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Smoking is a risk factor for multiple sclerosis: a metanalysis

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Several case control studies have probed a link between cigarette smoking and subsequent multiple sclerosis (MS). Data collection and statistical methods have varied, and frequently, case numbers have been small. Publications relating to MS and smoking are reviewed and combined where comparable methods have been used. Metanalysis of six informative studies show significantly elevated odds or rate ratios, ranging from 1.22 to 1.51, depending on the method of analysis, confirming that the risk of MS is increased for those who smoke prior to disease onset, as measured by commencement of symptoms. A variety of direct causative mechanisms are discussed, but an indirect association through health adverse conduct is favoured. *Multiple Sclerosis* 2007; **13**: 610–615. http://msj.sagepub.com

Key words: metanalysis; multiple sclerosis; smoking

Background

A smoking habit has been regularly examined for its possible aetiological association with multiple sclerosis (MS), but no firm conclusion can be drawn, in part due to variable methodology and problems with sampling. The following is a review of the available literature in chronological order.

One of the earliest papers to include smoking habit was from Israel [1], where 241 MS patients were questioned about ever smoking prior to disease onset (Table 1). The control group comprised 61 subjects individually matched to patients by age, sex and region of birth. They found a significant excess of patients who had smoked before the age of onset of MS (44% versus 36%, $P < 0.02$). Their survey included 141 questions without correction for multiple comparisons; hence their observations must be interpreted with caution. An investigation from North England [2], comprised 584 MS cases compared to information provided by the tobacco industry. Detail is provided of age of smoking onset and whether MS patients were current smokers. It was found that male MS sufferers smoked less than females, but males commenced smoking significantly earlier–by 1.1 years. No information is given on smoking habit prior to disease onset. No difference was found between current daily consumption of cigarettes and controls matched on age, but no tests of significance were undertaken. A group in Oxford, UK [3], studied obstetric patients–mainly in an attempt to dispel the fears of a MS risk in those taking the oral contraceptive–but they also evaluated smoking. This was a prospective incident study, based on the diagnostic coding records of 63 new MS patients, where it was shown there was a borderline significant trend between the number of cigarettes smoked at baseline and risk of MS ($P = 0.05$). At entry to the study, those smoking >15/day had a relative risk of 1.8 (95% CI: 0.8, 3.6), which is not significant. Ex-smokers displayed a similar magnitude of risk (RR 1.5; 95% CI: 0.6, 3.3). This study was extended five years later in a prospective cohort study of 114 incident MS cases [4], giving a rate ratio (RR) of 1.4 (95% CI: 0.9, 2.2) for those smoking 15 or more cigarettes per day at recruitment, which is again just outside conventional confidence intervals. Subsequently, Ghadirian *et al*. [5], showed a significant effect in a case-control study of 197 incident MS cases from Montreal. Their analysis was based on reported cigarette consumption in the year prior to MS diagnosis, and adjusted for age, sex and education. There was an association for 'ever-smokers'; more so for heavy smokers who

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Table 1 Summary of the six main studies which have examined smoking and subsequent MS

