

Parental smoking, socioeconomic factors, and risk of invasive meningococcal disease in children: a population based case-control study

P Kriz, M Bobak, B Kriz

Abstract

Aims—To investigate the effects of parental smoking, socioeconomic characteristics, and indoor environment on the risk of invasive meningococcal disease in children.

Methods—Population based case-control study. A total of 68 incident cases of invasive meningococcal disease in children less than 15 years old were compared with 135 controls selected from the same school and matched for year of birth, sex, and place of residence. Information on exposures was obtained in interviews with parents.

Results—Invasive meningococcal disease was strongly associated with parental smoking; rate ratios adjusted for socioeconomic factors were 3.5 (95% confidence interval 1.4–8.7) for smoking of mother, 3.2 (1.5–6.9) for smoking of father, and 2.7 (1.3–5.4) for every 20 cigarettes smoked at home on an average day. The risk of the disease was strongly inversely related to maternal education and, less strongly, to ownership of a car and of a weekend house, father's education, crowding, and the number of siblings, but these associations were reduced or eliminated in multivariate models. The type of heating and cooking (used as proxies for indoor air pollution) were not associated with the disease.

Conclusion—The risk of invasive meningococcal disease in children is strongly influenced by parental smoking and unfavourable socioeconomic circumstances.

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Keywords: meningococcal disease; smoking; socioeconomics; risk

Invasive meningococcal disease is a rare but important disease, mainly because of the relatively high case fatality rate. Most people make contact with *Neisseria meningitidis* during their life (the prevalence of carriers of *N meningitidis* at any given time is around 10%¹ and can reach 50% or more in some groups, such as army conscripts²) but the vast majority never get an invasive disease. The reasons why some people do get invasive meningococcal disease while most do not are only poorly understood. It is likely that besides the factors related to the infectious agent or the host, environmental characteristics also play a role.

Several recent studies have indicated that the risk of invasive meningococcal disease is influenced by environmental factors. Parental smoking appears to be a particularly strong risk factor for invasive meningococcal disease.^{3–7} The frequency of the disease seems higher in deprived areas,⁸ and all studies in individuals found that the risk was lower in children living in more favourable socioeconomic conditions.^{3–7}

In the Czech Republic, a new meningococcal clone, ET-15/37 (with prevailing phenotype C:2a:P1.2,P1.5) emerged in 1993, and caused epidemics with high case fatality.⁹ Together with a targeted vaccination programme,¹⁰ an active surveillance programme has been introduced, a part of which was a population based case-control study of environmental factors contributing to the risk of invasive disease. The main results of this study are described in this paper. The study covered all age groups but because the incidence was higher in children (5.2 per 100 000 in the age group 0–14 years in 1997, compared to 1.6 per 100 000 at all ages), this paper focuses on children.

Methods

We conducted a population based case-control study in 35 districts of the Czech Republic (districts participating in the intensive surveillance programme). All incident cases of invasive meningococcal disease diagnosed in the participating districts between October 1996 and May 1998 were eligible for the study. In total, 71 cases were identified in children younger than 15 years; 68 of them (their parents) agreed to participate in the study. The diagnosis was based on cultivation of *N meningitidis* from cerebrospinal fluid and/or blood (n = 59), antigen detection in cerebrospinal fluid (n = 1), direct microscopy of cerebrospinal fluid (n = 3), and clinical signs only (n = 5). The most common serogroups of *N meningitidis* were C (30 cases) and B (25 cases).

