Associations of moderate alcohol consumption with clinical and MRI measures in multiple sclerosis

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Objective: To examine the associations of alcohol consumption patterns with disability and brain injury in multiple sclerosis (MS) patients.

Design: This study included 423 subjects (272 MS patients, 151 healthy controls) participating in a study of clinical, environmental and genetic risk factors in MS. Disability was assessed with the Expanded Disability Status Scale (EDSS) and the MS Severity Scale (MSSS). Brain injury was assessed using the quantitative MRI measures of T2-lesion volume (T2-LV), T1-LV, normalized volumes of brain parenchyma (NBV), gray matter (NGMV) and lateral ventricle (NLVV). Information related to alcohol-consumption patterns was obtained with standardized questionnaire during an in-person interview. The associations of alcohol consumption variables with disability and MRI measures were assessed in regression analyses.

Results: The frequency of MS patients who did not consume alcohol after MS onset (19.4%) was higher than the frequency before MS (p = 0.001). The EDSS, NGMV and NLVV exhibited a non-linear dependence on duration of alcohol consumption after MS onset: non-linear regression analyses indicated that EDSS and NLVV were lower and the NGMV was greater in MS patients who had consumed for a period of 15 years or less after MS onset compared those who did not consume alcohol or consumed it for more than 15 years.

Conclusion: The duration of alcohol consumption is associated with disability and MRI measures in MS. Prospective, longitudinal studies of the role of alcohol in MS disease progression are warranted.

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1. Introduction and background

Central nervous system damage (CNS) in multiple sclerosis (MS) is believed to be predominantly the result of abnormal immune responses against the patient's nervous tissue (Sospedra and Martin, 2005; Frohman et al., 2006). However, MS is also associated with neurodegeneration and axonal loss (Trapp et al., 1998).

The alcohol (ethanol, ethyl alcohol) ingested from alcoholic beverages rapidly crosses the blood–brain barrier and is capable of exerting effects on the immune and nervous systems. Alcohol has direct pharmacological effects on many different parts of brain including the cerebral cortex, cerebellum, the limbic system and the hypothalamic–pituitary axis (Clapp et al., 2008). The short-term behavioral and physiological impairments caused by alcohol affect mood, speech, walking, vision, memory, judgment and reaction times. Alcohol is addictive and can cause longer-term functional and structural injury to the brain (Neiman, 1998) and other organs including the liver (Testino, 2008).

Alcohol generally suppresses innate immune responses at low and moderate doses and increases immune responses at high doses (Goral et al., 2008). Acute alcohol treatment reduces monocyte production of cytokines such as tumor necrosis factor-α and interleukin-1β whereas interleukin-10, transforming growth factor-β and interleukin-12 are enhanced (Mandrekar et al., 1996; Szabo et al., 1996). Acetaldehyde, which is produced as a result of alcohol metabolism, can react rapidly with proteins and the covalent modification can potentially render endogenous proteins immunogenic. This may explain why chronic alcoholics produce higher levels of immunoglobulins and autoantibodies (Cook, 1998). Excessive alcohol increases the risk of infections such as bacterial pneumonia and tuberculosis (MacGregor and Louria, 1997). Alcohol increases the activity of nuclear factor-kappa B and Fas in helper T cells (Barve et al., 2002). Alcohol is a disease-promoting co-factor in HIV and alcoholics with HIV express markers of chronic T-cell activation (MacGregor and Louria, 1997). Chronic alcohol intake also alters the production of sex hormones such as testosterone in men and estrogen in women (Kovacs and Messingham, 2002).
At low doses of alcohol, allosteric binding and activation of gamma aminobutyric acid-A receptors mediates its effects on anxiety, disinhibition and sedation (Mihic, 1999; Davies, 2003; Paul, 2006). However, alcohol can also have antagonistic effects on glutamate binding to the N-methyl D-aspartate receptor, which may mediate the alcohol-associated blackouts. Neuropsychological impairments and brain abnormalities including atrophy of nerve cells and loss of brain volume are frequent in alcoholics (Oscar-Berman et al., 1997). A study of 140 Canadian MS patients found that approximately 1 in 6 patients consumed alcohol to excess in their lifetime and drinking problems were associated with psychiatric diagnoses (Quesnel and Feinstein, 2004).

