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Association of Nutritional Intake with Clinical and Imaging Activity in Pediatric Multiple Sclerosis

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Abstract

Background: Understanding nutrition's role in multiple sclerosis (MS) can guide recommendations and intervention-based studies.

Objective: Evaluate the association between nutrition and pediatric-onset MS outcomes.

Methods: Prospective longitudinal multicenter study conducted as part of the US Network of Pediatric MS centers. Predictors were collected using a food screener estimating intake of various dietary food groups (e.g. dairy, fruits) and additional calculated indices (e.g. Healthy Eating Index (HEI)). Outcomes included time-from-enrollment to clinical relapse, new MRI T2 lesions, and EDSS increase.

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Results: 353 children with MS were enrolled (mean ± SD age 15.4 ± 2.9, follow-up 3.9 ± 2.6 years). Multivariable analysis demonstrated that increased dairy by 50% of recommended intake was associated with increased relapse risk by 41% (adjusted HR 1.41, 95% CI 1.07 to 1.86), and risk of T2 progression by 40% (1.40, 1.12 to 1.74). Increased intake of fruit or vegetable above recommended, and every 5-point HEI increase decreased relapse risk by 25% (0.75, 0.60 to 0.95), 45% (0.55, 0.32 to 0.96) and 15% (0.84, 0.74 to 0.96), respectively. No associations were found with EDSS.

Conclusion: This work supports the influence of dietary intake on MS course, particularly with dairy intake. Future prospective study is required to establish causation.

Keywords

pediatric onset multiple sclerosis; diet; dairy; clinical progression; radiographic progression

INTRODUCTION

Multiple sclerosis (MS) pathophysiology remains unknown, and an increasing number of environmental and genetic contributions have been discovered (1). Children with MS have higher clinical and radiographic disease activity early on compared to adults and are less likely to have accumulated confounding environmental influences (2). This provides an opportunity to more reliably study nutritional association with disease course. A better understanding of diet's contribution to MS activity could guide lifestyle recommendations for patients living with MS.

One of the first links between diet and MS course was described by Swank et al. in the 1940's, correlating MS severity with increasing consumption of saturated animal fats (3). Additionally, prior epidemiologic studies demonstrate a correlation between dairy consumption and MS incidence and disability progression (4–6). Our prior work suggests that in pediatric-onset MS (POMS), high energy intake from fat, especially saturated fat, may be associated with a higher risk of relapse, while vegetable intake may be independently protective (7). Otherwise, there is a scarcity of prospective clinical studies exploring the role of nutrition in the disease course of youth with POMS. The current work builds upon a previous preliminary study in this population (7). Longitudinal dietary associations with MRI activity have not been described previously; however, certain dietary lifestyles, such as a Mediterranean-based diet and high fat dairy intake, correlate with the degree of brain atrophy and MRI T2 lesion burden, respectively (8). These findings support the need to further explore more defined associations between nutritional intake and MS progression.

In this study, we aimed to evaluate the association between dietary intake and subsequent risk of POMS disease activity. We expand on our prior work, with more extensive data in terms of sample size, follow-up time, and nutritional predictors such as calculated dietary indices (e.g. Healthy Eating Index (HEI) and Dietary Inflammatory Index (DII). Importantly, the current study employs outcomes (e.g. neuroimaging and Expanded Disability Status Scale (EDSS)) that were not assessed previously.

MATERIALS AND METHODS

Study Participants

Nineteen US Network of Pediatric MS centers and collaborators participated in the study and prospectively entered relapse and MRI information into the network database (7,9). Cases were recruited between November 2011 and March 2018. Institutional review boards at each site approved the study. The participants and one parent/legal guardian signed informed consent and assent. POMS was defined as age <18 years at clinical onset. Subjects were eligible if disease duration was <4 years at time of enrollment and if they had ≥2 silent T2-hyperintense foci on brain and/or spinal cord MRI and met published criteria for MS or CIS at risk for MS (10). Only subjects who remained with a diagnosis of MS at the end of follow-up were used for analyses (i.e. 8 CIS, 2 NMO, and 12 'demyelinating disease not otherwise specified' subjects were removed).

All participants who completed the food frequency questionnaire (FFQ) and for whom prospective relapse data were collected were included. Subjects were excluded if >15 answers were missing from the FFQ or if reported FFQ estimates reflected biologically implausible daily energy intakes (<500 or >5000 kcal/day). Subjects were also excluded if they did not have at least one follow-up visit following completion of the FFQ.

