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Alcohol, coffee, fish, smoking and disease progression in multiple sclerosis

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Background: Certain lifestyle factors might influence disease activity in multiple sclerosis (MS).

Objectives: To investigate the consumption of alcoholic beverages, caffeinated drinks, fish and cigarette smoking in relation to disability progression in relapsing onset and progressive onset MS.

Methods: We conducted a cross-sectional survey amongst individuals with MS, registered by the Flemish MS society in Belgium. A time-to-event analysis and Cox proportional-hazard regression were performed with time to Expanded Disability Status Scale (EDSS) 6 (requiring a cane or support to walk for a distance of 100 m) as outcome measure. Hazard ratios for the time from onset and from birth were adjusted for age at onset, gender and immunomodulatory treatment.

Results: Data of 1372 persons with definite MS were collected. In the relapsing onset group, a decreased risk for reaching EDSS 6 was found in regular consumers of alcohol, wine, coffee and fish compared with those who never consumed these substances. Cigarette smoking was associated with an enhanced risk for reaching EDSS 6. In the progressive onset group, no association with the risk of reaching EDSS 6 was found, except for the type of fish. Preference for fatty fish was associated with an increased risk to reach EDSS 6, when lean fish was taken as the reference category.

Conclusion: Consumption of alcoholic beverages, coffee and fish were inversely associated with progression of disability in relapsing onset MS, but not in progressive onset MS. These findings allow to support the hypothesis that different mechanisms might underlie progression of disability in relapsing and progressive onset MS.

Introduction

Multiple sclerosis (MS) is a multifocal inflammatory disease of the central nervous system, leading to demyelination and neuronal damage. Evidence suggests that both genetic and environmental factors contribute to the development of MS [1]. The disease course appears to be associated by a number of factors, including several lifestyle factors [2]. Some studies have suggested that smoking promotes disease progression [3]. Results from a questionnaire in Northern California revealed a dose-response association between alcohol consumption and lower disability scores in patients with MS, irrespective of the course of MS [4]. The intake of saturated fatty acids and animal fat has been repeatedly correlated with MS mortality, whereas fish and vegetable fat intake were found to be inversely related [5,6]. The severity of experimental allergic encephalomyelitis (EAE), which is an animal model for MS, could be reduced using caffeine treatment [7] and a green tea polyphenol (EGCG) [8].

The mechanisms underlying the progression of disability in MS might be different in relapsing and progressive MS. The accumulation of disability in relapsing MS could be explained by focal inflammatory lesions, leading to demyelination and focal axonal injury. The progression of disability in progressive MS appears to be caused by diffuse axonal degeneration. Epidemiological studies and histopathological investigations have demonstrated that inflammation and degeneration are dissociated, at least partially [9]. Therefore, dis-

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ability progression, whether caused by focal demyelinating lesions or diffuse axonal degeneration, might be differentially affected by lifestyle factors.

The goal of our study was to investigate whether there is an association between the consumption of alcoholic beverages, caffeinated drinks, fish intake, cigarette smoking and disease progression in relapsing onset and progressive onset MS.

Materials and methods

The ethics committee of the Universitair Ziekenhuis Brussels and the local ethics committee of the National MS Center Melsbroek, Belgium, approved the study.

Study population

A request to participate in this study was sent by mail to the 3320 individuals with MS, registered by the Flemish MS society in September 2009. The invitation letter explained study goals and instructions. Persons with MS were asked to sign a consent statement if they decided to participate.

The MS society provides psychosocial support to individuals with MS and their families in each province of Flanders. A document of the diagnosis of MS is requested. On the basis of a regional MS prevalence of 74 per 100 000 in Flanders, Belgium [10], we estimate more than half of the total Flemish MS population is registered by the Flemish MS Society. The proportion of youngsters, registered by the Flemish MS society, is small. According to the annual report of 2009, 12.2% were younger than 40 years of age whereas 34.8% had reached the age of 60.

