No association of tobacco use and disease activity in multiple sclerosis

ABSTRACT

Objective: To study whether tobacco use is associated with MRI and clinical disease activity in patients with multiple sclerosis (MS).

Methods: Prospective cohort study of 87 patients with relapsing-remitting MS originally included in a randomized placebo-controlled trial of omega-3 fatty acids in MS (the OFAMS Study). Serum levels of cotinine (biomarker of tobacco use) were analyzed at baseline and every 6 months for 2 years. MRI activity was assessed at baseline and monthly for 9 months and after 12 and 24 months.

Results: Fifty-three patients (61%) had serum cotinine levels $\geq 85$ nmol/L on $\geq 60\%$ of the measurements and were considered tobacco users and 34 (39%) had cotinine levels $< 85$ nmol/L, consistent with non-tobacco use. There was no association between tobacco use and the occurrence of new gadolinium-enhancing T1 lesions, new or enlarging T2 lesions, or their aggregate (combined unique activity). Furthermore, there was no association between cotinine levels and MRI activity for the tobacco users, and tobacco users did not have more relapses or Expanded Disability Status Scale progression.

Conclusion: Our results indicate that tobacco use does not directly influence MRI activity or relapse rate in MS. This may imply that the reported association between smoking and MS disease progression could be mediated through other mechanisms. Neurology.org/nn © 2016 American Academy of Neurology
relapsing-remitting MS (RRMS) to secondary progressive MS (SPMS). It has been suggested that smoking influences the clinical progression in MS and several studies have explored this, with conflicting results. One study has reported that smoking cessation decreases the risk of Expanded Disability Status Scale (EDSS) progression, but a recent report did not find any association between tobacco use and MS activity or progression over a 5-year follow-up.

To address the effect of tobacco use in established MS, we examined the associations among serum cotinine levels, MRI, and clinical disease activity in a 2-year longitudinal study of 87 HLA-DRB1*15–typed patients with RRMS.

METHODS Standard protocol approvals, registrations, and patient consents. The study was approved by the Regional Committee for Medical and Health Research Ethics in Western Norway Regional Health Authority, and all participants gave written informed consent.

Study participants and design. The study design has been presented previously. Briefly, this was a cohort study of 87 patients with RRMS according to the McDonald criteria originally included in a randomized placebo-controlled trial of omega-3 fatty acids at 13 Norwegian MS centers from December 2004 until July 2008 (the OFAMS [ω-3 Fatty Acid Treatment in Multiple Sclerosis] Study). Included patients had ≥1 clinical relapse, a new T1-weighted gadolinium-enhanced MRI (T1Gd)-positive lesion or enlarging T2 lesions in the last 12 months before enrollment. The patients were followed for 24 months with thorough examinations including serum samples, MRI scans, and clinical scorings. MRI scans were performed at baseline and monthly for 9 months and then after 12 and 24 months according to a standardized protocol. The sum of T1Gd+ lesions and new or enlarging T2 lesions was denoted as combined unique activity. Clinical data were recorded by experienced neurologists, including EDSS scores every 6 months and clinical relapses throughout the study period. The patients did not use any immunomodulatory drugs at inclusion, but from month 6, all patients started subcutaneous injections with 44 µg of interferon beta-1a (IFN-β-1a) (Rebif; Merck KGA, Darmstadt, Germany) 3 times weekly. All patients were randomized to receive omega-3 fatty acids (Triomar; Pronova Biocare AS, Sandefjord, Norway) or placebo (corn oil) daily throughout the study period.

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RESULTS Cotinine levels and MRI disease activity. Of 87 patients, 53 (61%) had cotinine levels >85 nmol/L in ≥60% of the samples and were considered tobacco users, and 34 (39%) were considered non–tobacco users. Most patients had consistent cotinine levels on all samples, but 11 (13%) had consistent levels in 75% of the measurements and 4 (5%) in 60% of the measurements. There was no association between tobacco use and MRI activity, for new T1Gd+ lesions (odds ratio [OR] = 0.76; 95% confidence interval [CI] 0.41–1.43; p = 0.39), for new or enlarging T2 lesions (OR = 0.81; 95% CI 0.42–1.56; p = 0.52), and for combined unique activity (OR = 0.81; 95% CI 0.43–1.53; p = 0.51) for the total study period. The result was consistent for the 6 months before and 18 months
Abbreviations: BMI = body mass index; CI = confidence interval; CUA = combined unique activity; IFN-β = interferon beta; T1Gd = T1-weighted gadolinium-enhanced.

