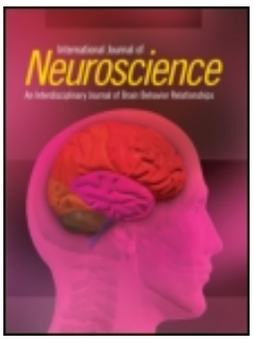

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Association of fish consumption and omega 3 supplementation with quality of life, disability and disease activity in an international cohort of people with multiple sclerosis

George A. Jelinek,[1,2] Emily J. Hadgkiss,[1] Tracey J. Weiland,[1,3] Naresh G. Pereira,[4] Claudia H. Marck,[1] and Dania M. van der Meer[1]

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The role of fish consumption and omega 3 supplementation in multiple sclerosis (MS) is controversial, although there is some evidence to support a beneficial effect. We surveyed a large cohort of people with MS recruited via Web 2.0 platforms, requesting information on type of MS, relapse rates, disability, health-related quality of life, frequency of fish consumption and omega 3 supplementation, including type and dose, using validated tools where possible. We aimed to determine whether there was an association between fish consumption and omega 3 supplementation and quality of life, disability and disease activity for people with MS. Univariate and multivariate analyses were undertaken. Of 2469 respondents, 1493 (60.5%) had relapsing–remitting MS. Those consuming fish more frequently and those taking omega 3 supplements had significantly better quality of life, in all domains, and less disability. For fish consumption, there was a clear dose–response relationship for these associations. There were also trends towards lower relapse rates and reduced disease activity; flaxseed oil supplementation was associated with over 60% lower relapse rate over the previous 12 months. Further dietary studies and randomised controlled trials of omega 3 supplementation for people with MS are required, preferably using flaxseed oil.

KEYWORDS: multiple sclerosis, MS, risk factors, prevention

Introduction

Around a quarter of the risk of developing multiple sclerosis (MS) is genetic [1]; a large, genome-wide collaborative study, however, found no evidence of genetic associations with clinical course or disease severity [2], suggesting a pivotal role for environmental factors in determining disease course. There is thus a substantial opportunity for primary, secondary and tertiary prevention of the illness through modification of amenable environmental risk factors. This approach has not been widely used; preliminary uncontrolled research on a comprehensive lifestyle risk modification program has shown significant improvements at 1, 2.5 and 5 years after undertaking the program [3,4].

Determining which modifiable risk factors are the most important is key to any preventive approach. To date, inadequate sun exposure and low vitamin D, and smoking, have been widely considered to be modifiable risk factors that warrant lifestyle advice [5]. Among other lifestyle factors, there is a large literature on dietary factors, suggesting a role in disease development and progression for fish and omega 3 fatty acid consumption [6].

Omega 3 and omega 6 fatty acids are essential fatty acids, that is, they cannot be synthesised and are essential components of the human diet for health. Omega 3s are found in large amounts in fish and seafood, particularly in oily fish, and in some plants, notably flaxseeds and purslane. Omega 6s are found particularly in vegetables and grains. While both omega 3 and 6 fatty acids

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have positive structural properties when incorporated into bodily cell membranes, in simple terms, omega 3s are essentially anti-inflammatory and omega 6s pro-inflammatory. Ideally, the ratio of omega 6 to omega 3 in the human diet should be around 4:1 to 2:1, although modern Western diets are typically deficient in omega 3s, with a ratio closer to 25:1 [7,8].

In the Health Outcomes and Lifestyle Interventions in a Sample of People with Multiple Sclerosis (HOLISM) study [9], we sought to determine the associations between a variety of lifestyle factors amenable to a risk modification, secondary and tertiary prevention approach to the management of MS, through analysis of data on health and lifestyle behaviours of a large international cohort of people with MS recruited through Web 2.0 platforms. In the current part of the HOLISM study, we aimed to examine the association of fish consumption and omega 3 fatty acid supplementation with quality of life and disability among our cross-sectional sample of respondents with MS, and relapse rate and disease activity in the subset of respondents with relapsing-remitting MS. We also sought to compare the effects of supplementation with the long-chain omega 3 fatty acids found in fish oil to shorter chain alpha linolenic acid found in flaxseed oil.