To each case, two controls were matched by the following criteria: age (within one year age group), sex, district, and urban–rural place of residence. (Because of the logistical problems, two cases had only one matched control and one case had three controls.) The controls were recruited from healthy children at the same school as the case as soon as possible after the reference case was identified. This method of incidence density sampling of controls (when controls may later become cases) means that the effect measures derived from the analyses may be directly interpreted as rate ratios.¹¹

National Reference Laboratory for Meningococcal Disease, Centre for Epidemiology and Microbiology, National Institute of Public Health, Srobarova 48, 100 42 Prague 10, Czech Republic
P Kriz
B Kriz

International Centre for Health and Society, Department of Epidemiology and Public Health, University College London, 1–19 Torrington Place, London WC1E 6BT, UK
M Bobak

Correspondence to:
Dr Kriz
email: paula.krizova@szu.cz

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Table 1 Numbers (percentages) of cases and controls by age group, parental smoking, and socioeconomic characteristics

	Cases (n = 68)	Controls (n = 135)
Age group (years)		
Less than 1	15 (22)	30 (22)
1–4	30 (44)	61 (45)
5–9	15 (22)	29 (21)
10–14	8 (12)	15 (11)
Parental smoking		
Mother smokes	33 (50)	25 (19)
Father smokes	42 (63)	43 (33)
None	22 (32)	82 (61)
Mother only	5 (7)	10 (7)
Father only	14 (21)	30 (22)
Both	27 (40)	13 (10)
Mean number (SD) of cigarettes smoked daily at homes with at least one smoker	28.5 (13.4)	19.6 (8.8)
Mother's education		
Primary	18 (27)	13 (10)
Apprenticeship	28 (42)	54 (41)
Vocational	18 (27)	54 (41)
University	3 (4)	12 (9)
Father's education		
Primary	12 (18)	14 (11)
Apprenticeship	37 (55)	70 (53)
Vocational	15 (22)	38 (29)
University	3 (4)	9 (7)
Material circumstances		
Family owns a car	32 (47)	84 (64)
Family owns a cottage	3 (4)	20 (15)
Crowding (>1 person per room)	36 (54)	49 (37)
Number of siblings		
None	15 (22)	33 (25)
1	33 (49)	71 (54)
2	11 (16)	21 (16)
3+	8 (12)	7 (5)
Spends weekends in countryside		
<1 day a month	22 (34)	30 (23)
1–5 days a month	18 (28)	33 (25)
>5 days a month	25 (38)	70 (53)
Heating		
Central	47 (73)	99 (77)
Gas	8 (12)	20 (16)
Coal	9 (14)	9 (7)
Cooking		
Gas	38 (69)	77 (62)
Electricity	15 (27)	44 (35)
Coal	2 (4)	3 (2)

Data on cases and controls were collected by a structured questionnaire completed by the children's parents during an interview. Interviews were conducted by the local epidemiologists, and took place either at the child's home or, if this was not convenient, at the District Public Health Service office. Parents reported whether they were currently smoking cigarettes, and how many cigarettes on average they smoked at home per day. From these variables, we computed a daily average number of cigarettes smoked at home by both parents.

Parental education was categorised into primary or less (up to 9 years), apprenticeship (two to three years of vocational training after primary school), secondary (equivalent to A level), and university (a completed degree). To assess the material conditions of the family, we collected data on car ownership; ownership of a weekend house or cottage (a common feature in the Czech Republic); crowding (more than one person per room); number of siblings of the child (none, one, two, and three or more); and the average numbers of days spent outside of town during a typical month. As an additional indicator of indoor air pollution, we have included questions on the type of cooking (gas, electricity, or coal) and heating (central, gas, or coal).

The data were analysed by conditional logistic regression. Crude rate ratios were estimated

first, and they were then adjusted for socioeconomic factors and parental smoking. Parental smoking was modelled both as a categorical variable (smoking of mother, father, or both) and as a continuous variable (average daily number of cigarettes smoked at home, with exposure equal to 0 where parents did not smoke at home). The latter variable was also used as categorical, with four groups (0, 1–9, 10–19, and 20 cigarettes or more smoked at home daily). In the multivariate analysis, only one indicator of parental smoking was entered in a model.

Results

Table 1 presents a description of the study subjects (the matching was broken in the table). Among controls, 19% of mothers and 33% of fathers smoked, and in 10% of controls both parents smoked. The proportion of smoking parents was substantially higher among cases, and in families with at least one smoker, the average daily number of cigarettes smoked at home was higher among cases than among controls. Parental education and family material conditions were also more favourable among controls.