Clinical and Demographic Information

Demographic and clinical data were stored in a web-based data entry system managed by the Data Coordinating and Analysis Center at the University of Utah (9). Case ascertainment was performed by a panel of at least 2 POMS experts, listed as co-authors. Race and ethnicity were self-reported according to National Institutes of Health criteria. Medical history, including relapse rate, was collected by each site at follow-up clinical visits at approximately 6-month intervals. Disease duration at enrollment was calculated from date of first demyelinating event to time of enrollment. Follow-up duration was calculated from time of enrollment to end of available follow-up. Baseline serum 25(OH) vitamin D level was measured by Heartland Assays laboratory. Body mass index (BMI) was categorized as "underweight," "healthy," "overweight," or "obese" based on Centers for Disease Control (CDC) percentiles for age and sex at the time of enrollment (11). Clinical relapses were defined as new or recurrent neurological symptoms localizing to the central nervous system (CNS), lasting for at least 24 hours at least 30 days after prior attack, in the absence of infection or fever. Only relapses that occurred after enrollment were included for analysis. Radiographic progression was defined as an increase in T2-hyperintense lesions on subsequent MRIs. Baseline MRI could have occurred up to 1 year prior to enrollment, as long as the midpoint between the first and second scan was after the time of enrollment. A clinically meaningful change on EDSS was defined as ≥1.0-point increase in patients with baseline EDSS score of 5.0 or lower or ≥0.5-point increase in patients with score of 5.5 or higher.

Nutrient and Energy Intake Assessment

Nutrition Quest Block Food Screeners 2007 Last Week version, a validated FFQ for children between 2 and 17 years of age was completed at enrollment. This questionnaire was

developed using the National Health and Nutrition Examination Survey 1999–2002 dietary recall data that aimed to capture ethnic and cultural groups across the US population (12,13). This FFQ consists of 41 items to evaluate the frequency and portion size of food/beverages consumed during the past week (7,14). Questionnaires were completed on paper and then scanned into electronic format. Energy and nutrient estimates were derived from the FFQ via Nutrition Quest algorithm. The questionnaire was completed by primary caregivers (in most cases, parents) or the participants themselves if they were able to.

Five age–sex categories were used to provide appropriate dietary estimates: males/females 4–8 years old, males 9–13 years old, males 14–17 years old, females 9–15 years old and females 16–17 years old. We examined caloric derivation (e.g. % calories from carbohydrates, % calories from protein) in addition to average daily intake of dairy (as cup equivalents, calculated using values from the USDA Food Patterns Equivalents Database and includes all types of milk, yogurt, cheese), saturated and unsaturated fat (in grams, and further characterized into sub-types), vegetables (as cup equivalents, excluding potatoes and legumes), fruit (as cup equivalents), cholesterol, fiber, carbohydrate, sugars, magnesium, iron, and folate. Percent energy intake from fat was calculated as a percentage of daily calories from fat, equal to 100*(9 kcals/gm fat x daily fat intake in grams)/energy intake in kcals. Energy intake from carbohydrate and protein was calculated similarly, using a multiplier of 4. Glycemic index was calculated by Nutrition Quest. Nutrient intakes were calculated as continuous variables, some categorized based on minimally recommended total intake for age group or using tertiles (based on U.S. Department of Agriculture and U.S. Department of Health and Human Services recommendations) (15).

HEI and DII, both dietary indices validated in prior algorithms, (16,17) were calculated from the raw data as additional predictors. A modified version of established HEI-2015 was used, aligning with Dietary Guidelines for Americans (16). Based on FFQ data availability, the modified HEI was based on 10 of the original 13 HEI food parameters: adequacy [total fruit, total vegetables, greens and beans, whole grains, dairy (milk, yogurt, cheese, and fortified soy beverages in the form of skim milk equivalents), total protein foods (lean fraction only), fatty acid ratio ((polyunsaturated fatty acids (PUFAs) + monounsaturated fatty acids (MUFAs))/saturated fatty acids (SFAs))] and moderation (sodium, calories from added sugars and saturated fats), and the DII was based on 28 of the original 45 DII food parameters (Vitamin B12 (μg), Vitamin B6 (mg), β-Carotene (μg), Caffeine (g), Carbohydrate (g), Cholesterol (mg), Energy (kcal), Total fat (g), Fiber (g), Folic acid (μg), Iron (mg), magnesium (mg), MUFA (g), Niacin (mg), n-3 Fatty acids (g), n-6 Fatty acids (g), Protein (g), PUFA (g), Riboflavin (mg), Saturated fat (g), Selenium (mcg), Thiamine (mg), Trans fat (g), Vitamin A (RE), Vitamin C (mg), Vitamin E (mg), Zinc (mg) and Alcohol) that are thought to impact systemic inflammation based on elevation or reduction of serum biomarkers IL-1β, IL-4, IL-6, IL-10, TNF-α and C-reactive protein).

