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Ultra-processed food consumption and multiple sclerosis incidence: A prospective cohort study

Pavlina Vagner [a], Barbara Brayner [a,b], Fernanda Rauber [c,d], Renata B. Levy [c,d,e], Eszter P. Vamos [f], Kiara Chang [f], Gavin Abbott [b], Bruce Taylor [g], Lucinda J. Black [a,b,1], Priscila Machado [a,b,**,1]

[a] Deakin University, School of Exercise and Nutrition Sciences, Geelong, Australia
[b] Deakin University, Institute for Physical Activity and Nutrition, School of Exercise and Nutrition Sciences, Geelong, Australia
[c] Center for Epidemiological Research in Nutrition and Health, University of Sao Paulo, Sao Paulo, Brazil
[d] Department of Preventive Medicine, School of Medicine, University of Sao Paulo, Sao Paulo, Brazil
[e] University of Salamanca, Institute of Biomedical Research of Salamanca (IBSAL), Salamanca, Spain
[f] Public Health Policy Evaluation Unit, School of Public Health, Imperial College London, London, United Kingdom
[g] Menzies Institute for Medical Research, University of Tasmania, Hobart, Australia

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SUMMARY

Background & aims: Emerging evidence suggests an association between ultra-processed food (UPF) consumption and neurodegenerative diseases, but there is limited evidence for multiple sclerosis (MS). Diets rich in UPFs promote inflammation and oxidative stress that both play an important role in modulating the immune system, and thereby, potentially the pathogenesis of MS. This study aimed to investigate the longitudinal association between UPF consumption and MS onset in middle-aged and older adults.

Methods: The study included 185,788 adults who completed at least one valid dietary assessment and did not have MS at baseline (2009–2012). Dietary data was collected at 5 time points using a web-based 24-h dietary recall, and UPFs were categorised using the Nova food classification system. MS cases were identified based on medical history and linkage to data on hospital admissions (using ICD-coded diagnoses ICD10-g35; ICD9-3409), and self-reported MS diagnosis. Prospective associations between UPF consumption (as a percentage of total food intake in grams per day) and risk of MS onset were assessed using multivariable Cox proportional hazards models were adjusted for age, sex, ethnicity, education, Townsend deprivation index, smoking status, total energy intake and serum 25-hydroxyvitamin D.

Results: Participants had a mean age of 56.0 years (SD 8.0) and 54% were female. UPFs comprised 19.1% of total dietary grams intake, with carbonated drinks, ready-to- eat/heat meals and industrial-processed breads being the most consumed UPF subgroups. Over a mean follow-up of 8.9 years (SD: 2.7), 384 incident MS cases occurred. Each 10% increase in UPF consumption was associated with an estimated 9% increase in risk of MS (HR 1.09; 95% CI: 1.003 to 1.19; p-value = 0.04).

Conclusion: This study found a weak yet significant association between higher UPF consumption and increased risk of MS in middle-aged and older adults. Given the modest effect size and inconsistency of statistical significance across sensitivity analyses, these findings should be interpreted with caution. Research to confirm these findings in other population groups and contexts is needed.

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; CI, Confidence interval; CSEs, Certificate of Secondary Education; FCD, first clinical diagnosis of central nervous system demyelination; GCSEs, General Certificate of Secondary Education; HR, Hazard Ratio; NHS, National Health Service; kJ, kilojoules; MS, multiple sclerosis; SD, Standard deviation; STROBE-nut, Strengthening the Reporting of Observational Studies in Epidemiology—Nutritional Epidemiology; ICD, International Classification of Diseases; UK, United Kingdom; UPF, ultra-processed food.

** Corresponding author. Deakin University Melbourne Burwood Campus, Institute for Physical Activity and Nutrition, School of Exercise and Nutrition Sciences, 221 Burwood Highway, Melbourne, Victoria, 3125, Australia.
E-mail address: p.machado@deakin.edu.au (P. Machado).
[1] Joint senior authorship.

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1. Introduction

In the modern, industrialised food system, extensive food processing to create convenient, hyper-palatable and low-cost products has resulted in a dramatic increase in the availability and consumption of ultra-processed foods (UPFs) [1,2]. UPFs are formulations of ingredients, mostly of exclusive industrial use, that result from a series of industrial processes [2]. Examples include fast food dishes, carbonated drinks, salty snacks, biscuits, ready-to-heat meals, and flavoured milk drinks [2]. Globally, UPFs are ubiquitous and highly consumed [3]. In the UK, UPFs comprise 57% of total energy intake in adults [4], and are directly associated with poor diet quality, including inadequate intake of nutrients linked to chronic diseases [5].