Smoking, exposure to Epstein-Barr virus and vitamin D are the most widely investigated environmental factors in MS; however, no single environmental factor has been identified as causal (Marrie, 2004). Notwithstanding, alcohol is a common environmental exposure whose effects on MS disease progression have not been widely investigated. Because the available data support the possibility that alcohol may be associated with immune-modulation and neurodegeneration, our working hypothesis was that clinical and MRI measures in MS patients could be adversely affected by alcohol use. Given the paucity of prior clinical data on effects of alcohol in MS, the goal of this study was to assess the associations of alcohol consumption patterns with brain injury and disability in MS.

2. Methods

2.1. Study population

2.1.1. Ethics statement

The study was approved by the University at Buffalo Human Subjects Institutional Review Board and all participants provided written informed consent.

2.1.2. Study design

This project utilized data from an ongoing study of genetic and environment risk factors in MS progression. A large cohort of patients with MS, clinically isolated syndrome (CIS), healthy controls (HC) and controls with other neurological diseases (OND) were enrolled.

All subjects provided responses to a structured questionnaire administered during an in-person interview at the time of the clinical visit. The responses to the questionnaire were transcribed to a computer by the interviewer.

The subjects received a neurological examination and an MRI scan of the brain. The evaluators were blinded to the subjects’ responses to the questionnaire.

The study enrolled a total of 499 subjects, including 289 MS, 21 CIS, 163 HC and 26 OND. MRI examinations, using a standardized protocol described below, were available for 20 (95.2%) CIS, 243 (84.1%) MS, 73 (45.6%) HC, and 15 (42.3%) OND subjects.

Patients with OND, CIS and neuromyelitis optica were also excluded to avoid the effects of small samples and confusion stemming from three more groups. Subjects under 21 years of age were excluded based on the legal drinking age (1 RR-MS case ≥18 years, 10 RR-MS children <18 years and 10 HC ≥18 years, 2 HC ≤18 years were excluded on age) yielding 423 subjects: 151 HC and 272 CDMS in the statistical analysis.

2.1.3. Alcohol consumption

The alcohol consumption questionnaire was comprised of selected questions obtained from a review of several validated questionnaire sources including those from the National Institute of Alcohol Abuse and Alcoholism (www.niaaa.nih.gov) and the National Health and Nutrition Examination Survey (NHANES) from the Centers for Disease Control (http://www.cdc.gov/nchs/about/major/nhanes/questexam.htm).

One drink was defined as a 12-ounce can (or bottle) of beer, a four-ounce glass of wine, one shot (1.5 oz) of liquor or a 12-ounce bottle of wine cooler (http://pubs.niaaa.nih.gov/publications/Practitioner/PocketGuide/pocket_guide2.htm). Never Drinkers were defined as individuals who had consumed ≤12 drinks in their life. The alcohol consumption information in MS subjects was obtained for the period before MS onset, the period after MS onset, and for the preceding 3 months.

The questionnaire obtained information on age of first alcohol consumption, years of drinking, frequency of alcoholic drinks and the type of preferred drink.

The total duration of alcohol consumption in MS patients was calculated as the sum of the midpoints of the scales for durations of alcohol consumption before and after MS onset. The calculated total duration of alcohol consumption for both MS patients and controls was categorized into four groups: None, >0 but ≤10 years, >10 but ≤20 years, and >20 years.

The duration of drinking before and after MS onset categories was reduced to four groups: None, ≤5 years, >5 but ≤15 years, and >15 years. The thresholds for the groups were based on having approximately equal numbers of MS patients after MS onset in each of the groups.

The preferred drinks were reduced to five groups: None, Beer (comprised of beer and wine coolers), Wines (comprised of red wine, white wine, sparkling wines and champagne), Spirits (comprised of whisky, gin, vodka etc.) and Other. The drinks were grouped based on alcohol content. Alcohol content was obtained from the National Institute for alcohol abuse web site: http://www.rethinkingdrinking.niaaa.nih.gov/ToolsResources.