Statistical Analysis

We investigated the longitudinal associations between the above nutritional assessments and MS course, measured as time to event of (1) clinical relapse, (2) MRI T2 progression, and (3) EDSS progression, as a survival analysis. Wilcoxon rank-sum test was used for

continuous variables and chi-squared test for categorical variables. We estimated the hazard ratio (HR) and 95% CI from multivariable Cox proportional hazard models. Descriptive statistics for patient characteristics are presented as percentages (%) or using mean and SD (Table 1a-1d).

Multivariable Cox proportional hazard regression model was adjusted for age, sex, race, ethnicity, duration of disease, BMI, baseline 25-(OH) vitamin D serum level, total energy intake, disease-modifying treatment (DMT), and duration of use. Participants who switched DMT were counted according to the DMT they were on for the longest. Covariates with p values <0.2 were retained.

Model checking, including testing and visual inspection for proportional hazard assumption, was performed. Assumption of proportionality was not violated in the Cox models. Statistical analyses were performed using SAS version 9.4. Findings were considered statistically significant if the confidence interval did not include 1.0 or if $p<0.05$.

Sensitivity Analysis

Some participants included in the analyses contributed to prior publication (7). We included these participants, now with longer follow-up and with MRI data. We performed sensitivity analysis to confirm reproducibility of results with current methodology (7). There were 320 participants who joined the study before 2017 included in the sensitivity analysis.

RESULTS

Patient characteristics

A total of 353 participants met inclusion criteria (Fig. 1). Demographics at time of enrollment are summarized in Table 1 and are further subcategorized as participants with and without clinical relapse (Suppl. Table 1a), MRI T2 progression (Suppl. Table 1b), and EDSS progression (Suppl. Table 1c). There were 3.9 ± 2.6 years of follow-up after enrollment, with the longest follow-up being 10.3 years. Supplemental Figure 1 shows histograms depicting distributions of dietary intake variables.

Diet and relapse association

Several associations were found between different food groups and risk of relapse (Table 2, Fig. 2). Specifically, we found that for subjects who had excess of dairy, each excess by 50% of recommended intake was associated with increased hazard of clinical relapse by 41% (adjusted HR 1.41, 95% CI 1.07 to 1.86, p=0.014) and each increase in dairy cup equivalent per day was associated with increased clinical relapse risk (CRR) of 32% (1.32, 1.05 to 1.66, 0.020).

For subjects with increased fruit intake, every cup of increased intake was associated with a 21% (0.79, 0.65 to 0.95, 0.014) decreased CRR. Further, both fruit and vegetable intake above that recommended was associated with a 25% (0.75, 0.60, 0.95, 0.016) and 45% (0.55, 0.32 to 0.96, 0.036) reduction in CRR, respectively. Each gram of total fiber above recommended intake was associated with a 6% decreased CRR (0.94, 0.90 to 0.99, 0.009). Higher intake of saturated fat (1.84, 1.08 to 3.14, 0.026) was associated with increased

CRR. Increased intake of Magnesium above minimum recommended was associated with a decreased CRR (0.21, 0.05 to 0.84, 0.028), though this relationship was not noted in the gross Magnesium intake. In terms of caloric allocation, greater percent of calories from carbohydrate associates with decreased CRR (0.79, 0.64 to 0.98, 0.032) while greater percentage of calories from fat (1.38, 1.03 to 1.85, 0.031) associates with an increased CRR.

For dietary indices, each additional 5-point increment on HEI was associated with a 16% (0.84, 0.74 to 0.96, 0.008) decreased CRR. Conversely, a higher DII score was associated with a 30% increased CRR (1.30, 1.03 to 1.65, 0.027). No significant associations for glycemic index were noted.

Diet and new T2 lesion association

For subjects who had excess of dairy, each excess dairy by 50% of recommended intake and increase in dairy cup equivalent were associated with increased hazard of T2 progression (RT2) by 40% (adjusted HR 1.40, 95% CI 1.12 to 1.74, 0.003) and 37% (1.37, 1.13 to 1.64, 0.001), respectively (Fig. 2).

Diet and EDSS progression association

Mean EDSS was 1.5 (+/− 1.3) at study enrollment (N=332), and 2.1 (+/− 1.1) at last follow-up (N=128). No significant dietary associations were found with EDSS progression, and there was no clinically meaningful change in EDSS over the study follow-up period (Table 2).

