



# Smoking is a risk factor for multiple sclerosis

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**Abstract**—The authors determined the relationship between tobacco smoking and the risk of developing multiple sclerosis (MS) in a general population of 22,312 individuals living in Hordaland, Norway in 1997. A total of 87 individuals reported having developed MS. The risk of MS was higher among smokers than among never-smokers (rate ratio 1.81, 95% CI 1.1 to 2.9;  $p = 0.014$ ). Studies on how smoking interacts with disease onset may contribute to determining the causal agents of this disease.

NEUROLOGY 2003;61:1122–1124

Substantial epidemiologic evidence implicates environmental factors in the etiology of multiple sclerosis (MS).<sup>1</sup> An infectious agent has been considered the most likely exogenous factor, but other environmental factors may also have a role in causing MS. A few case-control studies on the effect of smoking have all shown some association but, for most studies, non-significant results.<sup>2</sup> A recent prospective study of two large cohorts of female nurses found an increased frequency of MS among the smokers and demonstrated a dose-response relationship.<sup>2</sup>

We determined the relationship between tobacco smoking and the risk of developing MS in a general population of 22,312 people living in Hordaland, Norway (the Hordaland Health Study 1997–1999).

**Methods.** *Study population.* The study was cross-sectional and included questionnaires and a clinical examination.<sup>3</sup> The study population included the cohort of all 29,400 individuals born between 1953 and 1957 and a random sample of those born in 1950 and 1951, who all resided in Hordaland County on December 31, 1997. A total of 22,312 individuals participated, with an age of 40 to 47 years at the time of the study and with a participation rate of 65%. The clinical examination included measurements of blood pressure, height, weight, and waist and hip width. The questionnaire included information on a number of health variables and lifestyle factors.

*Measurements.* Information on smoking was obtained by asking about current and previous smoking, including the age at which smoking started. Information on education was given in five levels. The participants were asked to report whether they had developed MS or several common diseases, including myocardial infarction, angina pectoris, stroke, asthma, and diabetes. They were also asked to report the year of onset of the disease.

The study protocol was approved by the Regional Ethics Committee and by the Norwegian Data Inspectorate.

*Statistical analysis.* We determined the relationship between smoking and the risk of developing MS using a Cox proportional hazard regression model with smoking (never or ever) as a time-dependent covariate. Age was used as the time scale in the Cox model; individuals were considered nonsmokers up to the reported age of starting smoking and past or current smokers thereafter. The year of onset of MS was defined as the endpoint for the patients with MS and the non-cases were censored at time of the study. The parameter estimated in this model is a rate ratio (RR), which is approximately the ratio of risk of developing MS at any time between an individual who smoked and one who never smoked. Because early unrecognized symptoms of MS may have induced changes in smoking behavior, we also conducted analyses classifying individuals according to their smoking status 4 years before the onset of disease. The RR for the other chronic diseases were calculated using the same model. All analyses were performed stratified by sex.

**Results.** A total of 87 individuals reported having MS. This gives an age-specific prevalence rate of 390 per 100,000. All patients with MS who were current smokers and most who were former smokers had started smoking before the onset of MS. The only exceptions were two patients, one who began smoking 5 years after the onset of disease and one who started smoking the same year as the onset of disease. The mean duration from start of smoking to onset of disease was 15.2 years (range 1 to 31 years). Age at disease onset was missing for 16 patients with MS and was set to 32.6 years (mean age at onset in the remaining patients with MS) in the analysis. Six of those had never smoked, nine started smoking between 16 and 22 years of age, and one patient started smoking at age 35

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Received December 11, 2002. Accepted in final form May 22, 2003.

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**Table** The number of smokers and risk estimate (rate ratio) for six common diseases among 22,312 subjects in the general population of Hordaland County, Norway

Disease	No. of patients*	Never smoker, n (%)	Current or past smoker, n (%)	Ratio ratio† (95% CI)
Multiple sclerosis	86	21 (24.4)	65 (75.6)	1.81 (1.13–2.92)
Myocardial infarction	76	9 (11.8)	67 (88.2)	4.53 (2.26–9.01)
Angina pectoris	108	17 (15.7)	91 (84.3)	3.30 (1.96–5.55)
Stroke	93	27 (29.0)	66 (71.0)	1.48 (0.94–2.35)
Asthma	1,350	446 (33.0)	904 (67.0)	1.21 (1.05–1.39)
Diabetes	216	85 (39.4)	131 (60.6)	0.86 (0.65–1.13)
Total population	22,240	8,239 (37.0)	7,892 (35.5)	1.00

\* Information on smoking was missing for 72 individuals including one patient with multiple sclerosis.

