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Parental smoking at home and the risk of childhood-onset multiple sclerosis in children

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The possibility of a link between active smoking and incident multiple sclerosis (MS) has been raised. However, possible links between incidence of MS and passive smoking, particularly in children, have not been analysed. We conducted a population-based, case–control study. The cases were patients with incident MS occurring between 1994 and 2003, before the age of 16 years, in France. Each case was matched for age, sex and geographic origin with 12 controls, randomly selected from the French general population. Information about the smoking history of the parents of the cases and controls was collected with a standardized questionnaire. Conditional logistic regression was used to estimate the rate ratio (RR) of MS associated with parental smoking at home. The 129 cases of MS were matched with 1038 controls. Information about parental smoking was obtained for all these cases and controls. Exposure to parental smoking was noted in 62.0% of cases and 45.1% of controls. The adjusted RR of a first episode of MS associated with exposure to parental smoking at home was 2.12 (95% confidence interval: 1.43–3.15). Stratification for age showed that this increase in risk was significantly associated with the longer duration of exposure in older cases (over 10 years of age at the time of the index episode)—RR 2.49 (1.53–4.08)—than in younger cases. Children exposed to parent smoking have a higher MS risk. The duration of exposure also affects the level of risk.

Keywords: child; case–control; epidemiology; smoking; multiple sclerosis

Abbreviations: CI = confidence interval; MS = multiple sclerosis; RR = rate ratio

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Introduction

There is clear evidence that environmental factors play a role in the development of multiple sclerosis (MS) (Marrie, 2004). Migrant studies have provided strong evidence for the existence of such factors, and recent studies have shown marked changes in the incidence and geographic distribution of MS that cannot be attributed to genetic factors (Gale and Martyn, 1995; Hernán *et al.*, 1999; Wallin *et al.*, 2004). No single environmental factor has been consistently identified as a causal factor in MS, but a few have been reproducibly identified as associated with MS in epidemiological studies. One of these factors is smoking: smokers were found to have a 40–80% higher risk of MS than non-smokers in epidemiological studies (Antonovsky *et al.*, 1965; Villard-Mackintosh and Vessey, 1993; Thorogood and Hannaford, 1998; Hernán *et al.*, 2001; Riise *et al.*, 2003).

However, possible associations between MS and passive smoking, particularly in children, have not been evaluated. We carried out a population-based, case–control study based on an existing cohort of children with MS established for other purposes in France, to investigate whether exposure to parental smoking at home, at any time in the child's life, increased the risk of a first episode of MS before the age of 16 years.

Methods

Design and study population

As part of a research program evaluating the impact of environmental risk factors (parental smoking, infectious diseases, vaccinations) on childhood-onset MS, we evaluated the association between parental smoking at home and the risk of childhood-onset MS in children. The case series consisted of patients from the French neuropaediatric MS 'KIDSEP' cohort, which includes

most incident cases of childhood-onset MS occurring in France. The controls were selected from the general population. The base population for this study was the French general population of children and adolescents under the age of 16 years between 1 January 1994 and 31 December 2003.

Case ascertainment

The French KIDSEP neuropaediatric cohort has been described elsewhere (Mikaeloff *et al.*, 2004*a*, *b*). For the study described here, we included only patients with confirmed MS, with a first episode occurring between 1 January 1994 and 31 December 2003, before the age of 16 years. The final study cohort comprised 164 MS patients.

Cases had had at least two clinical episodes of acute inflammatory demyelination of the central nervous system—the criterion for the diagnosis of MS. The index date was the date of onset of the symptoms of the first episode of MS in case patients. A relapse was defined as a second episode of neurological symptoms lasting more than 24 h and followed by partial or complete stabilization or resolution (McDonald *et al.*, 2001; Mikaeloff *et al.*, 2006, 2007). All episodes were recorded by a trained paediatric neurologist, including a description of symptoms, and were identified based on systematic follow-up until June 2006, by means of routine clinical visits, phone calls and written questionnaires.