Sensitivity Analyses

There were no significant differences between the cohort that enrolled prior to 2017 (7) and the current cohort by age, sex, race, ethnicity, or categorical BMI. There was a significant difference between the longest DMT each participant was on during follow up ($p < 0.001$). Several associations were found between certain food groups and risk of relapse. Applying the same methodology to the prior cohort, (7) increased saturated fat intake was associated with increased relapse rate, as noted in the prior study (Suppl. Table 2). There were no major differences between the sensitivity and main analyses for new T2 lesions, and there were no dietary associations with EDSS progression in the prior cohort (Suppl. Table 2).

DISCUSSION AND CONCLUSION

This study is the first to note associations between dietary intake and both clinical and MRI activity in the same POMS population. Greater dairy intake was associated with increased clinical CRR and RT2, and higher saturated fat intake and DII score were associated with higher CRR. In contrast, there was a protective association of higher vegetable, fruit and fiber intake, as well as HEI scores against CRR.

We expand on prior work (7), with longer term data in a larger cohort and additional MS outcomes, including MRI activity and EDSS change. The previously observed association of vegetables as protective against relapses was noted again, with a narrower confidence interval. Previous trends towards increased fruit consumption as protective is now significant

in this larger dataset with longer duration of follow-up. In addition, fiber intake appears protective while saturated fat intake continues to associate with a higher risk of relapse. These more robust associations may be due to the larger cohort with longer follow-up and removing subjects who were found to have other diagnoses than MS by the end of the longer follow-up.

Dairy intake may be linked as an association with MS potentially due to a similar mechanism as has been noted with animal fat consumption (3). Although our study did not have the granularity to identify individual components of each dairy product, such as fat or sugar content, individual analysis did not yield a significant association. Other studies have reported the possible role of dairy in MS, though not in pediatric subjects. A correlation between world distribution of dairy consumption and MS incidence has been described (4). Since then, positive correlations have been found in several other studies (21–24). In the HOLISM (Health Outcomes and Lifestyle In a Sample of People with Multiple Sclerosis) database, MS participants who reported consuming dairy were more likely to report disease activity and have disability progression when monitored over 7.5 years (5,6). Our study, using prospectively-acquired clinical and radiologic assessments, supports these findings.

In contrast, a cross-sectional NARCOMS (North American Research Committee on MS) database study noted significantly reduced odds of severe disability among those in the top versus bottom quintile for dairy intake, although disability was self-reported (25). Additionally, a cross-sectional study exploring diet's relationship with imaging characteristics found that higher intake of only full, and not low, fat dairy was associated with lower MRI T2 lesion volumes in MS (8). It is possible these contrasting findings are due to different types and sources of dairy and fat, or due to differences in the approach to measuring dietary factors. More detailed analyses should be considered in future work.

Unlike prior studies, our study quantified the amount of dairy, including analysis of excessive consumption based on recommended amounts for sex and age. Even stronger associations were found with dairy consumption above recommended intake, though a general association was observed. Hence, we would not recommend limiting dairy to less than the minimum recommended intake, given the potential negative impact this may have on pediatric health and development, including for mineral requirements such as calcium (26).

Several mechanisms could either independently or in association account for dairy's impact on MS. Children and adults with MS have heightened immunologic responses to milk antigens,(27) and the milk protein butyrophilin has been deemed potentially harmful, due to antigenic mimicry with myelin oligodendrocyte glycoprotein and myelin-associated glycoprotein in animal models and MS subjects (28,29). Dairy is known to alters the gut microbiome, which could modulate MS activity (30). For instance, methanogens such as *Methanobrevibacter* and its species, *M. smithii,* were found to be more abundant in POMS patients with higher disease activity: consumption of organic yogurt and milk was positively associated with the presence of *M. smithii* in children, (31) a finding also noted in adult MS subjects (32).

The impact of fruits and vegetables on MS activity could be due to anti-inflammatory effects through altering serum metabolites and/or the gut microbiome (33). Similarly, higher fiber intake is also known to modulate metabolites such as short-chain fatty acids that have anti-inflammatory properties. An association between fruit and vegetable intake and lower CRR is concordant with the HOLISM study (5). In a cross-sectional MS study, a higher 'Mediterranean-DASH Intervention for Neurodegenerative Delay' index, which also incorporates fruit and vegetable consumption, correlated with greater thalamic volume, a possible marker of decreased MS activity (8). Both vegetable and fruit intake are important components of the HEI,(16) and higher consumption may contribute to a generally healthier diet. The use of food indices more broadly captures food groups that collectively may modulate disease, as higher HEI scores were associated with decreased CRR. Further, we found an association between DII scores and higher CRR, supporting the potential role of pro-inflammatory foods in promoting POMS disease activity.