Lead author and reference	MS patient Nos.	Control Nos.	Quantity smoked (MS case Nos. in brackets)	Odds ratio (OR) or rate ratio (RR)	95% CI	Adjustments	Method of MS diagnosis	Study type, region and comment
Antonowsky [1]	241	61	Ever smoked before age of disease onset (106)	1.4 OR	1.05, 1.86	Age, sex, region of birth	Not stated	Retrospective, case-control (Israel). Controls matched for age, sex and region of origin. No adjustment for multiple comparisons
Thorogood [4]	114	56 non-smokers at recruitment	1–14/day (33)	1.2 RR	0.8, 1.8	Age, social class	Family practitioner and hospital colleagues	Prospective, cohort incident cases. All smokers before disease onset. All female (Oxford, UK)
			15 or more/day (25)	1.4 RR	0.9, 2.2			
Ghadirian [5]	197	202	Ever smoked (138)	1.6 OR	1.0, 2.4	Age, sex, education	Contact with general physician, neurologists and local MS society	Incident case-control. Smoking in year prior to diagnosis (Montreal, Canada)
			20–40/day (71)	1.9 OR	1.2, 3.2			
			>40/day (16)	5.5 OR	1.7, 17.8			
Hernan [8]	315	128, 638	Ever smoked (175)	1.6 RR	1.2, 2.1	Age, latitude, longitude, ancestry, alcohol, coffee and body mass index	Poser criteria (1983)	Prospective, incident. Smoking four years prior to MS diagnosis. Only pooled data quoted here. All female nurses (USA)
			10–24 pack years before diagnosis (75)	1.6 RR	1.2, 2.1			
			>25 pack years before diagnosis (57)	1.7 RR	1.2, 2.4			
			Ever smoked (79)	1.5 OR	0.9, 2.4			
Riise [10]	87	22, 312	Smoking prior to disease onset[a]	1.8 RR	1.1, 2.9	Age, sex, educational level	Patient reported	Population based, prevalent case control (Norway)
			Females[a]	1.6 RR	Not given			
			Males[a]	2.7 RR				
Hernan [11]	201	1913	Ever smoked (92)	1.3 OR	1.0, 1.7	Age, sex and family practice	Poser criteria (1983)	Prospective, nested case-control study (UK)

[a]Nos. not supplied.

consumed 20–40 cigarettes per day with an odds ratio (OR) of 1.9 (95% CI: 1.2, 3.2), and higher still for those consuming >40 per day (OR 5.5; 95% CI: 1.7, 17.8). A questionnaire-based study from Alicante (Spain) used 47 patients paired with four controls ($n=188$), who were matched by gender, age and residence [6]. They claimed for males, an overall association of 'ever smoking' and MS, but the effect is not supported by their analysis with an implausibly 'significant' OR of 1.1. Confidence intervals are not given nor could they be derived from their paper. The same group undertook a similar case-control study in the Alcoi area, comprising 37 patients matched to four controls ($n=148$) [7]. Once again an association between 'ever smoking' and the whole MS group was shown (OR 1.56; $P<0.05$), but confidence intervals are not given and could not be derived, possibly reflecting the overall poor quality of analysis and, therefore, not included in the analysis. Of particular value is the prospective American Nurse Health Study, which is based on two large cohorts of female nurses, one of 121 700 established in 1976, and a second of 116 671 established in 1989. From this study, 315 incident cases of MS were identified [8]. Their pooled data showed an increased risk for MS in those 'ever smoking' (RR 1.6; 95% CI: 1.2, 2.1), and a similar ratio in those smoking >25 pack years (RR 1.7; 95% CI: 1.2, 2.4). The elevated risk was shown in those smoking prior to onset of MS diagnosis, and adjusted for age, latitude and ancestry. A further questionnaire-based study from Trieste in Italy [9], recruited 140 MS cases and 131 sex- and age-matched controls, and found that 41% of cases were current smokers compared to 27% blood donor controls (OR 1.9; 95% CI: 1.1, 3.2), although this was not significant for ever smokers (OR 1.5; CI: 0.9, 2.4). Patients were not questioned about smoking prior to disease onset. Riise *et al*. [10], used a population-based prevalent case control approach in 87 Norwegian MS cases, and likewise, showed near doubling of risk for those who smoked prior to disease onset (RR 1.8; 95% CI: 1.1, 2.9). On average, smoking commenced 15.2 years before symptom onset, which should have been before the disease began, given that the mean age of onset was 32.6 years. The male rate was higher than the female rate (RR 2.75; CI: not given), and just under half the risk found in the same study for myocardial infarction. The most recent study based on primary care records from the UK [11], not only confirmed the risk of prior smoking and MS, but also suggested that those who continued to smoke were more likely to progress from the relapsing-remitting to the secondary progressive stage. A drawback with all these studies is that although a smoking habit was usually explored before MS onset, patients regularly confuse the time of MS onset with the time of MS diagnosis, hence some results may relate to smoking after the condition has begun and possibly unknown to the patient. Two studies [8,11], make this objection unlikely as they are prospective, and data were derived at least four years prior to the first symptoms. A further problem, particularly with earlier studies, is that the diagnosis was not rigorously verified, and many surveys would have been undertaken before magnetic resonance imaging (MRI) was readily available.