Methods

Subjects and recruitment procedure

The methodology has previously been described in detail [9]. In short, we recruited participants through Web 2.0 platforms, including social media, via which we distributed our online survey using SurveyMonkey®. Individuals read a participant information sheet before giving consent. People of 18 years and over diagnosed with MS by a physician were invited. Ethics approval was granted by St Vincent's Hospital Melbourne Human Research Ethics Committee (LRR 055/12).

Data collected and tools used

In addition to demographic items, for the purposes of this study, the questionnaire explored: diagnostic details; self-reported, doctor-diagnosed relapse rate; health-related quality of life (HRQOL); level of disability; average weekly fish consumption and omega 3 supplementation, including whether participants used omega 3 supplements, what type (regular fish oil, high potency fish oil, flaxseed oil or 'other') and the average daily dose over the last 12 months.

Health-related quality of life

We used the Multiple Sclerosis Quality Of Life-54 (MSQOL-54) to measure HRQOL. The MSQOL-54 has 52 items in 12 scales, and two single items, resulting in mental and physical health composites, various domains and subscores, and an overall quality of life score. The tool has been validated extensively [10–12].

Disability

We used the Patient-Determined Disease Steps (PDDS), a self-reported tool used as a surrogate for the Expanded Disability Status Scale (EDSS) [13]. It uses an ordinal scale from 0 (normal) to 8 (bed bound) and correlates well with EDSS (Spearman rank $r = 0.64$), moderately with Multiple Sclerosis Functional Composite ($r = 0.58$), with excellent inter-rater reliability (kappa 0.8). It is practical in assessing people with MS over time [14], being used in several studies including the North American Research Committee on MS (NARCOMS) [15–17].

Diet

We used the Diet Habits Questionnaire, a dietary assessment tool with 22 items, developed in an Australian cardiac population [18]. Average weekly frequency of fish consumption was chosen from these items for this study.

Data analysis

Data were analysed using Statistical Package for the Social Sciences (SPSS) version 20.0. Three variables were collapsed across categories to allow sufficient numbers in each category for meaningful analysis: daily dose of omega 3 (ml) from eight categories (0, 1–5, 6–10, 11–15, 16–20, 21–25, 26–30, 31+) to three (0, 1–10, 11+); frequency of fish consumption from five categories (never or hardly ever, <once weekly, once weekly, 2 days weekly, 3 or more days weekly) to three categories (<once weekly, 1–2 days weekly, 3+ days weekly); PDDS from nine to three groups (normal mobility, mild disability, moderate disability = "normal/some disability"; gait disability, early cane, late cane = "gait/cane disability"; bilateral support, wheelchair and bedridden = "major mobility support").

Five year annualised relapse rates (doctor determined) were calculated by dividing the number of relapses over 5 years by the number of years of disease with an upper limit of 5. In addition, we derived the pre-planned variable "disease activity" from data recording relapse rates (doctor determined), categorised as increasing, decreasing or stable, where relapse rate in the preceding 12 months was higher, lower or the same (respectively) as the 5-year annualised relapse rate. For logistic regression, we collapsed disease activity into two categories, worsening (activity increasing) and stable/improving (stable or decreasing).

We undertook univariate and multivariate analyses. Continuous data are summarised using mean [95% confidence interval (CI)] and categorical data using number and percentage. Comparison of two groups

on continuous end points used independent samples *t* test, comparisons involving three or more independent groups used analysis of variance (ANOVA) with least significant difference as post-hoc analyses. Analysis of covariance (ANCOVA) was also used to explore the relationship between fish consumption and relapse rate while controlling for omega 3 supplementation. We analysed categorical data involving two by two contingency tables with the Fisher's exact test and categorical data involving more than two groups with the Pearson's chi square with adjusted standardised residuals to indicate under- or overrepresentation of groups.

Given the large number of associations found in univariate analyses, multivariate analyses were undertaken to identify independent predictors of each outcome (disability, HRQOL, relapse rate, disease activity). In all instances, variables included in regression models were age, sex and omega 3 supplementation dose, supplementation type and fish consumption. To overcome redundancies in the models, the predictors, omega 3 supplementation dose and type were tested in separate models, and the most parsimonious model selected. For disability (normal-mild/moderate/severe) ordinal logistic regression was undertaken after first checking that the proportional odds assumption was not violated.