Strengths of our study include the large and diverse cohort, proximity to MS clinical onset at time of enrollment, use of a validated FFQ, and prospective collection of MS outcome metrics. Additionally, adjustments were made for possible contributing factors, including DMT use. Lastly, similar associations between dairy with both clinical and MRI outcomes provides independent internal validation.

We acknowledge some limitations. Dietary data were only collected at enrollment so we cannot exclude the possibility that participants changed dietary habits over time, though diets are known to stay moderately stable over time in children and adolescents (34,35) and there are currently no specific dietary recommendations for MS. Additionally, the FFQ may poorly estimate dietary intake given the nature of self-reporting, though it is validated and collects week-long dietary intake data to help control for diet variability. MRI protocols were not standardized and, as such, lesion and brain volumes were not available. In addition, clinic visit timing was not strictly enforced, which could have introduced data variability, although this would mainly bias towards the null hypothesis. EDSS did not substantially increase during follow-up and as such may have limited our ability to detect potential associations, though the lack of EDSS progression is consistent with prior publications showing pediatric MS patients recover better from relapses than adults. Therefore, longer follow-up will likely be important to better assess this outcome measure (36,37). Similarly, conducting sensitivity analyses for all subjects versus only subjects meeting strict 2017 McDonald criteria for MS (N=353), we found similar associations (Suppl. Table 3). Another potential limitation may be that in order to explore associations and maximize power to detect effects, we did not correct for multiple comparisons - thus we cannot rule out that some significant findings could be false positives. Additionally, there could be other contributing factors (e.g. unmeasured nutrients, socioeconomic status), which could be controlled for in future studies.

In conclusion, higher self-reported dairy intake in POMS was associated with increased risk of both clinical relapse and MRI progression. However, it is important not to limit dairy to less than the recommended intake as dairy may be an important source of nutrition, and because we do not yet understand the reasons behind this association. Based on the saturated fat, vegetable, fruit and HEI/DII data, a healthier, balanced diet may be protective against

MS activity. Further research is needed to confirm and better define the relationship between dietary intake and MS course, so that targeted dietary interventional trials can be developed to help better guide people living with MS. In the interim, alongside DMTs, it may be prudent to focus on a healthy, balanced diet to minimize MS activity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements, Data Storage and Disclosures

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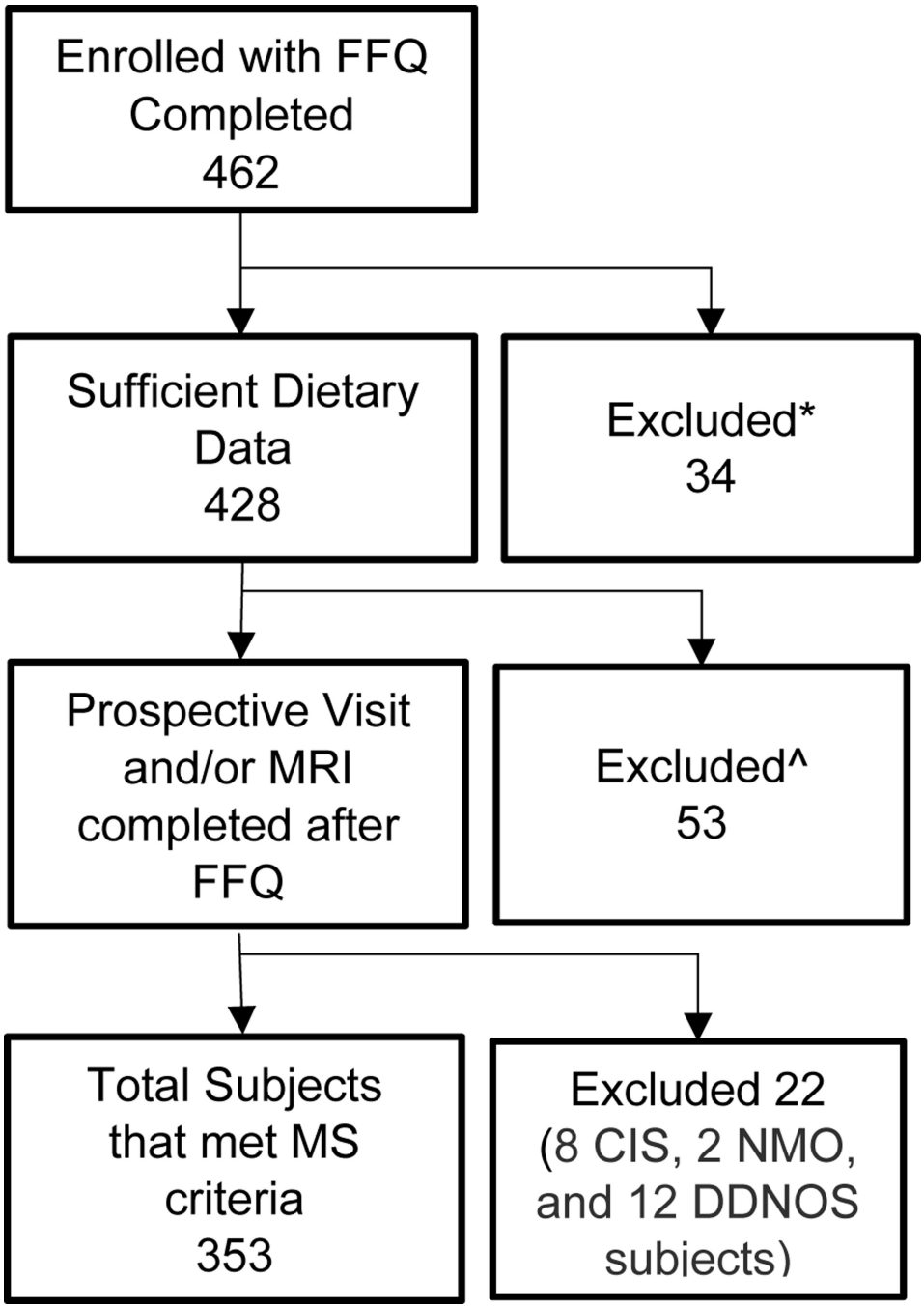