Among controls, parental smoking was associated with most indicators of socioeconomic status, most strongly with education. All socioeconomic factors were mutually associated: the correlation coefficient between mother's and father's education was 0.56; other coefficients were between 0.2 and 0.3 (not shown in table).

Table 2 shows the associations between invasive meningococcal disease and parental smoking and socioeconomic circumstances. Maternal smoking was related to an almost fivefold increase in the risk of the disease; smoking of the father increased the risk almost four times. Children of parents who both smoked had almost nine times higher risk than children of both non-smoking parents. An increase in the average number of cigarettes smoked at home by 20 was associated with a 3.5-fold increase in risk of meningococcal disease. When the number of cigarettes smoked at home was categorised, the relative risk (95% confidence intervals) compared to non-smoking homes were 1.86 (0.56–6.24) for 1–9 cigarettes, 2.74 (1.03–7.27) for 10–19 cigarettes, and 4.16 (1.89–9.16) for 20 cigarettes or more (not shown in the table). Although adjustment for parental education and material circumstances somewhat reduced these estimates, they remained strong and highly statistically significant. For example, each 20 cigarettes smoked at home were associated with a rate ratio of 2.65 (1.33–5.35). Using the adjusted effects, between 34% and 42% (depending on the indicator of parental smoking) of invasive meningococcal disease in children could be attributable to parental smoking.

Among socioeconomic factors, maternal education was the strongest predictor of meningococcal disease but education of the father, not crowded housing, ownership of a car, ownership of a weekend house/cottage, and spending weekends outside of town were all significantly associated with a reduced risk

Table 2 Crude and adjusted rate ratios of invasive meningococcal disease for parental smoking and socioeconomic circumstances

	Crude RR		Adjusted RR*	
	RR	95% CI	RR	95% CI
Parental smoking				
Mother (Yes v No)	4.89	2.29–10.5	3.52	1.42–8.68
Father (Yes v No)	3.73	1.95–7.15	3.21	1.49–6.94
None	1.0		1.0	
Mother only	2.01	0.54–7.43	1.00	0.21–4.79
Father only	1.57	0.70–3.53	1.47	0.55–3.95
Both parents	8.79	3.42–22.6	8.23	2.30–29.3
Smoking at home				
Per 20 cigarettes a day	3.48	1.89–6.42	2.65	1.31–5.35
Mother's education				
Primary	1.0		1.0	
Apprenticeship	0.23	0.07–0.72	0.50	0.11–2.30
Secondary	0.12	0.03–0.42	0.45	0.08–2.70
University	0.08	0.01–0.45	0.25	0.03–2.23
		p trend <0.001		p trend 0.287
Father's education				
Primary	1.0		1.0	
Apprenticeship	0.43	0.14–1.36	0.40	0.08–2.03
Secondary	0.33	0.10–1.14	0.58	0.09–3.59
University	0.30	0.06–1.58	0.52	0.05–5.53
		p trend 0.099		p trend 0.987
Car ownership				
Yes	0.44	0.22–0.85	0.49	0.19–1.24
Weekend house				
Yes	0.23	0.07–0.83	0.28	0.04–1.80
Crowding				
>1 person per room	2.18	1.12–4.25	1.13	0.44–2.88
No. of siblings				
None	1.0		1.0	
1	1.25	0.49–3.16	1.20	0.41–3.34
2	3.21	0.79–13.1	1.18	0.31–4.51
3+	3.67	0.40–33.3	0.80	0.10–6.17
		p trend 0.087		p trend 0.968
Spending weekends out of town				
<1 day a month	1.0		1.0	
1–5 days a month	0.43	0.15–1.21	0.94	0.20–4.32
>5 days a month	0.18	0.05–0.57	0.41	0.10–1.74
		p trend 0.004		p trend 0.166
Heating				
Central	1.0		1.0	
Gas	0.71	0.27–1.90	0.43	0.11–1.75
Coal	3.10	0.91–10.6	1.26	0.20–7.92
Cooking				
Gas	1.0		1.0	
Electricity	0.30	0.06–1.43	0.60	0.10–3.74
Coal	1.79	0.25–12.9	1.69	0.03–98.4