Participation consisted of completing a questionnaire with questions on demographics, MS characteristics, current consumption of alcohol, wine, coffee, tea, fish and cigarette smoking. Participants had to indicate whether they had a definite, probable or possible diagnosis of MS. MS characteristics included the year of first MS symptoms, relapsing or progressive disease onset and use of immunomodulatory drugs.

We used the self assessment scale of disability developed for the European study on costs and quality of life in MS [11], which is based on the original validated description in the Expanded Disability Status Scale (EDSS) [12] and on the patient determined disease steps instrument [13]. Subjects were asked to select from a series of statements describing limitations and walking disability. The self assessment scale of disability allowed participants to be categorized into 11 steps of disability, from 0 to 10 corresponding to an EDSS score of 0, 1–1.5, 2–2.5, 3–3.5, 4–4.5, 5–5.5, 6, 6.5, 7–7.5, 8–8.5, 9–9.5. The year of reaching EDSS 6 (using a cane or support to walk for a distance of 100 m) was recorded separately.

On the basis of consumption rates in other studies [14], participants were asked to classify the intake of alcoholic beverages into different levels, including, no drinking, less than one drink weekly, one to seven drinks weekly and two or more drinks daily. As a small number of heavy drinkers were expected [4,15], the answers were categorized into no drinking, minimal drinking (<1 drink weekly) and moderate drinking (from 1 drink weekly to two or more drinks daily). We did not ascertain the type of alcoholic beverage, but added a separate question assessing the intake of wine. Similar questions addressed the consumption of coffee and tea allowing categorization into no drinking, occasional drinking (less than one cup daily) and daily drinking. In analogy with other studies, the levels of fish intake were categorized into less than once monthly, once monthly to once weekly and 2 or more times weekly [16]. A separate question addressed the preference of fat versus lean fish to assess differential effects [17]. The current smoking status included the possibilities of no smoking, occasional smoking (not daily) or daily smoking.

Completed questionnaires and consent forms were returned to the investigators using a pre-addressed and pre-paid envelope. To increase the response rate, a reminder announcement was made in the journal and on the website of the Flemish MS society in December 2009. Upon receipt, questionnaires were checked to ensure the data were complete. When incomplete, participants were contacted whenever possible.

Only data from participants who reported a definite MS diagnosis were considered for further analysis. Data from probable and possible MS participants were excluded.

Outcome variables

The outcome measure was the time from onset to reach sustained EDSS 6 in the self assessment scale of disability, corresponding to EDSS 6. As this step signifies the use of a cane or support to walk for a distance of 100 m, it is considered a reliable milestone during the course of MS. Time from disease onset to EDSS 6 and time from birth to EDSS 6 were calculated using the year of MS onset, the year of birth and the year of reaching the irreversible disability step of EDSS 6.

Statistical analysis

All analyses were stratified according to relapsing onset or progressive onset.

Predictive variables included the consumption of alcoholic beverages, wine, coffee, tea, fish and cigarette smoking.

MS variables included gender, age at onset and current immunomodulatory treatment.

We accepted the year of survey as the year of reaching sustained EDSS 6 for participants with EDSS 6 or more, who did not indicate the year of reaching EDSS 6.

Time-to-event plots using time from disease onset to EDSS 6 and time from birth to reach EDSS 6 were constructed using the Kaplan–Meier method, with differences in survival analysis assessed using the log rank test. From these Kaplan–Meier curves, the median time-to-event and 95% CI were calculated.

For each predictive variable, Cox proportional-hazards regression modelling, adjusting for gender, age at onset and immunomodulatory treatment, was used to estimate hazard ratios for time from onset to EDSS 6 and for time from birth to EDSS 6. Never users were the reference group.

Data were analysed using PASW version 17.0 for windows (SPSS Inc., Chicago, IL, USA).

Results

Participant characteristics

We obtained responses from 1431 individuals (43%) with 1407 usable questionnaires. Data from 1372 subjects with definite MS were included in the analysis. Our study sample was representative of the people registered by Flemish MS society, as 14% were 40 years or younger and 30.3% were 60 years or older (data not shown). Characteristics of our study population are shown in Table 1. Almost 35% (479/1372) of the respondents reported a progressive onset. Fifty one per cent (704/1372) had reached EDSS 6 or more, after a mean disease duration of 19.7 years. We imputed the year of survey as the year of reaching EDSS 6 in 155/704 (22%) participants with EDSS 6 or more, who did not indicate the year of reaching this milestone.