Multiple regression (enter method) was used to identify predictors of HRQOL domains of overall HRQOL, physical health composite, mental health composite, pain subdomain and energy subdomain. Preliminary tests were undertaken to ensure that data satisfied the assumptions of normality, linearity and homoscedasticity. Variance inflation factor <7 was used as the criterion for absence of multicollinearity. Correlation matrices were checked for inter-correlated predictors; only correlations of <0.70 were accepted. Data were checked for standardised residual values outside the range -3.3 to 3.3 to ensure no outliers. Data for relapse rate were over-dispersed; consequently negative binomial logistic regression was used in preference to Poisson regression.

For disease activity (decreasing/stable versus increasing), binary logistic regression (enter method) was used to determine odds ratios (OR) of predictors. Preliminary tests of assumptions of logistic regression were performed, including an examination of multicollinearity to ensure that continuous independent variables were not closely correlated (bivariate correlation >0.70).

Two-tailed tests of significance were used with significance set at 0.05.

Results

Demographics, participation, fish consumption and omega 3 supplementation

Demographics have previously been described [9] and are summarised in Table 1. In short, the cohort was relatively young (median age 45 years), predominantly female (82.3%), well educated and widely dispersed geographically. The majority (60.6%) were married, approximately two thirds with children. Almost one quarter had retired for medical reasons or disability; approximately one third was working full time.

Of 2469 respondents with confirmed MS, up to 2290 reported on their consumption of fish (Table 2), with approximately 30% consuming fish three or more times weekly. Up to 2253 (91.3%) answered questions regarding omega 3 supplementation. Analyses of relapse rates and disease activity were performed only on those respondents (1493) with relapsing-remitting MS, of whom 1396 (93.5%) responded to questions regarding fish consumption and omega 3 use.

Table 1. Demographics and disease type of the HOLISM study population [*n* (%), unless otherwise stated].

Age, median (IQR), years	45 (37–53)
Age at diagnosis, median (IQR), years	37 (30–45)
PDDS disability score, median (IQR)	3 (1–5)
Disease duration, years	6 (3–12)
Gender	
Male	407/2303 (17.7)
Female	1896/2303 (82.3)
Type of MS (current)	
Relapsing–remitting	1493/2421 (61.7)
Primary progressive	175/2421 (7.2)
Secondary progressive	275/2421 (11.4)
Progressive relapsing	48/2421 (2.0)
Benign	100/2421 (4.1)
Unsure/other	330/2421 (13.6)
Country of location	
USA	807/2469 (32.7)
Australia	629/2469 (25.5)
UK	417/2469 (16.9)
Other*	616/2469 (24.9)
Employment status	
Employed full time	800/2459 (32.5)
Employed part time	524/2459 (21.3)
Unemployed or retired†	838/2459 (34.1)
Other‡	297/2459 (12.1)
Education status	
No formal schooling or primary only	55/2455 (2.2)
Secondary school	549/2455 (22.4)
Vocational training	395/2455 (16.1)
Bachelor's degree	888/2455 (36.2)
Post-graduate degree	568/2455 (23.1)

*Includes 54 other countries.
†Collapsed from unemployed: seeking work/not seeking work and retired due to age/ due to disability.
‡Includes student/stay at home carer.

Table 2. Fish consumption and omega 3 supplementation for all respondents and those with relapsing–remitting MS only [*n* (%)].

