–0.484	338.2	110.2	263.4	86.5
MUFA (g)	–0.009	34.7	14.2	23.8	10.1
Niacin (mg)	–0.246	26.8	10.4	19.2	7.8
n-3 PUFA (g)	–0.436	1.8	0.8	1.3	0.6
n-6 PUFA (g)	–0.159	11.4	5.3	8.1	3.9
Onion (g)	–0.301	7.9	7.7	6.2	5.6
Protein (g)	0.021	109.8	39.1	80.8	29.7
PUFA (g)	–0.337	13.9	3.8	13.6	6.2
Riboflavin (mg)	–0.068	2.7	1.1	2.2	0.8
Saturated fat (g)	0.373	41.6	18.4	28.2	16.1
Thiamin (mg)	–0.098	1.8	0.8	1.4	0.6
Vitamin A (RE)	–0.401	971.8	382.4	770.3	314.6
Vitamin C (mg)	–0.424	147.7	97.0	116.9	64.7
Vitamin E (mg)	–0.419	7.4	2.8	5.6	2.2
Zinc (mg)	–0.313	14.2	5.5	10.5	4.1
Tea (g)	–0.536	261.1	365.3	384.1	464.7

[1] Shivappa, N., Steck, S.E., Hurley, T.G., Hussey, J.R., Hebert, J.R., 2014. Designing and developing a literature-derived, population-based dietary inflammatory index. Public Health Nutr 17(8), 1689-1696.
MUFA, monounsaturated fatty acid; n-3, omega-3; n-6; omega-6; PUFA, polyunsaturated fatty acid; RE, retinol equivalents