The frequency of drinking categories was reduced to four groups: None, ≤1 drink a week, ≤1 drink a day and >1 drink a day. Subjects who indicated that they had never consumed alcohol (Never Drinkers) were assigned 0 for duration of drinking and frequency of drinking variables and “None” for the preferred drink category.

2.2. MRI acquisition and analysis

2.2.1. Image acquisition

Patients underwent brain MRI on a 3-T General Electric Signa 4x/Lx, scanner. Axial dual fast spin-echo (FSE) T2/PD-weighted image (WI), 3D-spoiled-gradient recalled (SPGR) T1-WI, spin echo (SE) T1-WI with and without gadolinium (Gd) contrast, fast attenuated inversion recovery (FLAIR) scans were acquired.

2.3. Image analysis

The MRI analysts were blinded to patients’ clinical characteristics and clinical status. The following MRI measures were computed: T1-, T2- and gadolinium (Gd) contrast-enhancing (CE) lesion volumes (LV), measures of central, global and tissue specific brain atrophy.

2.3.1. Lesion measures

T2- and T1-LVs were obtained with a semi-automated edge detection contouring-thresholding technique previously described (Zivadinov et al., 2001).

2.3.2. Global and central atrophy measures

The SIENAX cross-sectional software tool was used, with correction for T1-hypointensity misclassification, for brain extraction and tissue segmentation (Smith et al., 2002). We acquired and used normalized volume measures of the whole brain (NBV), GM (NGMV), white matter (NWMV), and lateral ventricles (NLV), as described previously (Zivadinov et al., 2007).
2.4. Data analysis

The Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, version 15.0) statistical program was used for all statistical analyses. The EDSS (categorized into four groups: 0–1.5, 2.0–3.0, 3.5–5.5 or ≥6.0) was assessed with ordinal regression. The MS Severity Scale (MSSS) (Roxburgh et al., 2005) was calculated from the EDSS, disease duration values and the global reference data set using software downloaded from http://www-gene.cimr.cam.ac.uk/MSgenetics/GAMES/MSSS/Readme.html. To reduce skewness (Weinstock-Guttman et al., 2011), the T2 lesion volume (LV) and T1-LV were normalized by cube-root transformation.

Independent sample t-tests were used to test for differences in means of continuous demographic variables such as age, age of onset, and disease duration. The chi-square test (or Fisher exact test where appropriate) was used for analysis of count variables for categorical data.

Age of onset (dependent variable) was assessed in regression analysis with sex, frequency of alcohol consumption before MS onset and alcohol content of preferred drink before MS as predictors.

The relationships between the disability and MRI variables with duration of alcohol use after MS were found to be non-linear in exploratory analyses. In regression analyses, the EDSS and the MRI variables were treated as independent variables in regression analysis with the following predictors: sex, disease duration, and linear and quadratic terms for duration of alcohol use after MS onset. The duration of alcohol use was centered around the mean prior to non-linear regression. MSSS was assessed using the same predictors except that disease duration was replaced by age.

A Type I error level of ≤0.05 was used to assess significance for demographic and disability measures. To correct for multiple testing, a conservative Type I error level of ≤0.01 was used for MRI variables. A trend was assumed if the Type I error level ≤0.15.

3. Results

3.1. Demographic and clinical characteristics

The statistical analyses were limited to healthy controls and MS patients according to the McDonald criteria (McDonald et al., 2001).

The demographic and clinical characteristics of the MS patients and HC are summarized in Table 1. Of the 272 MS patients, 180 had RRMS and 92 had progressive forms of MS, including both SP-MS and PP-MS.

3.2. Patterns of alcohol use in MS patients vs. healthy controls

Fig. 1 summarizes the salient characteristics of alcohol usage such as duration, frequency and preferred drink in the MS and Control groups.

The proportion of Never Drinkers in the MS group (17 of 268 or 6.3%) was similar (p = 1, Fisher Exact Test) to that in HC (9 of 147 or 6.1%). There was no evidence for difference in the age of first drink (17.8 ± 2.7 for the MS group vs. 17.9 ± SD 2.9 years for HC, p = 0.72, t-test).