	Whole sample	Relapsing–remitting
Frequency of fish consumption		
Never, or hardly ever	294/2290 (12.8)	186/1396 (13.3)
Less than once per week	362/2290 (15.8)	228/1396 (16.3)
Once per week	421/2290 (18.4)	266/1396 (19.1)
Two days per week	504/2290 (22.0)	294/1396 (21.1)
Three or more days per week	709/2290 (31.0)	422/1396 (30.2)
Taking omega 3 supplements	1447/2253 (64.2)	883/1377 (64.1)
Type of omega 3 supplementation		
None	806/2253 (35.8)	494/1377 (35.9)
Fish oil (standard and high potency)	794/2253 (35.2)	482/1377 (35.0)
Flaxseed oil	204/2253 (9.1)	129/1377 (9.4)
Both fish oil and flaxseed oil	395/2253 (17.5)	245/1377 (17.8)
Unspecified	54/2253 (2.4)	27/1377 (1.9)
Daily dose of omega 3 last 12 months (mls)		
None	806/2179 (37.0)	494/1340 (36.9)
1–10	993/2179 (45.6)	594/1340 (44.3)
11+	380/2179 (17.4)	252/1340 (18.8)

Disability

Those consuming fish most frequently and those taking the largest doses of omega 3s were more likely to have normal mobility or only some disability. Those not taking omega 3s were more likely to require major mobility support, and those taking omega 3s were more likely to be in the normal/some disability group (Table 3). With respect to type of omega 3, those taking both fish and flaxseed oil were more likely to have no or some disability.

After controlling for gender and age, which was a significant covariate (OR = 0.921, 95% CI = 0.913–0.930; $p < 0.001$), consuming fish three or more times weekly increased the odds of a lower level of disability (no disability/some disability) by 68% (OR = 1.683; 95% CI = 1.320–2.145; $p < 0.001$). Taking flaxseed oil or taking fish oil was also each independently associated with increased odds of a lower level of disability (no disability/some disability) (flaxseed oil: OR = 1.420; 95% CI = 1.149–1.754; $p = 0.001$; fish oil: OR = 1.289; 95% CI = 1.075–1.546; $p = 0.006$).

Quality of life

HRQOL, including all tested domains and composites, was significantly better ($p < 0.001$; except sexual function $p < 0.003$) for those taking omega 3 supplements and those consuming fish more frequently (Figure 1).

Multiple regression analyses revealed significant models for mental health composite ($p < 0.001$), physical health composite ($p < 0.001$), pain domain ($p < 0.001$), energy domain ($p < 0.001$) and overall HRQOL ($p < 0.001$); significant predictors and covariates are presented in Table 4. Fish consumption three or more times weekly had the strongest association after accounting for age, gender and supplementation type, and the association of flaxseed oil was stronger than for fish oil including in combination with fish oil.

Relapse rate

Mean 12-month doctor-diagnosed relapse rate was reduced with omega 3 supplementation; however, it did not reach statistical significance, with a trend towards a dose–response effect, and for all types of omega 3s were seen, but the reduction reached statistical significance for flaxseed oil only (52.6% relapse rate reduction; $p < 0.001$) in univariate analysis (Table 5). Fish consumption had no significant effect on 12-month relapse rate. Adjusting for omega 3 supplementation using ANCOVA did not affect the outcome; supplementation was not a significant covariate ($p = 0.145$). A combination of fish and flaxseed oils was associated with a relapse rate reduction somewhat higher than that for fish oil alone, not reaching statistical significance. Negative binomial regression was used to model predictors of relapse rate. For each increasing year of age the number of relapses in a 12 month period decreased by 3% (estimate = 0.973, 95% CI = 0.965–0.982, $p < 0.001$), while having female gender increased relapse rate by 31% (estimate 1.307, 95% CI 1.019–1.678, $p = 0.035$). Compared to eating fish less than once a week, consuming fish three or more times a week was associated with 51% reduction in relapse rate (estimate = 0.494, 95% CI 0.255–0.958, $p = 0.037$), while consumption of fish 1–2 times a week was associated with a reduction in relapse rate of 49% (estimate = 0.507, 95% CI 0.266–0.958, $p = 0.039$). There was no significant effect of taking fish oil alone, whereas those supplementing with flaxseed oil alone had a relapse rate reduction of 61% (estimate = 0.394, 95%

Table 3. Disability by omega 3 consumption, type and dose, and frequency of fish consumption for all respondents [*n* (%)].