Table 1 Baseline chacteristics of the relapsing and onset progressive onset MS

Characteristic	Relapsing onset (n = 893)	Progressive onset (n = 479)
Female- number (%)	675 (75.6%)	298 (62.2%)
Age at survey, year		
Mean	50.3	58.6
Median (range)	50 (17–85)	59 (23–89)
Age at onset, year		
Mean	31.5	37.3
Median (range)	30 (8–65)	37 (9–69)
Disease duration, year		
Mean	18.8	21.4
Median (range)	17 (0–63)	20 (0–62)
EDSS ≥6 at survey – number (%)	321 (35.9%)	383 (80%)
Treatment at survey – number (%)		
Interferon beta	358 (40.1%)	101 (21%)
Glatiramer acetate	95 (10.6%)	19 (4%)
Natalizumab or mitoxantrone	70 (7.8%)	19 (4%)
No immunomodulatory treatment	370 (41.4%)	349 (71%)

Kaplan Meier estimates

The results are shown in Table 2A (relapsing onset MS) and in Table 2B (progressive onset MS).

In relapsing onset MS, the time from onset to EDSS 6 differed significantly according to the consumption category of alcohol, wine and smoking status. The time from birth to EDSS 6 analysis resulted, in addition, in a significant difference according to the consumption category of coffee and fish. Consumption of tea did not reveal significant differences.

In the progressive onset MS, consumption of alcoholic beverages, wine, coffee, tea and fish as well as cigarette smoking did not significantly affect the time to reach EDSS 6.

Cox proportional-hazards analysis

The hazard ratios adjusted for age at onset and immunomodulatory treatment are shown in Table 3A (relapsing onset MS) and in Table 3B (progressive onset MS).

In the relapsing onset MS, alcohol, wine, coffee and fish consumption were associated with a reduced risk to reach EDSS 6. The decreasing hazards for alcohol, coffee and fish suggest a dose- effect relationship. The majority of the participants reporting moderate drinking of alcoholic beverages consumed 1–7 drinks weekly (81.5% of the participants for alcoholic beverages in general and 82.7% for wine). The type of fish, fat or lean, did not matter. Smoking was associated with an increased risk to reach EDSS 6 in relapsing onset MS.

In progressive onset MS, no association with the risk of reaching EDSS 6 was found, except for the type of fish. In progressive onset MS, preference for fatty fish was associated with an increased risk to reach EDSS 6, when preference for lean fish was taken as the reference category.

The contrasting results for alcohol and smoking called for additional confounder analyses in both the relapsing onset and the progressive group. The results of these Cox regression analyses, with alcoholic beverage, cigarette smoking, gender, age at onset and

Table 2 Kaplan–Meier estimates of the time to sustained EDSS 6 in (A) relapsing onset and (B) progressive onset multiple sclerosis