Figure 1: Flow chart of study participants

FFQ: Food Frequency Questionnaire

*If >15 answers were missing in the FFQ or if reported estimates reflected biologically implausible daily energy intakes (<500 or >5000 kcal/day)

^If no prospective study visit completed after completing FFQ

CIS: Clinically Isolated Syndrome, NMO: Neuromyelitis Optica antibody+, DDNOS: Demyelinating disease not otherwise specified

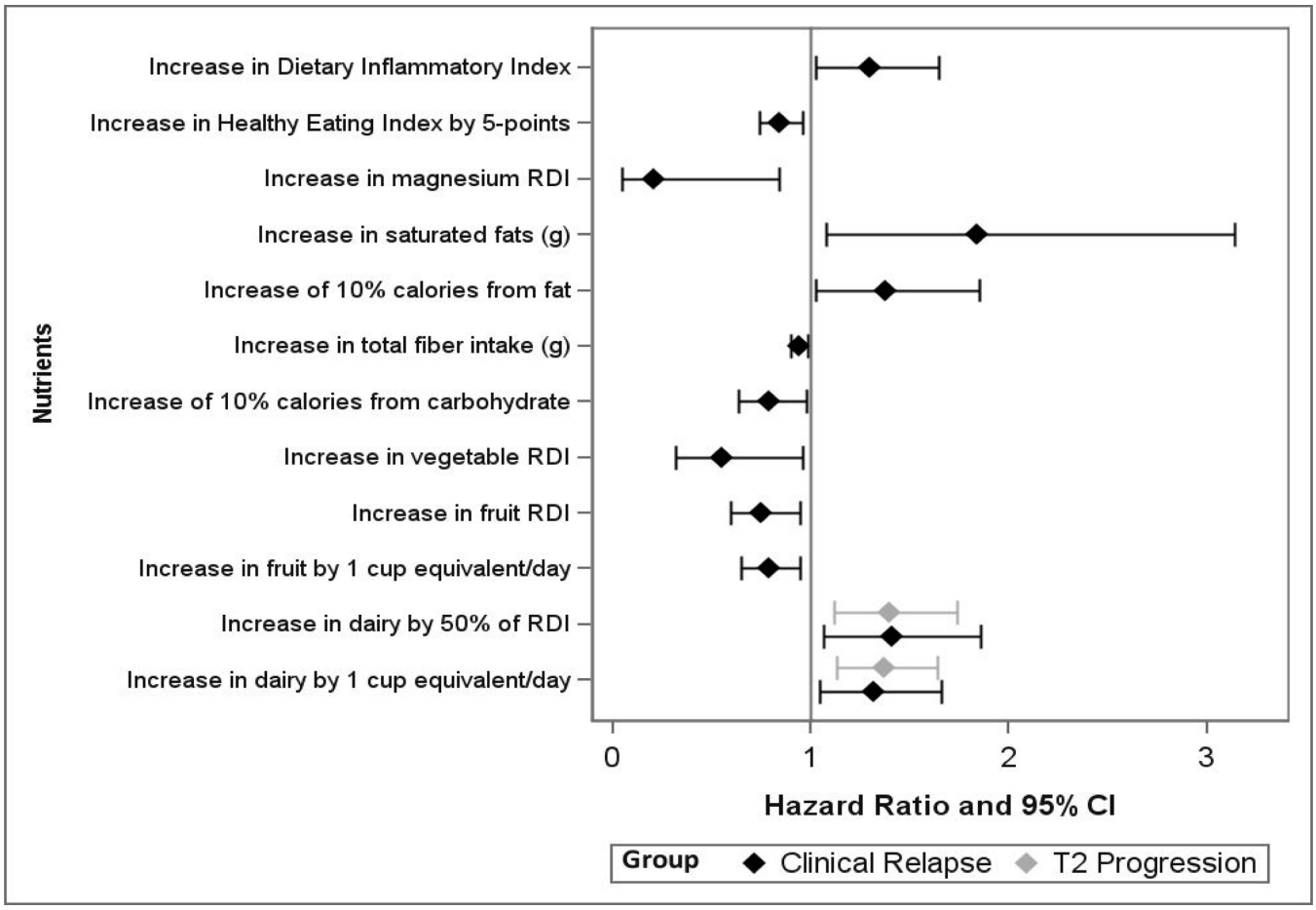

Figure 2: Summary plot of significant findings

CI: Confidence Interval, RDI: Recommended Dietary Intake (increments of 50%)

Table 1.

Overall Demographics

	Overall (N = 353)
Age at Enrollment: Mean (SD)	15.4 (2.9)
Sex	
Male	129/353 (37%)
Female	224/353 (63%)
Race	
White	225/329 (68%)
Black	59/329 (18%)
Other	45/329 (14%)
Ethnicity	
Hispanic or Latino	108/337 (32%)
Not Hispanic or Latino	229/337 (68%)
Categorical BMI	
Underweight	2/350 (1%)
Healthy	174/350 (50%)