Meta-analyses of large-scale population and experimental studies indicate a direct, dose–response association between UPF consumption and more than 30 health-related outcomes, including type-2 diabetes, cardiovascular diseases, and increased mortality [6]. There is emerging evidence that UPFs can impact neurological health and potentially play a role in the onset of neurodegenerative diseases. UPFs have been associated with increased risk of dementia, Alzheimer's Disease and cognitive decline [7–10], including in studies using the UK Biobank [7], but there is limited evidence for multiple sclerosis (MS) [11–13].

MS is a chronic inflammatory neurodegenerative disease of the central nervous system [14]. The incidence of MS is increasing globally, especially among females, with environmental risk factors being suggested [15], including diet [16]. Diets rich in UPFs promote inflammation and oxidative stress [17]: both play an important role in modulating the immune system [17], which is involved in the pathogenesis of MS.

Using data from a case–control study in Australia, we previously showed that higher consumption of UPFs was associated with a higher likelihood of a first clinical diagnosis of central nervous system demyelination (FCD), a common precursor to the diagnosis of MS [12]. To build on this evidence, we aimed to test the longitudinal association between UPF consumption and MS onset using data from the UK Biobank.

2. Methods

The UK Biobank is a large, population-based prospective cohort study, which included 502,536 individuals aged between 40 and 69 years in 2006–2010 living in the UK. Participants underwent baseline assessments at 22 assessment centres across England, Scotland and Wales. During the baseline assessment, participants signed a consent form and completed self-administered touch-screen questionnaire covering socio-demographic (e.g., age, sex), behavioural (e.g. smoking, physical activity), and health-related data. Physical measurements (e.g., blood samples) were collected by trained staff following standardised procedures. Participants were followed up via linkage to health records (e.g., hospital and primary care data) and national death registries (NHS England and NHS Central Register) [18].

This study was reported according to the Strengthening the Reporting of Observational Studies in Epidemiology—Nutritional Epidemiology (STROBE-nut) reporting guidelines [19] (Supplementary Table 1).

2.1. Dietary assessment

Dietary data were collected at baseline using the Oxford WebQ [20], a web-based, self-administered dietary assessment tool that records the consumption of over 200 common food and beverage items in the previous 24-h. The Oxford WebQ has been shown to capture similar food and drink items as well as estimate energy and nutrient intakes compared with an interviewer-administered 24-h recall [20]. The Oxford WebQ collects detailed information about dietary intake, including drinking water, tea and coffee and alcoholic beverages, and whether milk, sugar and other items were added. The Oxford WebQ questionnaire can be found elsewhere [21]. Dietary data were collected at 5 time points between April 2009 and June 2012. To estimate dietary intake, only participants with at least one valid 24-h recall (deemed valid if total energy intake was 500–3500 kcal/day for women and 800–4000 kcal/day for men) [22] were included. Dietary intake was averaged across these time points (2009–2012) and considered as baseline dietary data.

The UK Biobank provides the number of portions for each item consumed per day but does not provide the nutritional information (grams and energy) assigned to each food and beverage item. We derived our own estimates of grams consumed by assigning food and beverage item a typical portion size according to the Food Standards Agency [23] and then multiplying this by the number of serves consumed. For example, if a participant reported consuming 2 serves of broccoli, we multiplied 2 serves by 85 g, the medium portion size of broccoli according to the UK Food Standards Agency. We have also derived our own estimates for appropriate energy profile based on published data for the UK [24].

2.1.1. Ultra-processed food consumption

All food and beverage items were classified into four groups according to the Nova system, which considers the extent and purpose of industrial food processing [2]: Group 1 – unprocessed and minimally processed foods (e.g., fruits, vegetables, rice, lentils, milk, fish, nuts and seeds); Group 2 – processed culinary ingredients (e.g., table sugar, olive oil, butter); Group 3 – processed foods (e.g., cheese, canned fruits and legumes); and Group 4 – UPFs (e.g., carbonated drinks, flavoured milk drinks, mass-produced packaged breads, reconstituted meat, shelf-stable dishes). Details of the identification of UPFs in the UK Biobank have been described elsewhere [25]. In summary, investigators with expertise in the Nova system and UK food supply applied the classification to the items, following Nova definitions and examples [2,26]. Data from the UK National Diet and Nutrition Survey (2008–2014) was used to identify the most frequently consumed alternative when it was not possible to discriminate processing level of some food items (e.g., 'sliced bread') [5]. When both options were common, a lower level of processing (non-UPF) was assigned to the item. This approach is consistent with best practice recommendations for identifying UPFs in dietary surveys [27]. The main exposure variable was individuals' UPF consumption expressed as a percentage of total grams intake. This weight ratio was preferred over an energy ratio as it better captures UPFs with zero or low-calorie (e.g., artificially sweetened beverages). Nevertheless, as beverages generally account for a greater proportion when intake is measured in grams per day, the contribution of UPFs to total energy intake was also estimated.