Variable	Number	Median years from onset (95%CI)	*P*-value	Median years from birth (95% CI)	*P*-value
(A) Relapsing onset MS					
Alcoholic beverage					
No	218	25.0 (22.6–27.4)	**0.001**	57.0 (54.7–59.3)	**0.006**
Minimal	311	28.0 (24.8–31.2)		58.0 (55.5–60.6)	
Moderate	352	32.0 (26.7–37.3)		63.0 (59.3–66.7)	
Wine					
No	237	26.0 (23.3–28.7)	**0.028**	57.0 (54.8–59.2)	**0.002**
Minimal	355	27.0 (24.3–29.7)		58.0 (54.9–61.1)	
Moderate	289	30.0 (25.5–34.5)		63.0 (59.8–66.2)	
Coffee					
Never	134	25.0 (19.7–30.3)	0.09	56.0 (53.4–58.6)	**0.002**
Occasionally	172	25.0 (23.0–27.0)		57.0 (53.9–60.1)	
Daily	575	30.0 (27.5–32.5)		60.0 (57.5–62.5)	
Tea					
Never	356	28.0 (25.1–30.9)	0.98	58.0 (56.1–59.9)	0.62
Occasionally	345	28.0 (24.5–31.5)		59.0 (54.6–63.4)	
Daily	179	27.0 (24.9–29.1)		60.0 (54.9–65.1)	
Fish					
< 1 monthly	140	24 (18.3–29.7)	0.14	56 (53.0–58.9)	**0.01**
1 monthly–1 weekly	604	27 (24.7–29.3)		60 (56.9–63.1)	
2 times or more weekly	148	31 (28.9–33.1)		58 (54.0–62.0)	
Preference of fish					
Lean fish	310	28 (25.0–31.0)	0.98	58 (53.6–62.4)	0.79
No preference	409	27 (24.0–30.0)		58 (56.0–60.0)	
Fatty fish	149	28 (23.0–33.0)		62 (57.2–66.8)	
Current cigarette smoking					
No	655	28.0 (25.6–30.4)	**< 0.001**	60.0 (57.5–62.5)	**< 0.001**
Occasionally	23	20.0 (15.8–24.2)		50.0 (47.5–52.5)	
Daily	203	28.0 (23.3–32.7)		57.0 (54.4–59.6)	
(B) Progressive onset MS					
Alcoholic beverage					
No	171	16.0 (13.5–18.5)	0.92	55.0 (52.4–57.6)	0.99
Minimal	145	14.0 (9.3–18.7)		55.0 (52.0–58.0)	
Moderate	159	15.0 (12.1–17.9)		55.0 (52.6–57.4)	
Wine					
No	178	16.0 (13.3–18.7)	0.65	54.0 (51.7–56.3)	0.24
Minimal	149	13.0 (10.2–15.8)		55.0 (52.2–57.8)	
Moderate	148	15.0 (12.0–18.0)		56.0 (53.5–58.5)	
Coffee					
Never	85	17.0 (12.9–21.1)	0.23	55.0 (50.7–59.3)	0.42
Occasionally	69	13.0 (5.6–20.4)		53.0 (48.4–57.6)	
Daily	321	15.0 (13.2–16.8)		55.0 (53.2–56.8)	
Tea					
Never	257	15.0 (12.3–17.7)	0.08	55.0 (53.5–56.5)	0.34
Occasionally	122	12.0 (8.6–15.4)		55.0 (51.6–58.4)	
Daily	95	17.0 (12.9–21.1)		57.0 (53.6–60.4)	
Fish					
< 1 monthly	81	15.0 (10.4–19.6)	0.73	52.0 (44.8–59.2)	0.83
1 monthly–1 weekly	311	15.0 (12.6–17.4)		55.0 (53.1–56.9)	
2 times or more weekly	84	15.0 (12.7–17.3)		55.0 (52.5–57.5)	
Preference of fish					
Lean fish	171	19.0 (15.7–22.3)	0.11	55.0 (51.9–58.1)	0.10
No preference	205	14.0(12.0–16.0)		55.0 (52.9–57.1)	
Fatty fish	85	13.0 (10.0–16.0)		55.0 (52.3–57.7)	
Current cigarette smoking					
No	360	15.0 (13.1–16.9)	0.93	55.0 (53.3–56.7)	0.19
Occasionally	14	17.0 (12.7–21.3)		53.0 (44.9–61.1)	
Daily	100	15.0 (10.6–19.4)		53.0 (49.7–56.3)	

Bold values indicate ***P***-values < 0.05.