Control selection

We aimed to match each individual case with 12 controls selected from the French general population, on the basis of age (±6 months), sex and current area of residence, to control for possible geographic variations in MS occurrence. Each matched control was assigned the index date of the case for the evaluation of previous parental smoking at home. Controls were selected by a professional organization specializing in population-based opinion polls and case–control studies on health topics (CSA Institute). Controls were selected by a population-based random method. Telephone numbers were selected at random from the telephone directory corresponding to the geographic area of residence of each case. If the selected number corresponded to a household, the polling organization then determined whether the household included an eligible child, adolescent or young adult. If the household contained an eligible child or adolescent and consent for participation was obtained, the name and address of the eligible household was noted so that the information letter and questionnaire could be sent. Failure to reach the randomly selected phone number was defined as at least 10 unanswered calls to that number. Current area of residence was determined based on postcode (each postcode being associated with a *commune*—an administrative district generally corresponding to a town). Controls with the same postcode as the corresponding case were selected when possible. If too few individuals with the same postcode were available, current area of residence was defined as the *département* of residence (a *département* being a larger administrative district including a number of towns). No more than two controls per household were recruited.

Data acquisition

The cases and controls were each sent the same information letter, and then the same standardized questionnaire. The letter explained our research program evaluating the possible role of environmental risk factors (parental smoking, infectious diseases, vaccines). Environmental risk factors other than parental smoking were dealt with in other studies. The questionnaire requested information about environmental risk factors, familial MS (in siblings and parents), other familial autoimmune diseases (thyroiditis, rheumatoid arthritis, lupus, diabetes requiring insulin treatment and other diseases described as autoimmune by the family doctor, in siblings or parents). Information about the profession of the head of the family was assessed based on the categories defined by INSEE (the French National Institute of Statistics and Economic Studies) (INSEE, 2003).

If the family (for cases and controls under the age of 18 years) or young adult had not returned the requested information within 2 weeks of receiving the information letter and questionnaire, they were recontacted. We sent a maximum of two letters, 4 weeks apart, with two telephone calls, each 2 weeks after the sending of a letter, to try to obtain the required information. A recall was defined as a letter followed by a telephone call.

Assessment of exposure in cases and controls

Information about parental smoking at home at any time point was obtained by a question previously validated for its clarity in a pilot qualitative study. We asked cases and controls whether one or both parents had ever smoked within the home before the index date (the precise date was given).

Statistical analysis

Conditional logistic regression for matched case–control data was used to estimate matched rate ratios (RR) for first episodes of MS [and 95% confidence intervals (CI)] associated with current or past parental smoking at home. Cases and controls not exposed to parental smoking between birth and the date of onset of the symptoms of the first episode of MS (index date) were used as the reference group. In addition to inherent adjustment for the factors used for matching, we also adjusted the analysis for a family history of MS (siblings or parents) or of other autoimmune diseases (siblings or parents), and the profession of the head of the family. All analysis were performed with the use of SAS software (SAS Institute, 1996).

The study, including data input into a computerized system, was approved by the *Comité National Informatique et Liberté* (the French data protection agency). All patients gave oral informed consent for their inclusion in the study and sent back the filled questionnaire in the stamped envelope provided. The organization of the study was approved by the *Société Française de Neuropédiatrie*.

Results

We were able to obtain information about parental smoking for 129 of the 164 cases (response rate 79%). The baseline characteristics of the 129 patients retained for analysis, all of whom provided information on exposure to parental smoking at home, did not differ significantly from those of the 35 patients not included because of missing information (Table 1).