Overweight	67/350 (19%)
Obese	107/350 (31%)
Vitamin D: Mean (SD)	29.3 (14.7)
Disease Duration (years): Mean (SD)	1.1 (0.9)
Longest DMT (years): Mean (SD)	2.7 (2.0)
Follow-up (years): Mean (SD)	3.9 (2.6)
Longest MS Agent	
None	37/353 (10%)
Azathioprine	1/353 (0%)
Dimethyl Fumarate (Tecfidera, BG12)	49/353 (14%)
Fingolimod	37/353 (10%)
Glatiramer acetate (Copaxone)	66/353 (19%)
InterferonB-1a: Avonex	21/353 (6%)
InterferonB-1a: Rebif	15/353 (4%)
InterferonB-1b: Betaseron	3/353 (1%)
InterferonB-1b: Extavia	1/353 (0%)
Methotrexate	1/353 (0%)
Mycophenolate	2/353 (1%)
Natalizumab	43/353 (12%)
Ocrelizumab	16/353 (5%)
Peginterferon beta-1a	10/353 (3%)
Rituximab	50/353 (14%)
Teriflunomide	1/353 (0%)

The variable Race had 24 missing values. The variable Ethnicity had 16 missing values. The variable BMI had 3 missing values.

The variable Vitamin D had 12 missing values.

The variable time in study had 2 missing values.

Table 2.