Table 3 Adjusted hazard ratios for time to sustained EDSS 6 in relapsing onset (A) and progressive onset multiple sclerosis (B)

Variable	Number	From onset (95% CI)[a]	From birth (95% CI)[a]
(A) Relapsing onset MS			
Alcoholic beverage			
No	218	1.0 (Reference)	1.0 (Reference)
Minimal	311	0.84 (0.64–1.10)	0.85 (0.65–1.11)
Moderate	352	**0.61 (0.46–0.80)**	**0.60 (0.46–0.80)**
Wine			
No	237	1.0 (Reference)	1.0 (Reference)
Minimal	355	0.78 (0.60–1.01)	**0.76 (0.50–0.98)**
Moderate	289	**0.67 (0.50–0.89)**	**0.62 (0.47–0.83)**
Coffee			
Never	134	1.0 (Reference)	1.0 (Reference)
Occasionally	172	**0.67 (0.46–0.97)**	0.70 (0.48–1.00)
Daily	575	**0.60 (0.44–0.81)**	**0.59 (0.43–0.80)**
Tea			
Never	356	1.0 (Reference)	1.0 (Reference)
Occasionally	345	1.12 (0.86–1.43)	1.17 (0.91–1.52)
Daily	179	0.95 (0.70–1.28)	1.06 (0.79–1.43)
Fish			
< 1 monthly	140	1.0 (Reference)	1.0 (Reference)
1 monthly–1 weekly	604	**0.63 (0.47–0.85)**	**0.64 (0.47–0.86)**
2 times or more weekly	148	**0.60 (0.41–0.87)**	**0.60 (0.41–0.86)**
Preference of fish			
Lean fish	310	1.0 (Reference)	1.0 (Reference)
No preference	409	0.83 (0.63–1.10)	0.85 (0.64–1.11)
Fatty fish	149	0.94 (0.65–1.37)	0.97 (0.67–1.39)
Cigarette smoking			
Never	655	1.0 (Reference)	1.0 (Reference)
Occasionally	23	**3.03 (1.64–5.60)**	**3.05 (1.65–5.65)**
Daily	203	**1.35 (1.03–1.77)**	1.31 (0.99–1.72)
(B) Progressive onset MS			
Alcoholic beverage			
No	171	1.0 (Reference)	1.0 (Reference)
Minimal	145	1.02 (0.80–1.31)	0.97 (0.76–1.24)
Moderate	159	1.01 (0.79–1.30)	0.99 (0.77–1.27)
Wine			
No	178	1.0 (Reference)	1.0 (Reference)
Minimal	149	0.87 (0.68–1.11)	0.81 (0.63–1.03)
Moderate	148	0.93 (0.72–1.19)	0.90 (0.70–1.16)
Coffee			
Never	85	1.0 (Reference)	1.0 (Reference)
Occasionally	69	1.29 (0.90–1.85)	1.33 (0.93–1.91)
Daily	321	1.18 (0.90–1.55)	1.19 (0.90–1.56)
Tea			
Never	257	1.0 (Reference)	1.0 (Reference)
Occasionally	122	1.18 (0.92–1.53)	1.18 (0.92–1.52)
Daily	95	0.84 (0.64–1.10)	0.81 (0.62–1.06)
Fish			
< 1 monthly	81	1.0 (Reference)	1.0 (Reference)
1 monthly–1 weekly	311	1.01 (0.77–1.32)	0.92 (0.70–1.21)
2 times or more weekly	84	1.06 (0.76–1.49)	1.00 (0.72–1.40)
Preference of fish			
Lean fish	171	1.0 (Reference)	1.0 (Reference)
No preference	205	1.16 (0.89–1.51)	1.20 (0.92–1.57)
Fatty fish	85	**1.56 (1.12–2.17)**	**1.45 (1.04–2.03)**
Cigarette smoking			
Never	360	1.0 (Reference)	1.0 (Reference)
Occasionally	14	1.10 (0.54–2.24)	1.26 (0.62–2.56)
Daily	100	1.13 (0.87–1.47)	1.12 (0.86–1.45)

[a]Adjusted for gender, age at onset and immunomodulatory treatment. Bold values indicate confidence intervals (CI) that do not include 1.

immunomodulatory treatment simultaneously entered into each model, indicate that no obvious potential confounding is present for alcoholic beverage and cigarette smoking (data not shown).