For the selection of controls, we were able to recruit 1536 eligible households by random selection in the current area

Table 1 Baseline characteristics of cases known to have been exposed to parental smoking at home and of cases for whom this information was not available (total $N = 164$)

	Parental smoking information ($N = 129$) N (%) or mean (SD)	No parental smoking information ($N = 35$) N (%) or mean (SD)
Sex male	46 (35.7)	13 (37.1)
Age (years)	11.4 ± 3.7	11.6 ± 3.7
Paris and suburbs ('Ile de France')	40 (31.0)	10 (28.6)
Familial MS history (siblings and parents)	6 (4.7)	1 (2.9)
Familial history of another autoimmune disease (siblings and parents)	8 (6.2)	0 (0.0)
Low socioprofessional status of head of family	57 (44.2)	12 (34.3)
At onset of disease		
Infection during the previous month	38 (29.5)	8 (22.9)
Symptoms		
Multiple	62 (48.1)	14 (40.0)
Transverse myelitis	10 (7.8)	2 (5.7)
Optic neuritis	49 (38.0)	8 (22.9)
Severe mental status change	18 (14.0)	6 (17.1)
Brainstem dysfunction	49 (38.0)	13 (37.1)
Cerebrospinal fluid		
Oligoclonal bands in CSF	61 (47.3)	17 (48.6)
Cells in CSF $\geqslant 0/\mu l$	57 (44.2)	15 (42.9)
Proteins in CSF $\geqslant 500$	24 (18.6)	9 (25.7)
MRI		
Child-MS MRI criteria[a]	71 (55.0)	20 (57.1)
3 Barkhof MRI criteria[b]	64 (49.6)	17 (48.6)

[a]corpus callosum long axis perpendicular lesions or presence of well-defined lesions only (Mikaeloff *et al*., 2004)
[b]Three of the following four criteria: at least one gadolinium-enhancing T1 lesion or $\geqslant 9$ T2 lesions, at least one infratentorial T2 lesion, at least one juxtacortical T2 lesion, $\geqslant 3$ periventricular lesions.

of residence of the cases. Information about parental smoking at home was not provided for 498 of the eligible controls, despite initial consent, due to a lack of response despite the full recall procedure (57%), the selected telephone number never being reached (19%), refusal at first recall (15%) or an incorrect telephone number or address given, making further contact impossible (9%). Thus, we were able to include 1038 controls in the final analysis, individually matched with cases for age, sex and current area of residence. All these controls completed the question about parental smoking on the questionnaire. In total, 24 of the 1038 controls recruited (2%) belonged to the same household as another control (maximum of two controls recruited per household).

Our analyses therefore included 129 MS cases and 1038 matched controls (Table 2). The proportion of family heads with a low socioprofessional status was lower for cases than for controls. The proportion of subjects with a familial history of MS was higher for cases than for controls. The frequency of exposure to passive smoking was 62% for cases and 45.1% for controls (Table 3).

Table 2 Characteristics of the study subjects [N (%); means ± SD]

Characteristic	Cases ($N = 129$)	Matched controls[a] ($N = 1038$)
Sex male	46 (35.7)	385 (37.1)
Age (years)	11.5 ± 3.7	11.3 ± 3.8
Paris and suburbs ('Ile de France')	40 (31.0)	304 (29.3)
Familial MS history (siblings and parents)*	6 (4.7)	18 (1.7)
Familial history of another autoimmune disease history (siblings and parents)	8 (6.2)	77 (7.4)
Low socioprofessional status of head of family*	57 (44.2)	638 (61.5)

[a]Matched for age (±6 months), sex, geographic location (place of residence).
*$P < 0.05$ (χ^2 test for comparison of proportions or t-test for comparison of means).

Parental smoking at home was associated with a significant increase in the risk of a first episode of MS in children (Table 3). After adjustment for a family history of MS or of another autoimmune disease and for the socioprofessional status of the head of the family, the adjusted RR of a first episode of MS associated with exposure to parental smoking at home was 2.12 (95% CI: 1.43–3.15). Stratification for age showed that this increase in risk was significantly associated with a longer duration of exposure in older cases (over the age of 10 years at the index date): RR 2.49 (1.53–4.08), than in younger cases. The increase in risk was not associated with sex, socio-professional status or place of residence (North versus South of France). An analysis excluding the 24 controls recruited from the same household as another control gave similar results.