3.3. Alcohol use patterns in MS and age of onset of MS

The frequencies of alcohol consumption in MS patients before and after MS onset were significantly different ($\chi^2 = 229, p=0.001, \chi^2$ test). The frequency of MS patients who did not consume alcohol after MS (19.4%) was higher than the frequency before MS (9.4%, Fig. 1B); 35 of 267 (13.1%) patients indicated that they stopped drinking after their MS diagnosis; 8 of 267 patients (2.9%) who did not consume alcohol before MS indicated that they were drinking after MS. Correspondingly, the frequency of MS patients consuming more than 1 drink per day was lower in MS patients after MS onset (3.0%) compared to before MS (12.7%). These changes in alcohol consumption frequency are consistent with lifestyle modification. The type and duration of preferred drinks differed between the before and after MS onset groups ($\chi^2 = 418, p=0.001, \chi^2$ test). The proportion of MS patients drinking beers and spirits declined after MS onset and that of wines increased (Fig. 1C). These changes may be the result of changing demographics or lifestyle modification. There was no evidence for significant differences in frequency of drinking or the type of drink between patients with progressive MS compared to non-progressive MS both before MS onset and after MS onset.

The age of onset of MS was positively correlated with the frequency (Fig. 2A) and type of alcoholic drink (Fig. 2B) consumed before MS.

3.4. Association of alcohol use with MRI measures in MS

Fig. 3A–G, which summarizes the dependence of clinical and MRI variables and highlights the non-linear dependence of these variables on duration of alcohol use after MS. A quadratic term for duration of alcohol use after MS was therefore incorporated in regression to account for the non-linear dependence. The quadratic term for EDSS ($p=0.037$) was significant whereas for the MSSS only the linear term was significant ($r_p=-0.16, p=0.012$). The quadratic terms for NGMV ($r_p=-0.18, p=0.007$) and NLVV ($r_p=-0.18, p=0.006$) were both significant. A trend was found for the quadratic term for NBV ($r_p=-0.16, p=0.014$). The pattern of non-linear dependence suggests that moderate duration of alcohol use does not have adverse effects in MS.

3.5. Association of alcohol use with MRI measures in controls

Further, we had MRI on 68 HC and compared the dependence of their NBV, NGMV and NLVV on duration of alcohol use to better assess our findings in MS patients (Fig. 4). In regression analysis correcting for sex and age, the HC group exhibited higher NLVV trend with

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**Table 1** Demographic and clinical characteristics of the cohort. The continuous variables are expressed as mean ± SD and the categorical variables as frequency [%].

<table>
<thead>
<tr>
<th>Demographics</th>
<th>MS</th>
<th>Controls</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Females:males (%) female</td>
<td>207:65 (76%)</td>
<td>78:73 (52%)</td>
<td>&lt;0.001b</td>
</tr>
<tr>
<td>Disease course</td>
<td>Relapsing–remitting</td>
<td>180 (66.2%)</td>
<td>61 (42.4%)</td>
</tr>
<tr>
<td>Secondary progressive</td>
<td>61 (22.4%)</td>
<td>3 (2.0%)</td>
<td></td>
</tr>
<tr>
<td>Relapsing SP</td>
<td>19 (7.0%)</td>
<td>3 (2.0%)</td>
<td></td>
</tr>
<tr>
<td>Primary progressive or primary remitting</td>
<td>12 (4.4%)</td>
<td>3 (2.0%)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Race/ethnicity</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Caucasian-American</td>
<td>248 (93.6%)</td>
<td>134 (90.1%)</td>
<td>0.33c</td>
</tr>
<tr>
<td>African-American</td>
<td>12 (4.5%)</td>
<td>11 (7.4%)</td>
<td></td>
</tr>
<tr>
<td>Hispanic/Latino</td>
<td>4 (1.5%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>0 (0%)</td>
<td>3 (2.0%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>1 (0.4%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Missing data</td>
<td>7</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>47.8±12.5</td>
<td>46.8±12.6</td>
<td>0.42d</td>
</tr>
<tr>
<td>Disease duration, years</td>
<td>15.2±10.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median EDSS (IQR)</td>
<td>3.0 (4.0)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a 1 subject self-reported as transgender male, counted as a male.
b Fisher exact test.
c Fisher exact test for frequency of Whites to Non-whites in MS vs. Controls.
d t-test.
increased total duration of alcohol use categories ($p = 0.047, r_p = 0.25$). The associations of NBV and NGM in HC with total duration of alcohol use categories were not significant.