Discussion

Our study addressed the risk of progression to EDSS 6 in individuals with MS and found different associations between consumption patterns and progression of disability in relapsing onset and progressive onset MS. Higher consumption of alcoholic beverages, coffee and fish was associated with a decreased likelihood to reach milestone EDSS 6 in relapsing onset MS whereas smoking was associated with an increased likelihood to reach EDSS 6. In progressive onset MS, preference for fatty fish was associated with an increased risk to reach EDSS 6, when preference for lean fish was taken as the reference category.

These observations have to be distinguished from the results of case–control and cohort studies addressing the risk of developing MS in association of lifestyle factors. The risk of MS has been related to coffee and hard liquor consumption as well as smoking, but only smoking contributed independently [18]. An increased fish consumption has been been associated with a reduced risk of MS in a case–control study [19], but not in two large cohorts [20]. As the risk of developing MS might be affected by other factors than the risk for progression in established MS, we further focus on progression in MS.

A Californian survey revealed alcohol consumption to be associated with lower EDSS scores in individuals with MS, but did not distinguish between the different forms of onset [4]. Our findings are in accordance with this observation in subjects with relapsing onset MS. The decreasing point estimates, when compared minimal and daily consumers to a reference group of non-consumers suggest the possibility of a dose effect. The reduced risk to reach EDSS 6 in moderate alcohol drinkers corresponded to 1–7 drinks weekly in the large majority of respondents. The finding of a similar association for wine is in agreement with previous studies that found no significant differences in effects according to the type of alcoholic beverage (wine or beer) [21,22]. As the progression of disability may have changed lifestyle, we cannot exclude reverse causality. However, this association was not found in progressive onset MS. A possible protective effect of moderate alcohol consumption in relapsing MS might be explained by a beneficial impact on the immune system. Moderate consumption of either wine or beer has been associated with lower levels of systemic inflammation [22]. An inverse and dose-related association of alcohol consumption with both risk and severity has also been reported in rheumatoid arthritis [23]. Furthermore, resveratrol, a non-flavonoid polyphenol, which reaches high levels in red wine, has anti-inflammatory and antioxidant properties. In experimental models it has been shown to protect against various neurological disorders [24].

The association of coffee consumption with a reduced progression of disability in relapsing onset MS has not been reported before. Daily coffee drinkers are ingesting considerable amounts of caffeine. At concentrations relevant for human consumption, caffeine seems to suppress the production of the proinflammatory cytokines, such as tumour necrosing factor (TNF)-α [25] and also has neuro-protective properties, attributed to phosphodiesterase inhibition and non-specific antagonism of adenosine receptors [26]. Other factors related to coffee consumption may be involved as well. The possibility that the inverse relation between coffee consumption and progression of disability might be due to a reduced consumption in subjects with a higher disability cannot be excluded fully. However, a nearly identical pattern of coffee consumption was found in progressive onset MS and no association with progression to EDSS 6 was evident.

Tea contains high concentrations of polyphenols and other phytochemical compounds, including caffeine, with anti-inflammatory and neuroprotective properties in a wide array of experimental model [27]. A green tea polyphenol (EGCG) reduced the severity of EAE by both limiting inflammation and reducing neuronal damage [8]. However, the consumption of tea in our study did not affect the time to reach EDSS 6 in relapsing onset MS. A reason for the discrepancy with the findings of coffee might be the lower consumption rate of tea or the low dose of caffeine. A cup of tea contains approximately half the amount of caffeine of that found in coffee.

The association of a higher fish consumption with a lower progression rate in relapsing onset MS could be explained by a healthier lifestyle in younger and less disabled patients. Alternatively, a protective influence of a diet rich in fish might be suggested, which is in line with findings from laboratory studies and observations in various diseases [28]. Fish are a rich source of n-3 polyunsaturated fatty acids (PUFAs), which are involved in diverse physiological processes with potential health benefits. The anti-inflammatory effects of n-3 PUFA are thought to be mediated in part by a reduced production of interleukin-1 and TNF-α [28]. Intervention studies with PUFA supplementation in MS have, however, shown conflicting results [29]. A trend in favour of treatment with n-3 PUFA was found in a randomized clinical trial in 312 patients

with relapsing remitting MS without reaching significance [30]. Fish oil supplementation together with vitamins and dietary advice for 2 years in 16 relapsing MS patients resulted in reduced clinical disease activity compared with pre-study values [31]. Next to providing PUFAs, a diet rich in fish might also be a source of vitamin D, as has been suggested in a case–control study assessing the MS risk in Norway in relation to the latitude [19].