Nutritional associations with MS activity

	Clinical Relapse		T2 Progression		EDDS Progression	
	Hazard ratio (95% CI)	**P-value**	**Hazard ratio (95% CI)**	**P-value**	**Hazard ratio (95% CI)**	**P-value**
Dairy						
Dairy (cup equivalent/day)	**1.32 (1.05, 1.66)**	**0.020**	**1.37 (1.13, 1.64)**	**0.001**	0.87 (0.66, 1.14)	0.305
Recommended Dietary Intake for Dairy (Increments of 50%)	**1.41 (1.07, 1.86)**	**0.014**	**1.40 (1.12, 1.74)**	**0.003**	0.88 (0.64, 1.23)	0.467
Fruit						
Fruit /Fruit Juice (cup equivalent/day)	**0.79 (0.65, 0.95)**	**0.014**	0.94 (0.81, 1.09)	0.426	1.10 (0.90, 1.34)	0.354
Recommended Dietary Intake for Fruit	**0.75 (0.60, 0.95)**	**0.016**	0.90 (0.75, 1.08)	0.253	1.14 (0.91, 1.43)	0.253
Vegetables						
Vegetables (Excluding potatoes/ legumes) (cup equivalent/day)	0.68 (0.46, 1.02)	0.064	1.06 (0.79, 1.43)	0.691	0.95 (0.63, 1.43)	0.805
Vegetable Recommended Dietary Intake	**0.55 (0.32, 0.96)**	**0.036**	1.05 (0.70, 1.56)	0.821	1.11 (0.67, 1.84)	0.679
Energy						
Percent of Calories from Protein (Increments of 10%)	1.02 (0.96, 1.07)	0.564	1.01 (0.96, 1.05)	0.799	0.99 (0.94, 1.05)	0.842
Percent of Calories from Carbohydrate (Increments of 10%)	**0.79 (0.64, 0.98)**	**0.032**	1.00 (0.84, 1.18)	0.971	1.05 (0.83, 1.32)	0.692
Added Sugars/Syrups (10 tsp)	1.03 (0.78, 1.37)	0.827	1.08 (0.85, 1.37)	0.541	0.97 (0.69, 1.35)	0.841
Total Fiber Intake (g)	**0.94 (0.90, 0.99)**	**0.009**	0.99 (0.96, 1.03)	0.761	0.99 (0.95, 1.04)	0.783
Recommended Dietary Intake (Protein)	0.84 (0.45, 1.55)	0.572	0.84 (0.52, 1.36)	0.475	0.70 (0.35, 1.39)	0.307
Fat						
Percent of Calories from	**1.38 (1.03, 1.85)**	**0.031**	0.98 (0.77, 1.24)	0.856	0.94 (0.68, 1.29)	0.684
Fat (Increments of 10%)						
Saturated Fats (10 g)	**1.84 (1.08, 3.14)**	**0.026**	1.51 (0.95, 2.38)	0.079	0.77 (0.43, 1.39)	0.391
Total Monounsaturated Fat (10 g)	1.63 (0.92, 2.88)	0.097	0.94 (0.59, 1.51)	0.807	0.95 (0.50, 1.80)	0.864
Total Polyunsaturated Fat (10 g)	0.63 (0.23, 1.74)	0.377	0.46 (0.19, 1.08)	0.076	1.04 (0.32, 3.36)	0.954

	Clinical Relapse		T2 Progression		EDDS Progression	
	Hazard ratio (95% CI)	**P-value**	**Hazard ratio (95% CI)**	**P-value**	**Hazard ratio (95% CI)**	**P-value**
Fat Intake Exceeding the Recommended Amount	1.21 (0.84, 1.73)	0.303	0.96 (0.72, 1.29)	0.807	0.86 (0.59, 1.26)	0.438
Fat Intake Less Than the Recommended Amount	0.56 (0.20, 1.55)	0.263	0.81 (0.39, 1.69)	0.580	1.19 (0.46, 3.05)	0.721
Cholesterol (100 g)	0.97 (0.77, 1.23)	0.822	0.93 (0.77, 1.12)	0.439	0.97 (0.74, 1.26)	0.801
Micronutrients						
Magnesium (10 mg)	0.96 (0.90, 1.01)	0.131	1.02 (0.97, 1.07)	0.429	0.96 (0.90, 1.03)	0.269
Magnesium Recommended Dietary Intake	**0.21 (0.05, 0.84)**	**0.028**	0.64 (0.20, 2.00)	0.441	0.25 (0.05, 1.21)	0.085
Iron (10 mg)	0.87 (0.39, 1.96)	0.741	1.10 (0.56, 2.17)	0.790	0.64 (0.26, 1.60)	0.344
Iron Recommended Dietary Intake	0.78 (0.38, 1.62)	0.507	1.17 (0.66, 2.07)	0.595	0.69 (0.30, 1.62)	0.401
Folate (1 mg)	0.94 (0.74, 1.20)	0.618	1.07 (0.88, 1.30)	0.484	0.95 (0.73, 1.25)	0.735
Folate Recommended Dietary Intake	0.67 (0.30, 1.47)	0.316	1.07 (0.56, 2.05)	0.830	0.72 (0.29, 1.74)	0.459
Indices						
Healthy Eating Index (5 units)	**0.84 (0.74, 0.96)**	**0.008**	0.95 (0.85, 1.06)	0.356	0.92 (0.80, 1.07)	0.270
Dietary Inflammatory Index (1 unit)	**1.30 (1.03, 1.65)**	**0.027**	0.97 (0.80, 1.17)	0.716	0.94 (0.73, 1.22)	0.661
Glycemic Index (10 units)	1.15 (0.76, 1.74)	0.520	0.80 (0.55, 1.17)	0.246	1.00 (0.60, 1.65)	0.993

Results are based on multivariable model(s) adjusting for subject sex, age at enrollment, race, ethnicity, categorical BMI based on CDC Percentiles, MS DMT on longest during event-free follow-up, average daily calories (kcal/day).

Unless specified 1 unit increase leads to an increased or decreased hazard.

Significant findings are bolded.