In view of some borderline and apparently negative studies, a metanalysis was undertaken.

Search methods

Articles were extracted by a search in all languages in PubMed (1964–present), Google and Google Scholar, EMBASE, CINAHL, Cochrane collaboration, textbooks and conference proceedings. Search terms used were: 'multiple sclerosis', 'demyelinating disease', 'smoking', 'cigarettes', 'case-control study'. Studies were included if they met the following criteria: (a) had a control group; (b) the data were adequate to permit reanalysis if needed to obtain relative risks or OR and their confidence intervals; and (c) information was provided on smoking before the onset of MS symptoms.

This resulted in the six articles listed in Table 1. Articles excluded were: (i) the study from Trieste, Italy [9], which was positive for 'ever smokers', but no information was available on smoking prior to disease onset; (ii) a negative study from Canada [12], comprising 100 MS patients and 100 controls with either rheumatoid arthritis or other neurological disease. No case-control difference in smoking was detected, but there is just a statement to this effect without further supporting information. Furthermore, rheumatoid arthritis has a known association with smoking [13]; (iii) a study from Ferrara, Italy [14], containing 104 cases and 150 controls which showed no significant difference for 'smoking and drinking in adolescence', but further details are not given; (iv) two positive studies from Spain with insufficient data for analysis as described above [6,7]; (v) a negative study from North England [2], already described; (vi) the initial study from Oxford [3], which was supplemented by a later publication [4].

Statistical methods

The identified studies vary in design; some are retrospective, others prospective, and they differ in measure of effect, ie, OR or RR. Under the 'rare disease assumption', OR and RR are approximately equivalent [15], so results from studies with both

these measures have been combined. Differences in retrospective/prospective study design are susceptible to various types of bias, so two separate pooled results were obtained for these two study designs.

For the retrospective study metanalysis, ever versus never smoking (prior to disease onset) results were extracted from three sources [1,5,10]. For the prospective study metanalysis, results were extracted from four sources [4,8,11], but here two approaches were used because publications differed regarding the reported smoking categories: (a) conservative, which included, under the smoking group, those categories likely to produce the smallest smoking effect: 'ever' [11], 'previous smoker' [8] or smoking 1–14/day [4]; (b) less conservative: including in the smoking category 'ever' [11], plus the riskier categories 'current' [8], and 'over 15/day' [4]. Finally, all retrospective and prospective studies were combined, and once more split by conservative or less conservative approaches for the prospective part.

Relative risks were analysed on the log scale. The method of inverse variance weighting was used to obtain fixed effects estimates [16], using confidence limits reported or derivable from the studies. It should be mentioned that with this relatively small number of studies, random and fixed effects analyses cannot be distinguished. Analysis was performed in Stata 9.2 (StataCorp LP, College Station, TX).

Funnel plots

To examine the possibility of publication bias, two funnel plots (for more and less conservative analyses) were produced in Stata 9.2 for the six studies, by plotting the standard error of the study estimate (inversely proportional to study size) against the effect size. Larger studies are shown towards the top of plots. In the absence of publication bias, there should be symmetry around the pooled estimate for both small and large studies; with publication bias one expects smaller studies (towards bottom) mainly to have larger effects (towards right of plot).