2.2. Multiple sclerosis identification

MS cases were identified based on: i) medical history and linkage to data on hospital admissions, using ICD-coded diagnoses [ICD10-g35; ICD9-3409]; ii) self-reported MS diagnosis (including age); iii) or data recorded in primary care. Less than 10% of the diagnosis of MS was based on self-report data only. In those instances, participants were asked to report all health conditions diagnosed by a doctor and their answers were verified with a nurse during the verbal interview. Details of the method used to

combine the data from different sources to identify MS have been previously described and are available in the UK Biobank website (https://biobank.ndph.ox.ac.uk/ukb/field.cgi?id=131043).

2.3. Covariates

Covariates were identified using a directed acyclic graph (Supplementary Fig. 1). Baseline study covariates included: age, sex, Townsend deprivation index, education, ethnicity, smoking status, total energy intake (kJ/day), and deseasonalised serum 25-hydroxyvitamin D (25(OH)D) concentration.

Covariates were treated as follows: age as a continuous variable, sex as binary (male/female), and Townsend deprivation index as a continuous variable based on national census output area of their post code (higher values represent higher deprivation). Ethnicity was categorised into 1) White or 2) other; and education into: 1) college or university degree; 2) A levels or equivalent; 3) O levels, General Certificate of Secondary Education (GCSEs) or equivalent or Certificate of Secondary Education (CSEs); 4) professional qualification; and 5) none of the above/prefer not to say.

Serum 25(OH)D concentration (also generically called 'vitamin D') is the sum of metabolites produced from exposure to sunlight (approximately 80–90%) and food and supplements intake [28], and low concentration is known to be a risk factor for MS [29]. Serum 25(OH)D concentration was measured in non–fasted serum blood samples collected during baseline visits [30]. Non-fasted blood samples (mean 3.5 h after eating) were collected to optimise participant comfort [31]. Serum 25(OH)D was analysed using Chemiluminescent Immunoassay-direct competitive, using the DiaSorin Liaison XL(30). Serum 25(OH)D has a seasonal pattern; therefore deseasonalised (season-adjusted) 25(OH)D concentration was estimated fitting the data to a sine function with a period of 12 months in a nonlinear regression cosinor model. Although deseasonalised 25(OH)D concentration is not associated with the exposure, we included in the model as a covariate to account for potential residual confounding. Deseasonalised 25(OH)D concentration and total energy intake were treated as continuous variables.

2.4. Statistical analysis

This study included 185,788 UK Biobank participants with Oxford WebQ 24-h recall data (40.1%, 23.3%, 20.2%, 13.8% and 2.6% with one to five recalls, respectively) after excluding 291,592 participants without dietary assessment, 399 individuals with MS at baseline, 77 individuals who were pregnant/unsure, 3625 individuals with implausible energy intake (i.e., total energy intake was <500 kcal or >3500 kcal/day for women, and <800 or >4000 kcal/day for men), and 21,058 individuals (<10% of the sample) with missing data for covariates (Fig. 1). Complete case analysis was used, and characteristics of participants included in the analytic sample and those excluded were compared.

Characteristics of the study population at baseline were described according to whether participants developed MS during follow-up. Differences were examined using analysis of variance for continuous and $\chi 2$ test for categorical variables. The dietary contribution of UPF subgroups (% of total grams/day) was estimated and graphically presented.

Multivariable Cox proportional hazards regression models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) of MS incidence per 10% increment in UPF consumption (used instead of 1% increase to provide a more meaningful estimate). MS incidence was treated as a time-to-event outcome, with duration of follow-up for all participants estimated as the time between the last day of dietary data submission and the first event of MS, death (identified through linkages with death registry data), loss to follow up, or end of study period, whichever occurred first. A censoring date of 11 November 2023 was used. Models were fitted in a stepwise manner: Model 1 was adjusted for age, sex, ethnicity, education, Townsend deprivation index and smoking status; Model 2 was adjusted for Model 1 covariates along with total energy intake; and Model 3 further adjusted for deseasonalised serum 25(OH)D concentration.