As the risk to reach EDSS 6 did not differ according to the consumption levels of fish in progressive onset MS, the association of a preference for fatty fish with an increased risk to reach EDSS 6 is difficult to explain. This should be confirmed in further studies. However, if confirmed, one possible explanation might be that contaminants in fatty fish, such as heavy metals and dioxins may enhance the neurodegenerative process in progressive onset MS.

The association of cigarette smoking was limited to the relapse onset group. The pronounced effect in occasional smokers is probably due to the small number in this group. The number of pack-years has not been calculated, but our results are in line with previous reports. Although not all studies agree, smoking appears to promote disease progression [3,32–34]. Burning cigarettes produce 6000 different components in addition to nicotine, many of which are known to be toxic, mutagenic or carcinogenic. Cigarette smoking also affects the immune system, both increasing autoimmune reactions and decreasing systemic activity against infections [35]. The possible mechanisms in MS are not well understood.

Our study has a number of methodological limitations. First, the response rate is moderate and we have no clinical information on subjects who did not respond to the survey. The proportion of persons aged 60 or above in the registry of the Flemish MS Society (34.8%) and in our study sample (30.3%) is comparable, but high compared with prevalence studies (21–26%) [10,36]. So, our study sample is probably representative of the MS society population, but not of the entire MS population in Flanders. Second, the number of respondents with progressive onset MS is higher than expected, includes a mild female predominance and a substantial number of subjects treated with immunomodulation. In view of these observations and the lower difference in age at onset between both groups than expected, we cannot exclude some misclassification. However, the present distribution could also reflect a bias in the selection of patients due to the nature of the services provided by the MS society. Besides, some neurologists treat individuals with progressive onset MS off label in an attempt to reduce inflammation. Third, we relied on self-reported data with regard to MS diagnosis, disease onset and disability. However, previous studies have supported the validity of the diagnosis of MS reported by registry participants [37] and very good correlations have been found with self-administered EDSS using ambulation [38]. A recent study on the validity of patient-derived data concluded that self-reported questionnaires can provide reliable retrospective data on year of disease onset and time to disability milestones, including EDSS 6 [39]. Fourth, the cross-sectional nature of the study does not take into account the accumulated consumption and changes in consumption habits over time. This information might be helpful, but is difficult to get and prone to recall bias. We do not expect current consumption patterns to explain the accumulation of disability over years, but cannot exclude these patterns might be rather consistent over time and represent a certain lifestyle. Anyway, the reported associations do not necessarily imply causality. Fifth, with the exception of the question assessing the consumption of wine, we did not ascertain the types of alcoholic beverages. Sixth, there were missing values with regard to the time of reaching sustained EDSS 6. Entering the year of survey as the year of reaching sustained EDSS 6 could have affected our findings.

As we cannot exclude reverse causality, our results do not allow to establish a protective effect of the use of alcoholic beverages, coffee and fish on the disease course in relapsing MS. However, the difference in associations between relapsing and progressive onset MS is similar to the difference in effects of immune therapies in MS. These therapies reduce relapse-mediated progression of disability in MS, but do not alter the course of progressive MS. Our results should only be regarded as hypothesis-generating. To find out whether a lifestyle approach has potential benefits in relapsing MS, experimental trials with an improved methodology are needed.

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Disclosure of conflict of interest

No conflicts of interests are reported. Both M.B. D'hooghe and G. Nagels served as a medical advisory board member, received honoraria from Bayer-Schering, Biogen Idec, Merck-Serono, Novartis and Allergan as part of a consultancy agreement and research support from Sanofi-Aventis. P. Haentjens and J. De Keyser report no disclosures.

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