† Rate ratio estimated in a Cox proportional hazard regression model with smoking as a time-dependent covariate. Smoking individuals are being compared with nonsmoking individuals at the same age for the risk of developing the disease. All analyses were performed stratified by sex.

years. Exclusion of these cases from the analyses did not change the results.

The RR estimated by the Cox model comparing ever-smokers with never-smokers was 1.81 ( $p = 0.014$ ) (table). The RR was 2.75 for men and 1.61 for women. An analysis excluding the patients who started to smoke less than 4 years prior to the onset of disease gave an RR of 1.74 ( $p = 0.024$ ). Further, an analysis including educational level gave an RR of 1.75 ( $p = 0.023$ ). The RR was significantly increased also for myocardial infarction, angina, and asthma.

**Discussion.** This study of a large general population found that the risk of developing MS among individuals who smoked was nearly twice as high as in never-smokers. Taken together with the significantly increased risk of MS among smokers found in the recent prospective study of female nurses in the United States<sup>2</sup> and the similar (albeit nonsignificant) increases found in two prospective studies in the United Kingdom,<sup>4,5</sup> this result strongly suggests that cigarette smoking is a risk factor for MS. The results in the current study showed that the excess risk among men who smoke is at least as high as that among women who smoke. These findings add MS to the list of diseases, including various types of cancer, cardiovascular diseases, and rheumatoid arthritis, for which tobacco smoking represents a risk factor.

The diagnosis of MS for the patients in this study was based on self-report. Nevertheless, patients who have been diagnosed as having MS are well aware of their diagnosis, and individuals who have not been given this diagnosis will probably not report having MS. A large study of female nurses in the United States found that as many as 93% of the respondents who reported having MS were confirmed by hospital files.<sup>2</sup> A similar validity of the disease status is expected in the current study population, which represents a high-risk area that has been extensively studied and where the community is familiar with the disease.<sup>6-8</sup> The age-specific prevalence rate, including patients with neurologist-based diagnosis only, in a study of the same county in 1994 was 338

per 100,000 people 40 to 49 years old.<sup>8</sup> This is slightly lower than the rate found in the current study, assuming the same frequency of nonresponse among patients with MS as the rest of the population (390 per 100,000). This could reflect a small increase in the prevalence rate during these 4 years or that the patients with MS in the current study had a slightly higher response rate than did the total study population. In any case, any misclassification of disease status introduced by self-report is not likely to have resulted in the increased risk of MS found among smokers. Further, there is little reason to believe that patients with MS who smoke would be more likely to participate in the study compared with subjects without MS who smoke.

The validity of the smoking data was supported by a clear relationship with other smoking-related diseases such as myocardial infarction and angina pectoris. Further, because the questions on smoking were included in a large questionnaire with many questions and a possible relationship between smoking and MS is not well known, there is little reason to believe that the patients with MS would report their smoking history differently from the rest of the study population. Interpreting the level of education as an indirect measure of socioeconomic status, the results indicated that smoking was not a confounding factor for social-economic status.

Several biologic models could explain the increased risk of MS among smokers. These include effects of smoking on the immune system, direct effects of smoking on the blood-brain barrier, and toxic effects of smoking on the CNS.<sup>2</sup> The relevance of these mechanisms and the role of specific components of cigarette smoke such as nicotine or cyanide could be explored in experimental animal studies.

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# Hashimoto's encephalopathy

## Postmortem findings after fatal status epilepticus

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**Abstract**—The clinical features of Hashimoto's encephalopathy have been attributed to a cerebral vasculitis, but pathologic material is rarely available. The authors describe an individual with Hashimoto's encephalopathy complicated by fatal status epilepticus. Postmortem examination demonstrated mild perivascular lymphocytic infiltration throughout the brain and leptomeninges plus diffuse gliosis of gray matter in the cortex, basal ganglia, thalami, hippocampi, and, to a lesser extent, the parenchymal white matter.