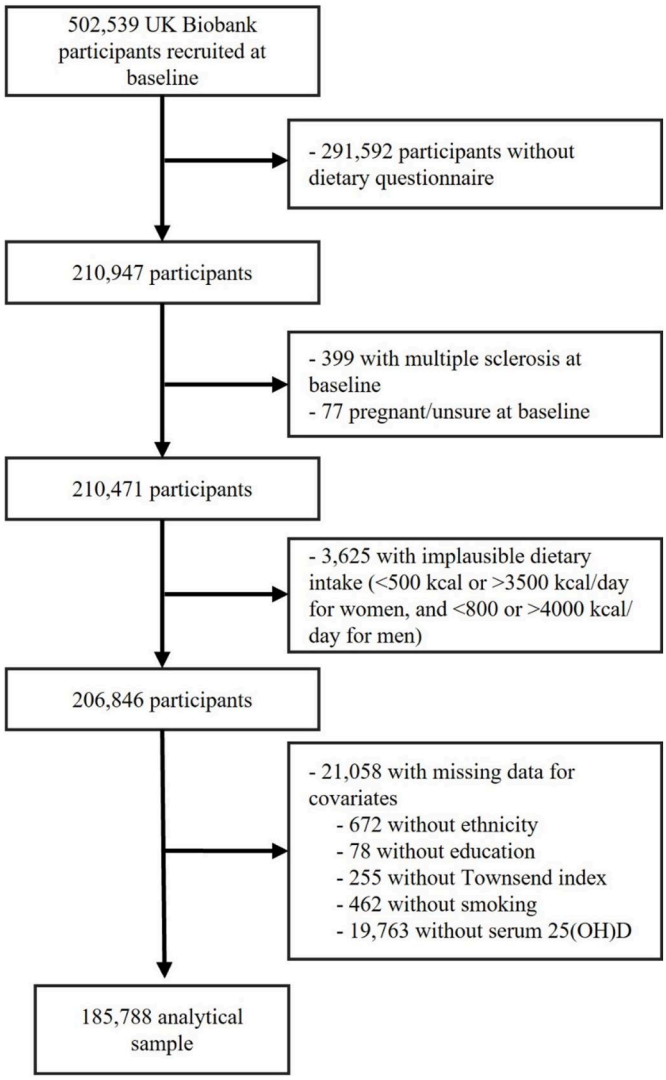

Fig. 1. Flow diagram of participants included in the analysis.

The proportionality assumption of the Cox regression model was verified by testing the Schoenfeld residuals against survival time and assessed graphically using plots of − log(−log(survival time)) against log of survival time for each covariate. We verified the assumption of linearity between UPF consumption and risk of MS using restricted cubic spline functions (5 knots at the 5th, 25th, 50th, 75th, and 95th percentiles of UPF consumption levels) and conducting a likelihood ratio test comparing the more complex restricted cubic spline model to the primary linear association model. Interactions with sex and age were tested by adding a multiplicative term in the Cox regression models.

Sensitivity analyses were conducted to test associations i) with the exposure as percentage of total energy intake (kJ/day), ii) using a 'missing' category for covariates to test any common effects among those with missing data; iii) using data from those who had

at least two 24-h dietary recalls); iv) excluding participants who developed MS within two years of follow-up; v) removing all bread types from the UPF category; vi) including adjustment for physical activity level; and vii) adjusting for baseline body-mass index (BMI) to account for residual confounding (not to test mediation). Physical activity level was measured using the validated and self-administered International Physical Activity Questionnaire (IPAQ), and categorised as low, moderate and high [32]. A separate category was introduced for those who had no available data on physical activity (15.1% missing). Although there is no evidence that physical activity level is associated with MS risk [33], this variable was included in additional analysis to account for potential residual health behaviour confounding. Height and weight were collected by trained fieldworkers and used to calculate BMI (kg/m^2) [32]. BMI was used as continuous variable, and no 'missing' category was created due to the low proportion of missing data (0.2%).

All statistical analyses were conducted using Stata v17. *P*-values <0.05 were considered statistically significant.

3. Results

Characteristics of participants (n= 185,788) are presented in Table 1. Participants had a mean age of 56.0 y (SD 8.0), 54.4% were female, most were white (96.0%), 42.8% had a college or university degree, and 56.6% had never smoked. The mean deseasonalised serum 25(OH)D concentration was 49.9 nmol/L (SD 20.9), total energy intake was 8725.8 kJ/day (SD 2359.1), and UPFs contributed to 19.1% (SD 11.1) of total dietary grams intake and 47.5% (SD 16.3) of total energy intake. Comparison of included and excluded participants can be found in Supplementary Table 2, with characteristics of the analytical sample with a slightly higher percentage of white, higher educated and non-smoker participants in comparison to the excluded sample.

After a mean follow-up time of 8.9 years (SD 2.7), a total of 384 incident MS cases occurred. Among the individuals who developed MS at follow-up, the majority were female (72.1%) and had a history of smoking, either currently or previously (53.4%). MS participants were also younger and had a lower total energy intake. Differences in education, Townsend deprivation index, deseasonalised serum 25(OH)D concentration, and proportion of UPFs to both total grams and energy intake were not statistically significant between participants with and without MS (Table 1).

