Timing of cigarette smoking as a risk factor for multiple sclerosis

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In a recent review evaluating the evidence concerning the association between smoking and multiple sclerosis (MS), the author specifically calls for: (1) studies investigating this association using *objective* markers for smoking in *prospective* datasets; and (2) studies addressing the timing of smoke exposure [Wingerchuk, 2012]. We have recently reported the findings of a nested case-control study where levels of cotinine, a recognized biomarker for tobacco use, were measured in biobank blood samples collected median 9 years prior to disease onset [Salzer *et al.* 2012a]. Elevated levels of cotinine suggestive of smoking (≥ 10 ng/ml) [Vineis *et al.* 2005] were associated with a 50% increased risk of MS when analyzing the entire cohort. When we stratified the cohort according to age at blood sampling, it was evident that it was only among young subjects (below median age at blood sampling, <26.4 years) that this effect was seen. In addition, we used samples collected in the first trimester from 37 pregnant women, whose offspring had later developed MS, and 185 pregnant women whose offspring had not (further described by Salzer and colleagues [Salzer *et al.* 2012b]) to study the effects of gestational levels of cotinine on the risk of MS in the offspring (previously unpublished data). In this dataset $n = 13$ (35%) of case mothers and $n = 71$ (39%) of control mothers had cotinine levels ≥ 10 ng/ml. There was no association between elevated cotinine levels during gestation and the risk of MS in the offspring (odds ratio [OR] 0.87, 95% confidence interval [CI] 0.41–1.8, matched logistic regression). In conclusion, our data indicate that smoke exposure during young adulthood is associated with an increased MS risk, but exposure during early gestation according to our limited gestational material, or exposure after the age of 26.4 years is not. This age-of-exposure-dependent effect of smoking on MS risk converges with similar findings for other risk factors of MS (vitamin D levels, elevated body mass index [BMI], Epstein–Barr virus [EBV] seroconversion, infectious mononucleosis) suggesting that young adulthood is a crucial time for establishing an

individual's risk of the disease [Hedstrom *et al.* 2012; Munger *et al.* 2006; Thacker *et al.* 2006].

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