As expected, the HC had higher values of NBV ($p = 0.009$, Mann Whitney test) and NGMV ($p = 0.003$, Mann Whitney test) and lower values of NLVV ($p < 0.001$, Mann Whitney test) than the MS group. Fig. 4 also shows the mean values of NBV, NGMV and NLVV for MS patients in the $\leq 20$ years and $> 20$ years for total duration of alcohol use. The mean age of the MS and HC groups in the $\leq 20$ year (MS: 39.4±7.9 years vs. HC: 36.6±5.0 years) and the $> 20$ year (MS: 52.6±6.8 years vs. HC: 50.7±6.7 years) total duration of alcohol use categories was comparable. Of the three MRI measures evaluated, NLVV showed the most prominent changes between MS and HC. The remaining comparisons are not shown because the None category had only 1 HC subject with MRI and the MS patients (40.1±12.0 years) in the $\leq 10$ years category were older than corresponding HC group (25.8±5.5 years).

4. Discussion

In this report, we investigated the associations of alcohol use patterns with clinical and MRI measures in MS. We found that age of onset increased in MS patients with the frequency and the alcoholic content of the preferred drink prior to MS. The EDSS, NGMV and NLVV showed non-linear dependence on the duration of alcohol use after MS onset.

Regression analyses incorporating quadratic dependence on duration of alcohol use indicated that mean EDSS and NLVV were lower
Fig. 3. Fig. 3A–G shows the dependence of EDSS, MSSS, T2-LV, T1-LV, NBV, NGMV and NLVV on the duration of alcohol use after MS onset. The bars represent means and the error bars are standard errors of the mean.
and the NGMV was greater in MS patients who had consumed for a period of 15 years or less after MS onset compared to those who started consuming alcohol after 15 years. From these results, we conservatively surmise that moderate duration of alcohol consumption does not have adverse effects on disability or MRI measures in MS patients. Larger, prospective longitudinal studies are necessary to definitively determine whether effects of intermediate duration of alcohol use on EDSS, NGMV and NLVV are indeed protective or not.

Our results suggesting an increase in age of onset with alcohol use can be viewed as consistent with the disability and MRI findings. However, these results must be interpreted cautiously because the statistical significance was sensitive to the inclusion of MS patients 21 years of age or older who had pediatric-onset MS. Because MS patients <21 years of age were excluded from the analyses based on the legal drinking age, it is possible the subset of adult MS patients with pediatric-onset MS may have skewed the analysis because they would have lower age of onset but would lack significant exposure to alcohol prior to the onset of MS.

In addition, the alcohol consumption levels in the majority of subjects were moderate to low: only 12.7% of MS patients consumed >1 drink a day before MS onset and 3% of MS patients consumed >1 drink per day after MS onset. The findings from this study may be difficult to extrapolate to alcohol abuse. However, we had a low proportion of the Never Drinkers, which is probably representative of their prevalence in the population at large because the proportion of HC who were Never Drinkers was similar to that in the MS group. Young adults frequently consume alcohol upon reaching drinking age and in their college years.

It has been suggested that MS patients have a greater propensity for risk taking behavior and that this may be a unifying explanation for the lack of a single immunological or environmental factor in MS (Hawkes, 2005). Analysis of the North American Research Committee on Multiple Sclerosis (NARCOMS) Registry indicates that adverse health behaviors including prevalence of smoking, alcohol abuse, risk, obesity, and lack of physical activity were frequent in MS (Marrie et al., 2009). Alcohol intoxication can also cause blackouts wherein memory loss is severe enough that key events are not remembered and there is an increased risk of potentially dangerous behaviors such as vandalism, driving and unprotected sex. These blackouts may occur even among social drinkers (White, 2003). Although our sample was a smaller clinic-based rather than population-based, the comparisons with HC and the After MS onset groups did not provide evidence for greater alcohol consumption in MS patients. Instead, we found decreases in the frequency of alcohol consumption that are consistent with lifestyle modification after MS onset in comparisons of the Before and After MS onset groups. However, questions regarding alcohol use may be considered personally sensitive by some subjects and bias due to our use of in-person interview methodology cannot be precluded. Nonetheless, our methodology enabled us to obtain data from disabled and possibly fatigued MS patients who might otherwise not have responded to mail and internet-based surveys. Another weakness of our study is that we did not confirm self-reported data on alcohol consumption via clinical tests (e.g. via breath tests); however, breath and biochemical tests are intrusive and more sensitive for acute intoxication and chronic alcohol abuse.