Across the study population, the most consumed UPFs were carbonated drinks (3.7% of total grams), ready-to-eat/heat foods (3.5%), industrial-processed breads (2.7%), dairy-based drinks (2.4%) and pastries, buns and cakes (2.2%) (Fig. 2).

Table 2 presents the associations between UPF consumption and risk of MS onset. A direct association between UPF consumption and MS onset was observed (fully adjusted model 3). Every 10% increment in UPF consumption was associated with an estimated 9% increase in risk of MS onset (HR 1.09; 95% CI: 1.003 to 1.19; p-value = 0.04). There was no evidence of a nonlinear relationship (p= 0.286) (cubic spline graphs presented in Supplementary Fig. 2). Findings were similar when using the exposure as percentage of total energy intake (fully adjusted linear model: HR 1.09; 95% CI: 1.02 to 1.16; p-value = 0.007).

Both the direction and magnitude of the associations remained similar when including participants with missing data for covariates (Supplementary Table 3), when using data from those who had at least two 24-h dietary recalls (Supplementary Table 4), when excluding participants who developed MS within two years of follow-up (Supplementary Table 5), when removing bread from the UPF category (Supplementary Table 6), adjusting for physical activity (Supplementary Table 7), and for baseline BMI (Supplementary Table 8). However, when using data from those who had at least two 24-h dietary recalls, when excluding participants who developed MS within two years of follow-up, and when adjusting for physical activity level, both the direction and magnitude of the associations remained similar to that observed in the main analysis, but the association was no longer statistically significant. No interactions with age and sex were found (p> 0.05).

Table 1
Baseline characteristics of participants according to whether participants developed multiple sclerosis at follow-up in the UK Biobank (n= 185,788).

Baseline Characteristics	Total (n= 185,788)	MS at follow-up		*P*-value[a]
		Yes (n= 384)	No (n= 185,404)	
Age, mean ± SD	56.0 ± 8.0	54.7 ± 7.9	56.0 ± 8.0	**0.0011**
Sex, n (%)				**<0.001**
Male	84,812 (45.6)	107 (27.9)	84,705 (45.7)	
Female	100,976 (54.4)	277 (72.1)	100,699 (54.3)	
Ethnicity, n (%)				
White	178,366 (96.0)	380 (99.0)	177,986 (96.0)	**0.003**
Other	7422 (4.0)	4 (1.0)	7418 (4.0)	
Education, n (%)				0.749
College or university degree	79,457 (42.8)	162 (42.2)	79,295 (42.8)	
A level or equivalent	24,309 (13.1)	589 (15.4)	24,250 (13.0)	
O level, GCSE, CSE or equivalent	46,296 (24.9)	94 (24.5)	46,202 (25.0)	
Professional qualification	19,357 (10.4)	38 (9.9)	19,319 (10.4)	
None of the above/prefer not to say	16,369 (8.8)	31 (8.1)	16,338 (8.8)	
Townsend deprivation index, n (%)				0.750
Low	61,942 (33.4)	135 (35.1)	61,801 (33.3)	
Medium	61,942 (33.3)	125 (32.6)	61,802 (33.3)	
High	61,942 (33.3)	124 (32.3)	61,801 (33.3)	
Smoking status, n (%)				**<0.001**
Never	105,156 (56.6)	179 (46.6)	104,977 (56.6)	
Previous	66,210 (35.6)	156 (40.6)	66,054 (35.6)	
Current	14,422 (7.8)	49 (12.8)	14,373 (7.8)	
Serum 25(OH)D (nmol/L), mean±SD	49.9 ± 20.9	48.9 ± 27.1	49.9 ± 20.9	0.345
Total dietary intake (g/d) mean±SD	4841.9 ± 1611.0	4819.1 ± 1628.1	4842.0 ± 1611.0	0.781
Total energy intake (kJ/d), mean±SD	8725.8 ± 2359.1	8180.0 ± 2191.7	8726.9 ± 2359.3	**<0.001**
% UPF (g/d), mean±SD	19.1 ± 11.1	19.6 ± 11.1	19.1 ± 11.1	0.427
% UPF (kJ/d), mean±SD	47.5 ± 16.3	48.7 ± 16.1	47.5 ± 16.3	0.163

CSE; Certificate of secondary education, GCSE; General certificate of secondary education, kJ, kilojoule; MS, Multiple Sclerosis; SD, Standard Deviation; UPF, Ultra-processed food; 25(OH)D, deseasonalised 25-hydroxyvitamin D concentration.
[a] $\chi 2$ tests (for categorical variables) and t-test (for continuous variables) were used to compare characteristics of cases and non-cases of MS at follow-up; *P*-value <0.05 indicates statistical significance (highlighted in bold).