	Normal/some disability	Gait/cane disability	Major support	Total	p^*
Frequency of fish consumption					$p < 0.001$
<1/week	323 (49.8)†	249 (38.4)*	77 (11.9)	649 (100.0)	
1–2/week	493 (53.5)	326 (35.4)	102 (11.1)	921 (100.0)	
3+/week	439 (62.0)*	209 (29.5)†	60 (8.5)†	708 (100.0)	
Total	1255 (55.1)	784 (34.4)	239 (10.5)	2278 (100.0)	
Taking omega 3					$p = 0.013$
No	410 (51.3)†	291 (36.4)	98 (12.3)*	799 (100.0)	
Yes	827 (57.3)*	480 (33.2)	137 (9.5)†	1444 (100.0)	
Total	1237 (55.1)	771 (34.4)	235 (10.5)	2243 (100.0)	
Omega 3 type					$p < 0.001$
None	410 (51.3)†	291 (36.4)	98 (12.3)*	799 (100.0)	
Fish oil	441 (55.8)	256 (32.4)	94 (11.9)	791 (100.0)	
Flaxseed oil	120 (58.8)	70 (34.3)	14 (6.9)	204 (100.0)	
Fish and flaxseed oil	247 (62.7)*	126 (32.0)	21 (5.3)†	394 (100.0)	
Total	1218 (55.7)	743 (34.0)	227 (10.4)	2188 (100.0)	
Dose of omega 3 (ml)					$p = 0.004$
0	410 (51.3)†	291 (36.4)	98 (12.3)*	799 (100.0)	
1–10	552 (55.8)	333 (33.6)	105 (10.6)	990 (100.0)	
11+	236 (62.1)*	119 (31.3)	25 (6.6)†	380 (100.0)	
Total	1198 (55.2)	743 (34.3)	228 (10.5)	2169 (100.0)	

*denotes significantly overrepresented as determined by standardised adjusted residuals.
†denotes significantly underrepresented as determined by standardised adjusted residuals.

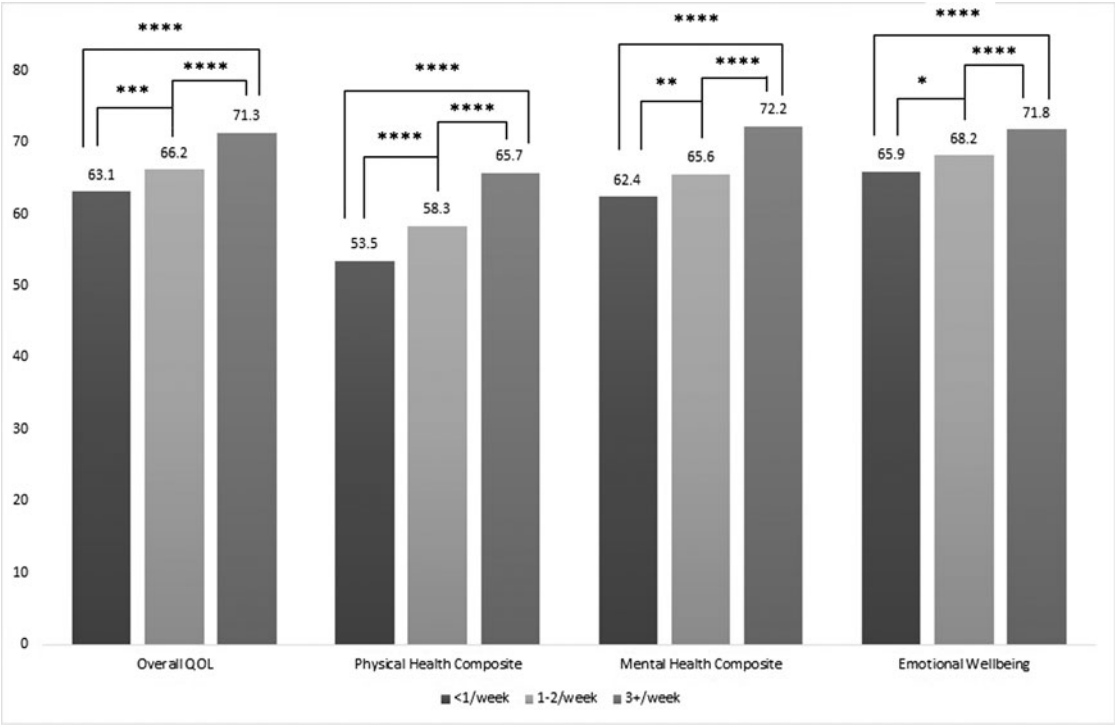

Figure 1. HR-QOL outcomes of all respondents by frequency of fish consumption. Groupwise comparisons: all $p < 0.001$. Pairwise group comparisons: $^{****}p < 0.001$, $^{***}p = 0.002$, $^{**}p = 0.003$, $^{*}p = 0.013$.