There are some limitations to our study. We used serum cotinine levels as a proxy for smoking behavior, but being a marker for tobacco use, the levels will also be high among snuff users or users of nicotine gum, and one study has suggested possible protective effects of these considering MS risk. The total proportion of smokeless tobacco of all tobacco consumption in Norway during the study period was, however, less than 20% and even lower among women. It is therefore reasonable to assume that the cotinine levels in our samples mainly reflect smoking. The patients were classified as tobacco users or non–tobacco users based on cotinine level in ≥60% of the measurements, and there is a risk of misclassification, possibly mostly for light smokers since the half-life of serum cotinine is 15 to 40 hours. However, we had serum measurements at 5 different time points and most patients had consistent serum cotinine levels on all measurements, indicating that this is not a major issue. It has also been demonstrated that serum cotinine levels are well correlated with patient-reported smoking behavior. The follow-up period of 24 months is relatively short and our results might have been different with longer follow-up. However, our findings are in coherence with those of a recently published study with a follow-up period of 5 years. Also, the lack of any of the results being even close to significant toward influence of tobacco use on MRI disease activity make it unlikely that there is any association. Our MRI findings were supported by no association between cotinine levels and clinical disease activity. The follow-up period was short and few relapses were reported, thus the sensitivity for clinical activity is low. However, our main outcome was MRI activity, which is a sensitive and well-known assessment for subclinical disease activity.

| Table | Odds ratios for MRI disease activity associated with tobacco use (serum cotinine ≥85 nmol/L) in patients with relapsing-remitting multiple sclerosis |
|-------|------------------------------------------------------------------------------------------------------------------|
| MRI measure | Total study period (n = 87) | Before IFN-β treatment, months 1-6 | p Value | Odds ratio (95% CI) | Odds ratio (95% CI) | p Value | Odds ratio (95% CI) | p Value |
| New T1Gd+ lesions | 0.76 (0.41–1.43) | 0.39 | 0.80 (0.34–1.87) | 0.61 | 0.56 (0.19–1.63) | 0.28 |
| New T2 lesions | 0.81 (0.42–1.56) | 0.52 | 0.74 (0.30–1.81) | 0.74 | 0.85 (0.35–2.08) | 0.72 |
| CUA | 0.81 (0.43–1.53) | 0.51 | 0.75 (0.31–1.82) | 0.52 | 0.80 (0.32–1.98) | 0.62 |
| Adjusted for sex, age, BMI, and HLA-DRB1*15 status (n = 81) | | | | | | |
| New T1Gd+ lesions | 0.76 (0.39–1.50) | 0.43 | 0.72 (0.28–1.81) | 0.47 | 0.68 (0.21–2.19) | 0.51 |
| New T2 lesions | 0.87 (0.43–1.75) | 0.69 | 0.65 (0.26–1.68) | 0.37 | 1.04 (0.40–2.72) | 0.94 |
| CUA | 0.84 (0.42–1.68) | 0.63 | 0.63 (0.25–1.61) | 0.33 | 0.98 (0.37–2.61) | 0.97 |

Abbreviations: BMI = body mass index; CI = confidence interval; CUA = combined unique activity; IFN-β = interferon beta; T1Gd = T1-weighted gadolinium-enhanced.
The lack of any association between smoking and EDSS progression in our study could be attributable to the relatively short follow-up time of 24 months, and the fact that few patients experienced EDSS progression during the study period. A number of earlier studies have reported increased risk of disease progression among smokers.14,15 The mechanism for this association is largely unknown, but one possibility could be that smoking increases the inflammatory activity in MS. It has been demonstrated in the experimental autoimmune encephalitis model of MS that proinflammatory T cells are activated in the lungs before they attack the brain.29 Although our negative results may implicate that this mechanism does not have a major role in patients with established MS, they do not exclude this possibility, or that smoking has an important role during the initiation phase of the disease. Smoking is one of the most attractive and studied environmental risk factors for MS. The first reports on an association between MS and smoking were published in the 1990s,30,31 and since then, a number of studies have confirmed smoking as a risk factor for MS.3–7,26,32 Even passive smoking has been associated with MS.33 Recent studies have also described the association between cotinine levels in serum and the risk of MS.34,35 Previous reports have found an association with clinical disease and earlier progression from clinically isolated syndrome to RRMS and from RRMS to SPMS among smokers.10–13,36 However, others have not been able to confirm an association between smoking and the risk of MS or an earlier progression to SPMS in smokers.16,37 Only a few studies have examined how smoking influences disease activity in MS. One study explored the association between MRI lesions in MS and smoking and found that the T2-weighted lesion volume increased faster in smokers,10 and a recently published study reported no association between MRI activity and serum cotinine levels.17 The result of our study supports this latter report. Other hypothesized mechanisms of adverse effects of smoking in MS include chronic cyanide intoxication leading to demyelination, the direct effect of cigarette-smoke components on the blood–brain barrier and smoking-mediated increased frequency and persistence of infections.11 There are also several other possible reasons for the increased impairment and disability in patients with MS who smoke and it is not clear whether it is a direct effect of tobacco use or a consequence of comorbidities associated with smoking.38

Our results do not support a short-term (2 years) influence of tobacco use on MRI and clinical disease activity in MS. Long-term effects and the importance of comorbidities influenced by smoking in MS need to be explored.
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