4. Discussion

This study found a weak yet significant association between higher UPF consumption and a higher risk of MS in UK adults. Each 10% increase in UPF consumption was significantly associated with an estimated 9% increase in risk of MS. No evidence of interactions

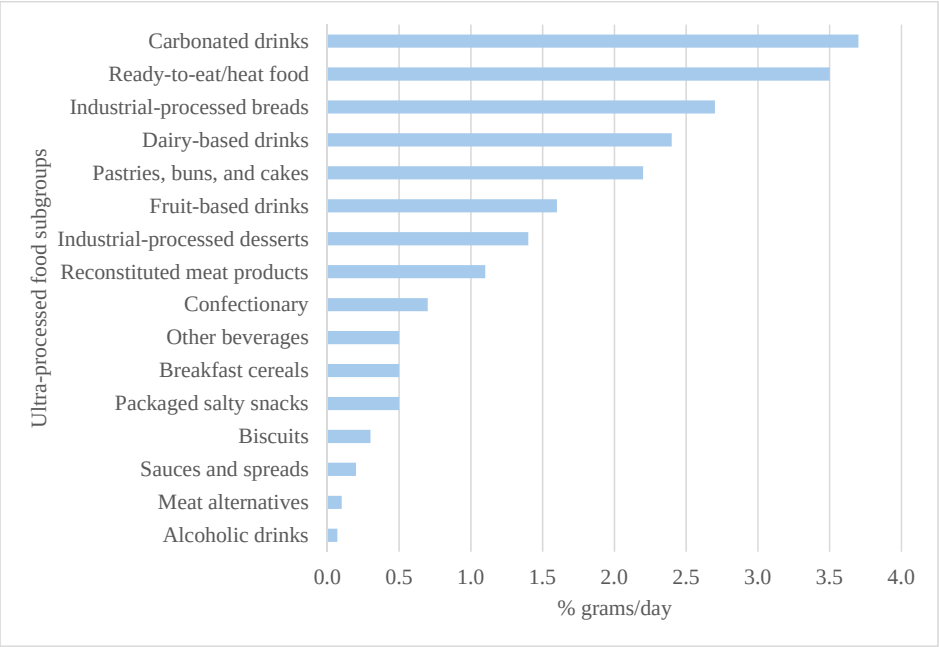

Fig. 2. Contribution (%) of ultra-processed food subgroups to total daily grams intake.

Table 2
Associations between ultra-processed food consumption and risk of multiple sclerosis onset in the UK Biobank (n= 185,788).

	Per 10% increase in UPF consumption			
	% total grams/day HR (95% CI)	*P*-value	% total energy/day HR (95% CI)	*P*-value
Model 1[a]	1.06 (0.98, 1.16)	0.15	1.07 (1.003, 1.14)	0.040
Model 2[b]	1.09 (1.005, 1.20)	0.04	1.09 (1.02, 1.16)	0.007
Model 3[c]	1.09 (1.003, 1.19)	0.04	1.09 (1.02, 1.16)	0.007

HR: Hazard Ratio, CI: Confidence Interval, UPF: ultra-processed food.
[a] Model 1 was adjusted for age, sex, ethnicity, education, Townsend deprivation index and smoking.
[b] Model 2 was additionally adjusted for total energy intake.
[c] Model 3 was additionally adjusted for deseasonalised serum 25(OH)D concentration.

with sex and age were observed. The association was not robust to sensitivity analyses excluding participants with at least two 24-h dietary recalls (n= 74,553 excluded; lost 138 people with MS) or those who developed MS within the first two years of follow-up (n= 53 people with MS excluded), and when adjusting for physical activity level. The direction and effect size remained similar, though was no longer statistically significant. However, given the lower sample size and reduced power for the sensitivity analyses, and considerable number of missing data for physical activity, these findings should be interpreted cautiously. The adjustment for BMI slightly increased the magnitude of the associations and did not affect the statistical significance. These findings suggest that baseline BMI may be acting as a confounder rather than a mediator, potentially influencing baseline dietary behaviours and thereby affecting the observed associations. Our findings contribute to the limited, but growing, literature on UPF consumption and risk of neurodegenerative diseases, including MS.