Table 4. Significant predictors and covariate for components of HRQOL.

Outcome	Variable	Adjusted R^2	Beta	SE	p
Mental health composite	Age	0.049	0.100	0.044	0.023
	Fish consumption 1–2/week		2.734	1.148	0.017
	Fish consumption 3+/week		7.789	1.269	< 0.001
	Consumption of fish oil only		4.609	1.110	< 0.001
	Consumption of flaxseed oil only		8.003	1.727	< 0.001
	Consumption of both flaxseed oil and fish oil		5.562	1.402	< 0.001
Physical health composite	Age	0.122	−0.471	0.046	< 0.001
	Fish consumption 1–2/week		4.365	1.182	< 0.001
	Fish consumption 3+/week		9.984	1.305	< 0.001
	Consumption fish oil only		5.027	1.143	< 0.001
	Consumption flaxseed oil only		9.603	1.766	< 0.001
	Consumption of both fish oil and flaxseed oil		9.323	1.443	< 0.001
Pain domain	Age	0.084	−0.366	0.051	< 0.001
	Fish consumption 1–2/week		5.365	1.350	< 0.001
	Fish consumption 3+/week		11.248	1.490	< 0.001
	Consumption fish oil		4.276	1.127	< 0.001
	Consumption flaxseed oil		5.765	1.276	< 0.001
Energy domain	Age	0.073	−0.098	0.045	0.029
	Fish consumption 1–2/week		4.905	1.186	< 0.001
	Fish consumption 3+/week		10.278	1.311	< 0.001
	Consumption of fish oil only		6.105	1.143	< 0.001
	Consumption of flaxseed oil only		9.249	1.790	< 0.001
	Consumption of both flaxseed oil and fish oil		8.227	1.448	< 0.001
Overall HRQOL	Age	0.054	−0.200	0.039	< 0.001
	Gender, female		−3.225	1.080	0.003
	Fish consumption 1–2/week		2.707	1.011	0.007
	Fish consumption 3+/week		7.145	1.118	< 0.001
	Omega 3 dose 1–10 ml/day		4.258	0.930	< 0.001
	Omega 3 dose 11–20 ml/day		6.332	1.493	< 0.001

Results are derived from multiple regression analyses and include model fit, and parameters for each predictor or covariate.
Comparisons for type of supplementation are compared against no supplementation.
Comparisons for frequency of fish consumption are compared with fish consumption <1/week.
Comparison for omega 3 dose is compared with no supplementation.

CI 0.225–0.692, $p < 0.001$). The association of a combination of fish oil and flaxseed oil supplements did not reach statistical significance.

Disease activity

In univariate analyses, omega 3 supplementation had significant effects on disease activity (Table 5) but with no significant dose–response effect, and there was no significant association with fish consumption. Chi Squared analysis using standardised adjusted residuals showed that those not taking omega 3s were more likely to have increasing disease activity and less likely to be stable, and conversely, those taking omega 3s were less likely to have increasing disease activity and more likely to be stable. With respect to type of omega 3, those taking flaxseed oil were more likely to have decreasing disease activity and less likely to have increasing disease activity; those taking a combination of fish and flaxseed oil were more likely to have stable disease activity (Table 5).

In multivariate analyses, the odds of increasing disease activity increased for women by 52% (OR 1.518, 95% CI 1.042–2.211, $p = 0.03$). After controlling for age and gender, the odds of increasing disease activity was not significantly affected by fish consumption but decreased with flaxseed oil supplementation alone by 61% (OR = 0.394, 95% CI 0.230–0.673, $p = 0.001$).