Discussion

We provide here the first evidence of an increase in the risk of a first episode of MS in childhood associated with parental smoking at home, largely due to the prolonged duration of exposure in older cases.

Several cohort studies have reported an increase in the risk of MS among active smokers. The Nurses' Health Study and the Nurses' Health Study II—reported a pooled incidence rate of MS in women who were current smokers 1.6 (95% CI 1.2–2.1) times higher than that in women who had never smoked. The incidence of MS increased with cumulative exposure to smoking in these studies (Hernán *et al*., 2001). In the general population of Hordaland

Table 3 Relationship between parental smoking at home and the risk of multiple sclerosis (all-population and stratified analysis)

Exposure to parental smoking *N* (%)	Cases	Matched controls[a]	Crude RR	Adjusted RR (95% CI)[b]
Total population	**129**	**1038**		
Unexposed	49 (38.0)	570 (54.9)	1	Reference
Exposed	80 (62.0)	468 (45.1)	2.09	2.12 (1.43–3.15)
Age at index date ⩾10 years	**90**	**708**		
Unexposed	28 (31.1)	371 (52.4)	1	Reference
Exposed	62 (68.9)	337 (47.6)	2.54	2.49 (1.53–4.08)
Age at index date <10 years	**39**	**330**		
Unexposed	21 (53.8)	199 (60.3)	1	Reference
Exposed	18 (46.2)	131 (39.7)	1.37	1.47 (0.73–2.96)
Sex male	**46**	**385**		
Unexposed	18 (39.1)	214 (55.6)	1	Reference
Exposed	28 (60.9)	171 (44.4)	1.99	2.12 (1.09–4.13)
Sex female	**83**	**653**		
Unexposed	31 (37.3)	356 (54.5)	1	Reference
Exposed	52 (62.7)	297 (45.5)	2.15	2.17 (1.33–3.55)
Low socioprofessional status of head of family	**57**	**638**		
Unexposed	22 (38.6)	338 (53.0)	1	Reference
Exposed	35 (61.4)	300 (47.0)	2.40	2.38 (1.28–4.43)
Medium or high socioprofessional status of head of family	**72**	**400**		
Unexposed	27 (37.5)	232 (58.0)	1	Reference
Exposed	45 (62.5)	168 (42.0)	2.46	2.41 (1.33–4.36)
Living in northern France	**88**	**712**		
Unexposed	32 (36.4)	381 (53.5)	1	Reference
Exposed	56 (63.6)	331 (46.5)	2.08	2.06 (1.28–3.30)
Living in southern France	**41**	**326**		
Unexposed	17 (41.5)	189 (58.0)	1	Reference
Exposed	24 (58.5)	137 (42.0)	2.11	2.04 (1.02–4.06)

[a]Matched for age (± 6 months), sex, geographic location (current place of residence).
[b]Adjusted for covariates: familial MS history, familal history of another autoimmune disease, socioprofessional status of the head of the family (except for stratified analysis concerning socioprofessional status).
RR = rate ratio, with 'unexposed' as the reference group, CI = confidence interval.

(Norway), the risk of incident MS among current and past smokers was 1.81 (95% CI 1.1–2.9) times higher than that in subjects who had never smoked (Riise *et al.*, 2003). In the Oxford Family Planning Association Study, the incidence of multiple MS in women who smoked more than 15 cigarettes per day was 1.8 (95% CI 0.8–3.6) times higher than that in women who had never smoked (Villard-Mackintosh and Vessey, 1993). In the Royal College of General Practitioners' Oral Contraception Study, the incidence of MS in women who smoked more than 15 cigarettes per day was 1.4 (95% CI 0.9–2.2) times higher than that in women who had never smoked (Thorogood and Hannaford, 1998).