An important caveat and limitation of our study is its cross-sectional study design. There is the possibility that higher levels of disability resulted in alterations in alcohol consumption. More disabled patients may also be less able to obtain alcohol or may alter alcohol consumption to cope with MS. The differential effects of lifestyle changes consequent to disability could therefore potentially confound our study results and limit the ability to obtain cause-effect assessments from these associations. Altogether different life-styles and alcohol use just may be a surrogate. The recall of past alcohol consumption patterns may also be less able to obtain alcohol or may alter alcohol consumption via clinical tests (e.g. via breath tests); however, breath and biochemical tests are intrusive and more sensitive for acute intoxication and chronic alcohol abuse.
New findings implicate Toll receptor-4 (TLR4) in mediating the effects of alcohol in the central nervous system. The sedation and motor effects of alcohol administration were reduced in mice that received TLR4 antagonists and in TLR4-knockout mice (Wu et al., in press). Alcohol activation of TLR4 signaling initiates a cascade of phosphorylation in mitogen-activated protein kinase and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) signaling pathways (Wu et al., 2011). The activation of inhibitor of NF-κB (IκB-α) also occurs in hippocampal cell cultures (Wu et al., 2011). NF-kB plays a key role in mediating diverse immune responses including those directed against viral and bacterial infection, stress, free radicals and cytokines. Likewise there is emerging evidence that NF-kB is important for learning and memory in mice (Albensi and Mattson, 2000; Albensi, 2001; Meffert et al., 2003). The findings related to the TLR-4, and its signaling via the NF-kB pathway establishes a link between the immune system and its central nervous system effects of alcohol. Alcohol also stimulates the hypothalamus–pituitary–adrenal and hypothalamus–pituitary–gonadal axes (Ogilvie et al., 1998; Eskandari and Sternberg, 2002), which increases glucocorticoid hormone levels in males and females and decreases estradiol levels in females. These hormonal changes may mediate immune suppressive effects of alcohol (Kovacs and Messingham, 2002).

The U- and J-shaped dependence of disability and MRI measures with duration of alcohol use after MS onset that we observed share qualitative similarity with the patterns reported for alcohol dependence in cardiovascular disease and stroke risk (Vliegenthart et al., 2004; Emerson and Bennett, 2006; Arriola et al., 2010) and sleep (Stone, 1980; Williams et al., 1983). Moderate drinking at a dose of 1–2 drinks per day is protective against coronary heart disease (Vliegenthart et al., 2004; Arriola et al., 2010) and increases high-density lipoprotein levels (Thornton et al., 1983; Bertiere et al., 1986; Paunio et al., 1994; Sillanaukee et al., 2000).

In conclusion, we found associations between disability and MRI measures in MS patients with the duration of alcohol use after MS onset. Although the known effects of alcohol on the immune and central nervous systems may be consistent with our findings, more mechanistic studies and larger prospective longitudinal clinical studies are necessary to more completely elucidate the effects of alcohol on MS disease progression.

Note: In a paper available after acceptance of this paper, M.B. D’Hooge et al. (European Journal of Neurology, doi:10.1111/j.1468-1331.2011.03596.x) reported that moderate alcohol consumption was associated with decreased risk of reaching EDSS of 6.0.

Disclosures

Dr. Matthew Foster has nothing to disclose.

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Ms. Miriam Tamao-Blanco has nothing to disclose.

Ms. Darlene Badgett has nothing to disclose.

Ms. Ellen Carl has nothing to disclose.

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