Discussion

Evidence supports a role for fish consumption and omega 3 intake in the pathogenesis and expression of MS. Early work by Swank [19] suggested a considerably lower incidence of the disease in coastal parts of Norway where fish consumption was higher than in more central parts where meat and dairy consumption was more common. Large scale epidemiological studies have supported this observation [20,21], with MS incidence by country strongly inversely related to fish consumption. The effect is biologically

Table 5. Relapse rate (last 12 months rate, 95% CI) and disease activity [*n* (%)] in those with relapsing–remitting MS by fish consumption, omega 3 supplementation, dose, and type.

	Relapse rate[+]			Disease activity			
	Doctor-diagnosed 12-month relapse rate	Reduction #	*p*#	Decreasing	Increasing	Stable	*p*
Frequency of Fish Consumption							
<1/week	0.78 (0.68–0.88)		0.158[‡‡]	149 (38.4)	129 (33.2)	110 (28.4)	0.104
1–2/week	0.71 (0.61–0.81)	9.0%		224 (43.6)	161 (31.3)	129 (25.1)	
3+/week	0.64 (0.54–0.73)	17.9%		177 (45.3)	101 (25.8)	113 (28.9)	
Total				550 (42.5)	391 (30.2)	352 (27.2)	
Taking omega 3							
No	0.78 (0.67–0.89)			191 (41.8)	155 (33.9)*	111 (24.3)†	0.043
Yes	0.67 (0.60–0.74)	14.1%	0.085^	349 (42.6)	229 (28.0)†	241 (29.4)*	
Omega 3 type							
None	0.78 (0.67–0.89)			191 (41.8)	155 (33.9)*	111 (24.3)	0.005
Fish oil	0.72 (0.63–0.82)	7.7%	0.848[‡]	191 (42.3)	137 (30.3)	124 (27.4)	
Flaxseed oil	0.37 (0.26–0.48)	52.6%	< 0.001[‡]	67 (54.5)*	21 (17.1)†	35 (28.5)	
Fish and flaxseed oil	0.68 (0.56–0.79)	12.8%	0.610[‡]	85 (38.6)	62 (28.2)	73 (33.2)*	
Dose omega 3 (ml)							
0	0.78 (0.67–0.89)		0.186[‡‡]	191 (41.8)	155 (33.9)	111 (24.3)	0.212
1–10	0.68 (0.59–0.76)	12.8%		234 (42.3)	158 (28.6)	161 (29.1)	
11+	0.65 (0.53–0.77)	16.7%		106 (45.3)	64 (27.4)	64 (27.4)	

[+]Self-reported doctor diagnosed relapses.
[#]Compared with no supplementation, or for fish consumption to <1/week.
[^]Independent samples *t* test.
[‡]ANOVA, post hoc test, Fisher's least significant difference.
[‡‡]ANOVA, between groups comparison.
*Denotes significantly overrepresented as determined by standardised adjusted residuals.
†Denotes significantly underrepresented as determined by standardised adjusted residuals.

plausible, with omega 3s, which are naturally high in fish and seafood, being neuroprotective [22,23] and in high dose shown to modulate the immune response significantly in a cohort of people with MS [24]. Recent work has suggested more frequent fish consumption slows progression to disability [25].

Intervention studies have not produced uniform results. Swank and Dugan's [26] landmark case series of people with MS reducing saturated fat consumption and supplementing with marine oils showed dramatic reductions in long-term disability. Early randomised controlled trials of omega 6 supplementation suggested slowing of disability for people with early MS [27], but subsequent studies of omega 3 supplementation have not shown significant benefit over omega 6 supplementation [28,29].

Our data, from a large international cohort of people with MS, provide sound evidence of a significant association for fish consumption and omega 3 supplementation with a variety of important outcome measures. Consuming fish more frequently and taking omega 3 supplements, particularly flaxseed oil, were highly significantly associated with improvements in all measured components of quality of life, with a clear dose–response relationship for fish consumption. The improvements were not only statistically significant but were substantial in magnitude and therefore likely to be clinically significant.