A few case–control studies have considered this issue. An Israeli study including 241 prevalent MS cases (92% of all the cases identified in the country in 1960) and randomly selected population controls found that the proportion of smokers before the age at onset was significantly higher among cases than among controls (44% versus 36%, $P = 0.02$) (Antonovsky *et al.*, 1965). Conversely, a case–control study carried out in Ferrara, Italy, found no statistically significant differences in adolescent smoking between 104 prevalent MS cases and 150 controls (Casetta *et al.*, 1994). The other studies carried out were subject to methodological limitations. The prevalence of current smoking was similar in MS patients and controls in a British study, but this result is less informative because many patients stopped smoking because of the disease (Simpson *et al.*, 1966). No significant differences in the prevalence of smoking during the year before the onset of the disease were found between 100 MS patients and 100 controls in Alberta, Canada (Warren *et al.*, 1982). However, the control group included patients with arthritis, a condition associated with smoking (Vessey *et al.*, 1987; Silman *et al.*, 1996).

Ascertainment of the first episode of MS was reliable in our study, as previously shown (Mikaeloff *et al.*, 2004*a*, *b*, 2006, 2007). Patients were recruited from the French KIDSEP neuropaediatric cohort, which was constituted for other purposes. We were able to collect the vast majority of incident cases nationwide (in France). For each first episode, the precise date and a description of symptoms were recorded. MS was diagnosed based on the gold-standard clinical criterion of relapse. The precise dates of the first and second episodes were known, avoiding the bias associated with the potential gap between the date of onset of first symptoms and the identification of MS onset or diagnosis of MS.

The selection of controls is a major challenge in case–control studies, because they must come from the same study population base as the cases (Rodrigues and Smith, 1999; Grimes and Schulz, 2005; Bernstein, 2006). As the cases in our study were taken from the French population as a whole, we carried out random sampling for the selection of controls from the French population, but selected subjects of the same age and sex and from the same geographic area as the corresponding case. A potential selection bias may result from the relatively high non-responder rate among controls, although this rate remains low for this type of population-based, case–control study (Grimes and Schulz, 2005). Indeed, as we have no information about non-responders, our results may be biased if non-responders were more likely to be heavy smokers, as smoking may be associated with low socio-economic status. However, this bias is probably modest because the prevalence of smoking among controls was consistent with that expected for the general population of parents of children in France over the same period (between 40% and 50% of newborns are exposed to parental smoking at home either *in utero* or after birth) (Tubiana, 1997). The response rate was lowest for controls in which the head of the family had a low socioprofessional status, as reported in similar studies (Rodrigues and Smith, 1999). There could be a potential confounding bias related to the difference in socioeconomic status between cases and controls. Socioeconomic status is associated with exposure (smoking) but is not known to be associated with incident MS. Indeed, there is no known socioeconomic risk factor other than smoking that could be identified in childhood-onset MS, with strong evidence to suggest causality (Marrie, 2004). We therefore believe that this possible source of bias could not account for the higher risk observed and was probably controlled for by our adjustment method. A complementary analysis showed that the low proportion of controls recruited from the same household as another control, with a similar pattern of exposure, did not affect our results.

The reliability of the information about exposure to passive smoking provided in a study of this type could be called into question. Differential reporting of exposure to parental smoking at home between cases and controls is unlikely, because smoking is not widely recognized as a risk factor for MS among the general public. The amplitude of the potential recall bias is likely to be very low in this study, given the clear and simple way in which the question was asked. Moreover, the information letter explained our research program evaluating the possible role of several potential environmental risk factors, the main focus was on vaccines, in line with the public health debate. Information about parental smoking at home is relevant to the true exposure of children to passive smoking, as demonstrated by previous studies (El Ansari, 2005; Tanaka *et al.*, 2006; Olivieri *et al.*, 2006). A spurious positive association between smoking and childhood MS could occur if controls with non-smoking parents were more likely to participate than controls with smoking parents. This possible selection bias is probably modest, because the prevalence of smoking among controls was consistent with that expected for the general population of parents of children in France over the same period, as previously reported (Tubiana, 1997). Moreover, the effect of exposure duration (related to cumulative dose) in older patients, as observed in our study, provides evidence for the causality of the association (Kramer, 1988).