Results

For the retrospective metanalysis (ever versus never smoking), a pooled estimate was derived of 1.51 (95% CI: 1.22, 1.87; $P < 0.001$) (Figure 1). For the prospective 'conservative' approach, the three categories gave a pooled estimate of 1.24 (95% CI: 1.04, 1.48; $P = 0.01$) (Figure 2). The less conservative analysis yielded a pooled risk of 1.43 (95% CI: 1.20, 1.71; $P < 0.001$). The pooled analysis of all six studies (retrospective and prospective) using the most conservative comparisons gave OR 1.34 (95% CI: 1.17, 1.54; $P < 0.001$) (Figure 3). The pooled analysis using less conservative prospective comparisons gave OR 1.46 (95% CI: 1.28, 1.67; $P < 0.001$).

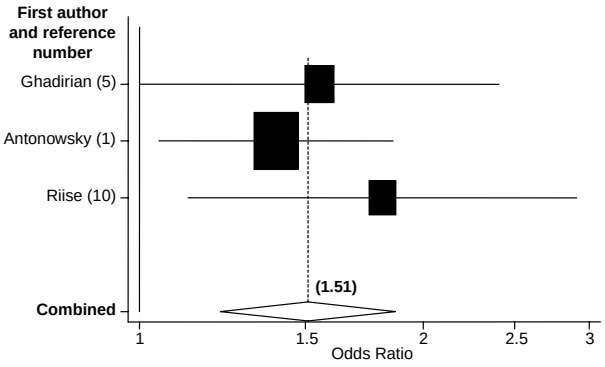

Figure 1 Metanalysis of retrospective studies using ever:never smoking prior to MS onset. The size of the black rectangles is inversely proportional to the confidence interval.

The funnel plots are consistent with some publication bias, as shown by the visible asymmetry (Figure 4). However, for OR metanalyses, some asymmetry observed in the funnel plot may be due to a mathematical connection between the two axes measures [17]. The Egger test for publication bias, which tends to have a high false positive rate for OR metanalyses [17], gives P-values of 0.199 and 0.302, suggesting no evidence of publication bias in these data.

Discussion

The metanalysis of six studies and the relationship to increasing quantity smoked in some individual investigations imply that smoking is a weak but

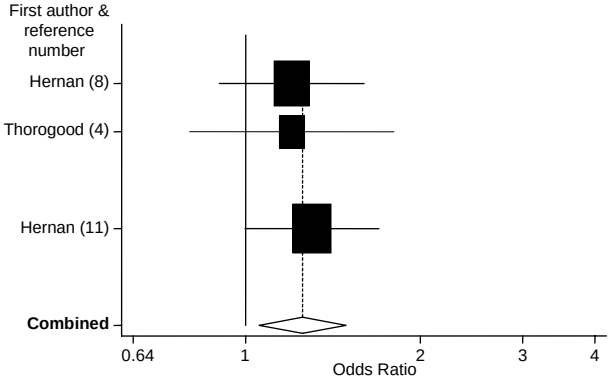

Figure 2 Metanalysis of prospective studies using most conservative analysis. The size of the black rectangles is inversely proportional to the confidence interval.

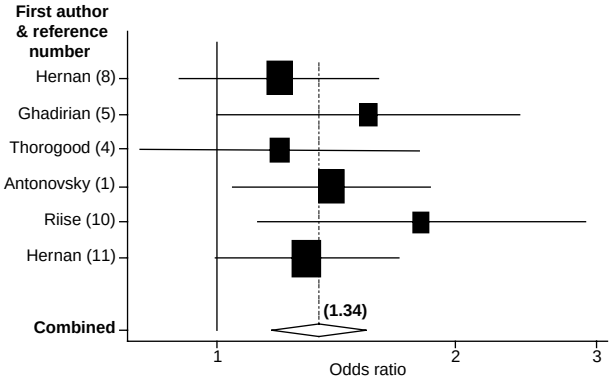

Figure 3 Retrospective and prospective studies combined using most conservative analysis. The size of the black rectangles is inversely proportional to the confidence interval.