Our data for an effect on disease activity among participants with relapsing–remitting MS were also strong, with regression analyses showing markedly less likelihood of disease activity increasing for flaxseed oil supplementation. The very large (over 52%) reduction in relapse rate seen for those taking flaxseed oil in univariate analysis, and 61% reduction in likelihood of worsening relapse rate in multivariate analysis suggests that future randomised trials should test the relationship between MS relapse rate and flaxseed oil rather than fish oil as a supplement. There was also significantly less disability for those taking omega 3 supplements, again with flaxseed oil having the strongest association, and for those eating fish more frequently, with a significant dose–response relationship. Our finding that flaxseed oil appears to have stronger associations with quality of life, disease activity and disability than fish oil is worthy of further study and may suggest that flaxseed oil is a preferred method of omega 3 supplementation for people with MS. The congruence between our multivariate and univariate results lends weight to the validity of the findings, and the clear associations of quality of life, and

to a lesser extent disease activity, with fish consumption and omega 3 supplementation, and the dose–response effect for fish consumption with many of these measures, lend strong biological plausibility to this being a real effect mediated by omega 3 fatty acids, although fish consumption appears to have an independent effect on these measures that may indicate some biological effect in addition to omega 3 content. Recent theories about MS causation have focused particularly on the dysregulation of fats as a key feature of the pathogenesis [30]. People with MS have been shown to have lower levels of polyunsaturated fatty acids in cells and higher levels of saturated fats [31,32]. Omega 3 fatty acids have immunomodulatory effects in people with MS [24], including inhibition of matrix metalloproteinase-9 [33], and are neuroprotective [22,23].

Limitations

Our data were self-reported; hence, there may have been inaccuracies due to recall difficulties, particularly for omega 3 supplementation and relapse rates over the previous 5 years. We were unable to verify any of the reported data. While ideally we would have had access to physician data on diagnosis and disease activity, this was not possible given the nature of our study. The NARCOMS has, however, previously reported 98.7% accuracy of self-reported diagnosis of MS in a validation study [34]. The large number of participants in our study should to an extent have compensated for occasional inaccuracies in self-reported data. We did not have data on serving size, only frequency of consumption, nor the extent to which oily fish was eaten, and hence omega 3. We also had no data on other types of seafood. We did not specifically request data on omega 6 consumption, and that may be a confounder in our results.

Given that this cohort of people is highly educated, has engaged with Web 2.0 platforms related to MS management and is particularly engaged [14] with lifestyle interventions shown to affect the risk of progression of MS and quality of life [3,4,6,35], omega 3 supplementation and fish consumption may be acting as surrogates for other healthy lifestyle behaviours and not in themselves be responsible for the associations. Once data analysis is complete for other lifestyle variables, planned regression analyses of these factors should elucidate more clearly these potential associations. Reverse causality may be involved in this association, as people with MS who do not deteriorate may be more likely to persist with recommended lifestyle behaviours and supplements, and disabled people may be more likely to lose heart and adopt unhealthy behaviours. It is clear that many healthy newly diagnosed people with MS use the internet to seek suggestions about how to stay well; diet and omega 3 supplementation in particular are often discussed in internet forums and are widely adopted, as our data show.

Reverse causality seems an unlikely explanation however of reduced disability and relapse rate with increasing frequency of fish consumption; such an explanation would require hypothesising that people who are less disabled and have fewer relapses are more likely to eat fish, and proportionately more fish the less disabled. This might be plausible in situations where increasing fish consumption was widely recommended around the world by treating doctors to people with MS wishing to delay disease progression, but this does not appear to be widely or commonly recommended.

Our data can be generalised widely to people with MS, particularly in western countries, given the geographical representation in this sample.

Conclusions

More frequent consumption of fish and omega 3 fatty acid supplementation are strongly associated with improved quality of life, reduced disease activity and disability in this large international cohort of people with MS. Further studies of dietary modification and randomised controlled trials of omega 3 supplementation for people with MS are required.

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Declaration of Interest

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Notice of Correction

The version of this article published online ahead of print on 3 Jun 2013 contained a number of minor typographical errors. These have been corrected for this version.

Following the previous notice of correction which was published online ahead of print on 17 Jun 2013, the authors noticed further errors in the text. These errors have been corrected for this version.