We controlled for potential confounding factors previously identified in epidemiological studies of risk factors for MS (Compston and Coles, 2002; Mikaeloff *et al.*, 2004*a*, *b*). We checked that the cases that did not respond to our questionnaire had similar baseline characteristics to the cases retained in the analysis. As the probability of exposure might vary according to geographic location and the socioprofessional activities of the parents, controls were matched with cases on the basis of geographic location (current area of residence) and the analysis was adjusted for the socioprofessional status of the head of the family. We also matched cases and controls for age and sex and adjusted for the main potential confounding factors: family history of MS and of other autoimmune diseases.

The basis of the relationship between smoking and a higher incidence of MS is unclear in both children and adults. Smoking has been found to be associated with a high risk of developing other autoimmune diseases, such as rheumatoid arthritis (Silman *et al.*, 1996) or systemic lupus erythematosus (Hardy *et al.*, 1996). The underlying mechanism may involve a direct effect of cigarette smoke components on the blood–brain barrier or a nicotine effect on microvascular blood flow in the brain (Hans *et al.*, 1993). Alternatively, some components of cigarette smoke may have direct toxic effects on the central nervous system. Serum concentrations of cyanide, a component of cigarette smoke, and its main metabolite, thiocyanate, are strongly correlated with the level of tobacco consumption (Lundquist *et al.*, 1987). The administration of high doses, as in adults who actively smoke, has been shown to cause demyelination in the central nervous system of animals, but similar effects were also observed at lower doses, equivalent to those resulting from passive smoking in children (Smith *et al.*, 1963; Bass *et al.*, 1968). It was recently demonstrated that exposure to passive smoking could induce a deficiency of interferon gamma producing cells in adenoids of children (Avanzini *et al.*, 2006). Smoking may increase the risk of MS by increasing the frequency and persistence of respiratory infections (Graham, 1990; Sriram *et al.*, 1999).

In conclusion, this first, population-based, case–control study in children found that the risk of MS occurrence was higher in the children of parents who smoked at home than in the children of parents who did not smoke at home. The duration of exposure also had an effect on this risk. However, further studies would be required for a more

precise assessment of the effect of the duration and intensity of exposure, quantified by a cumulative evaluation of cigarette smoking in parents. Another important issue worthy of further investigation in children is the association between passive smoking and a severe course of the disease. One study in adults has reported an increase in the risk of clinical MS progression associated with cigarette smoking (Hernán *et al.*, 2005).

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Appendix

Pediatric neurology departments (France): D. Amsallem (Besançon); P. Aubourg (Hôpital Saint-Vincent de Paul, Paris); M. A. Barthez, P. Castelnau (Tours); P. Berquin (Amiens); O. Boespflug (Clermont-Ferrand); J. C. Carrière, C. Cances, Y. Chaix (Toulouse); J. M. Cuisset, J. C. Cuvelier, L. Vallée (Lille); A. de Saint-Martin (Strasbourg); I. Desguerre, O. Dulac (Necker-Enfants Malades, Paris); V. Des Portes, C. Rousselle, D. Ville (Lyons); B. Echenne, F. Rivier (Montpellier); P. Evrard (Hôpital Robert Debré, Paris); A. Joannard (Grenoble); P. Landrieu, Y. Mikaeloff, M. Tardieu (Bicêtre); M. O. Livet (Aix en Provence); J. Mancini, B. Chabrol (Marseilles); J. Motte, N. Bednarek, P. Sabouraud (Reims); S. Napuri, L. Lazaro (Rennes); S. N. Guyen (Nantes); S. Peudenier (Brest); F. Pouplard (Angers); J. M. Pedespan (Bordeaux); S. Perelman, C. Richelme (Nice); N. Perez (Belfort); D. Rodriguez, T. Billette de Villemeur, M. L. Moutard, G. Ponsot (Hôpital Trousseau, Paris); M. C. Routon (Orsay); H. Testard (Annemasse), C. Van Hulle (Rouen).

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