These findings support our previous investigations of diet and risk of FCD, a common precursor to the diagnosis of MS, in Australia. Using data from an Australian case–control study (Ausimmune Study), we previously showed that higher consumption of UPFs [34] and a more proinflammatory diet [35] were associated with higher risk of FCD [36], while a healthy dietary pattern, and a Mediterranean diet were associated with lower risk of FCD [37,38]. Our findings complement recent analyses from the UK Biobank investigating ultra-processed food intake and neurodegenerative diseases. [13]. While that study reported higher risk of MS among participants in the highest tertile of UPF consumption, the association was not statistically significant when UPF intake was modelled continuously. In contrast, our analysis observed a positive linear association between UPF intake and MS risk. Our study included a larger analytical sample and accounted for deseasonalised serum 25(OH)D concentration, an established environmental risk factor for MS. These new findings using data from UK adults suggest that reducing UPF consumption may be important to reduce MS risk in the general population. Nevertheless, given the mean baseline age of 56 years, the UK Biobank cohort primarily reflects late-onset or delayed-diagnosis MS, and caution is needed when generalising to younger adults, who represent the typical age of MS onset. Reverse causality also remains a potential concern in our study given the long prodromal phase of MS, and the association was no longer statistically significant after excluding cases occurring within the first two years of follow-up. Although it is unclear whether this reflects reduced statistical power, future research on diet and MS would benefit from: i) larger sample sizes and longer follow-up; ii) including more diverse populations, as UK Biobank and Ausimmune Study participants are predominantly white and highly educated; and iii) exploring these associations in populations at higher risk of MS, particularly adults aged 20–40 years, who are most commonly affected by the disease.

UPFs may increase the risk of MS through multiple biological pathways. Firstly, exposure to UPFs can lead to disruption of the gut microbiome and consequent production of pro-inflammatory cytokines [39]. Diets high in salt, saturated fat and free sugar can damage the gastrointestinal wall through increased levels of dysbacteriosis, mucus-degrading bacteria and increased membrane permeability, resulting in inflammatory responses [39]. Secondly, UPFs may contain contaminants from processing (e.g., advanced

glycation end products) and plastic packaging (phthalates, bisphenol), that are endocrine disruptors and can increase oxidative stress [40]. Reactive oxygen species are implicated as mediators of axonal damage and demyelination in MS onset as well as damaging cardinal cellular components, resulting in cell death [40]. Elevated levels of oxidants and various oxidant-stress markers in the brain tissues have been found in MS cases [40]. Lastly, diets rich in UPFs are associated with the displacement of a healthy, balanced diet, leading to a reduction of protective, anti-inflammatory compounds, such as short chain fatty acids, fibre, phytochemicals, vitamins and minerals [39]. Future mechanistic research investigating how different dietary factors within ultra-processed dietary patterns influence physiological, hormonal, and immunological responses would strengthen the evidence linking UPF to MS.

UPFs are also designed to be overconsumed and displace unprocessed and minimally processed foods [3]. Their affordability, convenience, long shelf life and quick preparation make them widely appealing [3]. Hyper-palatable ingredients like high-fructose corn syrup, hydrogenated fats, and additives further drive demand, reinforced by aggressive marketing, branding, and promotions [3]. All these factors are contributing to the global rise in UPF consumption [41] and associated chronic diseases globally. An umbrella review of systematic reviews found direct, dose–response associations between UPF consumption and more than 30 health-related outcomes, including type-2 diabetes, cardiovascular diseases, and mortality [6].

Our study contributes to a novel area of research exploring the role of UPFs in the onset of neurodegenerative diseases [7–10]. Using UK Biobank data, Li et al. found that over a 10-year follow-up, every 10% increase in UPF consumption was associated with a 25%, 14% and 28% increased risk of all-cause dementia, Alzheimer's disease, and vascular dementia, respectively [7]. Similar findings for Alzheimer's disease were found in The Framingham Heart Study, though the associations with all-cause dementia were less robust [10]. In a Brazilian cohort study, participants at the highest quartile of UPF consumption had a 28% faster rate of global cognitive decline and a 25% faster rate of executive function decline compared to the first quartile [8]. This collective body of evidence demonstrates the adverse impacts of UPFs on various health outcomes, highlighting the need for evidence-based dietary guidance and targeted strategies to reduce UPF consumption [42], including for prevention of MS.

4.1. Strengths and limitations

Strengths of this study include its prospective cohort study design, using a large sample of 185,788 adults followed for a mean of 8.9 years. The large sample size increases statistical power, while the longitudinal nature of the study allows for the observation of long–term associations, to establish temporality and reduce reverse causality by assessing the exposure before the outcome occurs. The use of the Oxford WebQ, an effective dietary assessment tool, enhanced the validity of the findings, as it has been validated against biomarkers, such as total energy expenditure [43]. A key strength of our study was the application of the Nova food classification system to identify UPFs and categorise items based on their level of processing using standardised criteria [25]. This system is widely recognised and extensively used in scientific literature, making it the most used system to classify foods based on the industrial processing [44]. By employing the Nova classification, we ensured greater standardisation and consistency in our findings, allowing for clearer comparisons with other studies and enhancing the reliability of our results. Finally, several covariates were accounted for, including deseasonalised serum 25(OH)D concentration and smoking status, both of which are established risk factors for MS [45,46].