significant risk factor for subsequent development of MS, with an overall OR 1.25–1.51. In an initial analysis (not shown), the data were grouped by OR or RR, conservative/non-conservative, but the result was essentially the same with RR or OR, all significant, ranging from 1.3 to 1.6. The non-prospective studies that rely on recall of smoking habit prior to symptom onset are vulnerable to selective recall bias, the effect of cognitive decline and delay in diagnosis, especially for those undertaken in the pre-MRI era, but this objection cannot be levied against more recent prospective studies unless there is predisposition to smoking in the preclinical phase. This potential objection was addressed and shown to be not significant in one study [8], which furthermore suggested that those patients with relapsing-remitting disease who continue to smoke are more likely to enter the secondary progressive phase [11].

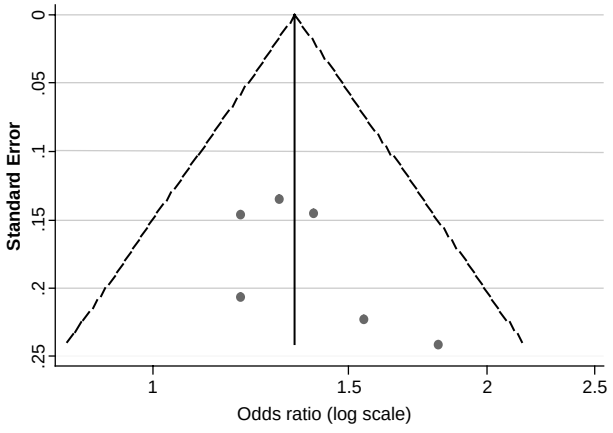

Figure 4 Funnel plot using most conservative analysis.

As expected, the less conservative analysis gives a higher OR than the conservative approach, but both are significant and this adds weight to the analysis. The true risk probably lies midway between these two estimates. There is potential bias from unpublished studies which, if negative, might lessen the significance of the analysis, and this is shown, in part, by the funnel plots which reveal a deficit of small, less significant studies. With relatively few investigations, this test (and the Egger test) has little power, implying there is no conclusive evidence for or against publication bias with these data. The funnel plots infer that restoring some symmetry by introducing smaller studies with lesser effects would still be likely to result in an overall effect, albeit of reduced magnitude.

A variety of mechanisms have been suggested to explain the association – either by immune stimulation or suppression (see discussion in [8]). Smoking is claimed to be linked to autoimmune disease, such as rheumatoid arthritis, systemic lupus erythematosis, Grave's disease and Crohn's disease [13,18]. Nicotine may increase blood–brain permeability to allow entry of abnormal T cells, or tobacco smoke may poison the central myelin, as it does in tobacco amblyopia, possibly by elevation of blood levels of its metabolite, thiocyanate. An alternative mechanism might be through axonal exposure to nitric oxide (NO). Smoking is claimed to elevate NO levels in plasma [19,20], conceivably leading to an increase of NO levels at the site of demyelinated axons. Physiologically active or demyelinated neurones are particularly susceptible to NO exposure, and this, in turn, could result in axonal degeneration or conduction block [21,22]. This theory provides a mechanism for both initiation of MS or the claimed accelerated progression of disability, as observed in one study [11]. Smoking might increase a subject's vulnerability to respiratory infection which, in turn, may allow entry of a causative virus or bacterium [8]. All this is speculation and confounded by evidence from several case-control studies which suggests that smoking is probably protective for Parkinson's disease [23–26] – but in MS, the opposite appears to be the case. Both associations might be correct and are consistent with a unifying explanation involving contrasting behavioural characteristics of the two conditions: ie, patients with Parkinson's disease may lead a conservative lifestyle – avoiding smoking, alcohol, coffee etc. [23–26] – while those with MS may do the opposite – that is they have 'impulsive seeking traits' leading to health adverse conduct [26,27]. This proposition could be tested by a case-control questionnaire or, better still, by a prospective cohort study.

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