NEUROLOGY 2003;61:1124–1126

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In 1966 Brain et al.<sup>1</sup> described an individual already known to have autoimmune thyroid disease who presented with recurrent stroke-like episodes occurring independently of the thyroid status. The term "Hashimoto's encephalopathy" was coined, and gradually it has become apparent that the clinical features of this condition include intermittent confusion and impairment of consciousness, psychosis and hallucinosis, stroke-like episodes, myoclonus, and tremor.<sup>2,3</sup> These features have at times been attributed to a vasculitic process, although the pathologic evidence is extremely limited.<sup>4,5</sup> We report brain pathology in a case of Hashimoto's encephalopathy.

**Case report.** A 40-year-old man was brought to the accident and emergency department after collapsing at home. A series of generalized tonic-clonic convulsions were witnessed by the paramedical staff with, on one occasion, apparent interruption of respiration and cardiac output for a period of 1 minute. Cardiopulmonary resuscitation was given throughout this period of time. Inquiry revealed no prior history of epilepsy, but 3 months earlier, the patient had presented to his general practitioner with a history of malaise, weight loss, and tremor of several weeks' duration. Hyperthyroidism was suspected, and propranolol was prescribed while the thyroid status was investigated. Hypothyroidism was demonstrated, and thyroxine 100 µg daily was then given. During the next month, the patient's condition deteriorated. According to his family, he became intermittently confused and incapable of running his computing business. Impaired concentration was evident, and recent conversations and events were not well recalled. In addition, the patient developed rapid, brief, jerking movements of the limbs that made writing impossible. The movements persisted in sleep and compelled the patient's wife to sleep separately.

On admission, the patient was afebrile. The cardiovascular, respiratory, and abdominal systems were normal. There was no response to verbal or painful stimuli. The eyes were open and the pupils dilated but reactive. The fundi were normal. The corneal reflexes and the response to nasal tickle were absent. The limbs were flaccid. The tendon reflexes were present but depressed, and the plantar response was equivocal. Rhythmic twitching of the eyelids and right hand was observed.

Biochemical and hematologic indexes were normal. Toxicology, cryoglobulin, and porphyria screens were negative. Thyroid-stimulating hormone was increased at 16.6 mU/L (0.1 to 5.0 mU/L), but free thyroxine was normal at 16.3 pmol/L (10 to 30 pmol/L). Thyroid peroxidase (TPO) antibodies were present in the serum at an initial concentration of 1,271 IU/mL. The remainder of the autoantibody screen was negative. A CT scan of the brain revealed no abnormality. The CSF was proteinaceous (153 mg/dL) but acellular and sterile. TPO antibodies were present in the CSF. EEG revealed bifrontal spike and sharp wave activity occurring at a frequency of approximately 1/s on the left and 1 to 3/s on the right.

A diagnosis of Hashimoto's encephalopathy was made.

The patient was prescribed IV hydrocortisone 200 mg 6-hourly on the day of admission, methylprednisolone 500 mg daily on the following 3 days, and hydrocortisone 200 mg twice daily thereafter. He also received tri-iodothyronine 20 µg 8-hourly and initially acyclovir 10 mg/kg 8-hourly plus ceftriaxone 2 g daily. Seizures were treated using diazepam and a loading dose of phenytoin on admission followed by thiopentone anesthesia when clinical examination and EEG monitoring revealed ongoing epileptic activity. Subsequently, prolonged EEG monitoring revealed continuing independent bifrontal ictal activity with occasional generalization. Propofol was introduced and augmented by a series of anticonvulsants including sodium valproate, phenobarbitone, and chlormethiazole; however, ictal activity was never fully suppressed.

Three days after admission, the TPO titer had fallen to 727 IU/L and by the sixth day to 118 IU/L. On the fourth day, plasma exchange was commenced and was continued for 5 further days. Nine days after admission, the patient became bradycardic and

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Received February 11, 2003. Accepted in final form May 29, 2003.

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