Important limitations need to be considered. First, dietary intake was self-reported, thus recall bias and over/under-reporting due to social desirability cannot be ruled out. To minimise these effects, participants were only included if they provided one or more valid dietary assessment at baseline (i.e., total energy intake between 500 and 3500 kcal/d for women and 800–4000 kcal/day for men), and the online administration of the questionnaire may have contributed to minimising any reporting bias due to social desirability. Nevertheless, despite the attempt to average multiple 24-h recalls for the best representation of habitual dietary intake, 40% of the cohort had only one valid 24-h recall. Therefore, misreporting of the dietary contribution of UPFs may have occurred. Second, the Oxford WebQ was not specifically developed to measure UPF consumption, therefore some food items may have been misclassified. Several steps were conducted to minimise this, including classifying items to the most probable food group based on published findings of common foods and drinks consumed in the UK, as described in detail elsewhere [25]. Third, ascertaining a diagnosis of MS was based on the method provided by the UK Biobank, which included both medical records and self-reported data, therefore potential measurement error cannot be ruled out. Nevertheless, less than 10% of the reported MS was based on self-report data only, and studies have found that self-reported MS diagnoses are reasonably accurate when compared to medical records in epidemiological studies [47]. Self-report data in the UK Biobank was also doctor-diagnosed, i.e. participants were asked to report all health conditions diagnosed by a doctor and their answers were verified with a nurse during the verbal interview. Fourth, despite the effort to account for a range of potential cofounders, there is the possibility of residual confounding (e.g., exposure to Epstein–Barr virus, an important risk factor for MS) [48]. Despite its large sample size, the generalisability of the findings is limited, as the UK Biobank is not nationally representative and has a predominantly (96%) white demographic. Finally, some participants may have been in the prodromal or pre-clinical phase of MS when their diet was assessed, as this phase can begin many years, possibly decades, before diagnosis. Evidence from nationally representative UK data shows that UPF consumption levels are similar in both younger and older adults (~53% of total energy intake), suggesting that dietary habits remain relatively stable over time [4]. Nevertheless, we conducted sensitivity analysis excluding those who developed MS within two years of follow-up to account for potential reverse causality (n= 53 people with MS excluded), and also those who had one 24-h dietary recalls (n= 74,553 excluded; lost 138 people with MS) as this may not represent habitual intake. Both the direction and magnitude of the associations remained similar to that observed in the main analysis, but the association was no longer statistically significant. Since the outcome was rare (occurring in only 0.2% of the sample), it is unclear whether these were impacted by a loss of statistical power in the models.

5. Conclusion

In this prospective population-based cohort study, a weak yet statistically significant association between higher UPF consumption and increased risk of MS was observed. The findings should be interpreted cautiously, given the modest effect size and limited robustness across sensitivity analyses. This study contributes to a novel, but growing area of research on the role of UPFs in neurodegenerative diseases, including MS. This highlights the need for guidance and strategies focused on UPFs, as well as

further research to confirm these findings in other population groups and contexts.

Author contributions

Pavlina Vagner: Conceptualization, Writing- Original draft preparation, Writing - Review & Editing; **Barbara Brayner**: Conceptualization, Methodology, Data curation, Writing - Review & Editing, Supervision; **Fernanda Rauber**: Data curation; Writing - Review & Editing; **Renata B. Levy**: Data curation; Writing - Review & Editing; **Eszter P. Vamos**: Data curation; Writing - Review & Editing; **Kiara Chang**: Data curation; Writing - Review & Editing; **Gavin Abbott**: Methodology, Formal analysis, Writing - Review & Editing; **Bruce Taylor**: Writing - Review & Editing; **Lucinda J. Black**: Conceptualization, Methodology, Writing - Review & Editing, Supervision; **Priscila Machado**: Conceptualization, Methodology, Data curation, Formal analysis; Writing - Review & Editing, Supervision.

No one eligible for authorship has been excluded from the list of authors.

Data sharing statement

The data that support the findings of this study are available from UK Biobank but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Access to the classification of dietary variables according to the NOVA system, as well as portion sizes and energy profiles applied to each item can be accessed under reasonable request.

Ethical approval

The UK Biobank was approved by the Northwest Multi-centre Research Ethics Committee (reference 21/NW/0157). The project “Investigating the association between diet and multiple sclerosis incidence in the UK Biobank” (number 2024-107) was declared exempt from ethical review at the Deakin University Human Research Ethics Committee on 26/3/24 in accordance with the National Statement on Ethical Conduct in Human Research 2023 5.1.17 a-d.

Declaration of generative AI and AI-assisted technologies in the writing process

None to declare.

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Conflict of interest

None declared.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2026.106673.

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