*Each variable was adjusted for smoking, mother's and father's education, ownership of car and cottage, and crowding. Only one indicator of smoking was included in each model. Non-smoking variables were adjusted for categorical measure of parental smoking (none, mother only, father only, both).

of the disease in bivariate analyses (table 2, second column). In multivariate analyses, none of these variables remained significantly related to the disease (table 2, third column). However, the loss of statistical significance of the effects of car and weekend house ownership was primarily a result of loss of statistical power, rather than to the removal of a confounding factor.

Finally, we examined in more detail to what extent were the effects of socioeconomic factors mediated by parental smoking. The effect of crowding was eliminated after adjustment for parental smoking (fully adjusted rate ratio 1.24, 95% confidence interval 0.54–2.84). The effect of maternal education was also reduced after controlling for parental smoking; the adjusted rate ratios were 0.36 (0.08–1.59), 0.38 (0.06–2.36), and 0.14 (0.01–1.57) for children of mothers with apprenticeship, secondary, and university education, respectively, compared to children of primary educated mothers (p value for trend 0.232, not shown in table). The rate ratios for car and weekend house ownership did not change substantially after controlling for pa-

rental smoking, but the confidence intervals became wider owing to loss of power (not shown).

Discussion

This study suggests that parental smoking and the socioeconomic environment strongly influence the risk of invasive meningococcal disease in children; among socioeconomic factors, maternal education seems to play a prominent role in this population.

There are two main potential methodological problems with case-control studies: selection bias (related to recruitment of cases and selection of appropriate controls), and reporting bias (related to the retrospective nature of exposure ascertainment). In this study, selection bias is not likely. The study was population based, and subjects were recruited prospectively, as cases occurred in the study population. Reporting of invasive meningococcal disease is compulsory in the Czech Republic, and the coverage has been good.¹² In addition, an active surveillance was introduced after the outbreaks in 1993, in order to improve the accuracy and completeness of data collection and to speed up the reporting.^{9–10} Local epidemiologists searched for new cases in collaboration with local clinicians in district hospitals. It is extremely unlikely that a substantial number of cases were missed. Diagnostic bias is also unlikely; excluding the five cases who were diagnosed on the basis of clinical signs only did not change the results. The controls were selected from the same population from which the cases came, and their characteristics were similar to census data or to distribution found in previous studies in the Czech parents.^{13–14}

Reporting bias is also improbable. The socioeconomic factors examined in this study are relatively stable and objective and, as mentioned above, their distribution among controls was similar to other recent population samples. It is not likely that parents of cases would systematically overestimate their smoking or underestimate their socioeconomic status and education. One would rather expect that parents of cases, if they suspected that smoking may be related to the disease, would tend to underreport their smoking habits; this would underestimate the effects of parental smoking. We think that it is unlikely that selection or reporting bias have affected the validity of this study.

Several biological mechanisms can provide the link between tobacco smoke and meningococcal disease. Smoking is negatively associated with cell mediated and humoral immunity,¹⁵ causes a fall in salivary IgA and a rise in IgM concentrations,¹⁶ affects respiratory epithelial functions, and increases bacterial adherence and the risk of inflammation and other infections.^{17–19} The observation that smokers are more likely to be meningococcal carriers is consistent with the increased risk of invasive meningococcal disease.²⁰ Exposure to smoke causes direct damage to the nasopharyngeal mucosa; passive smoking is associated with an increased risk of respiratory disease in young children.^{21–23} As children have

more delicate mucous membranes, they may be more likely to acquire meningococcal disease if they are chronically exposed to passive smoking.²⁰

The epidemiological literature, although not extensive, is also consistent. Two British studies^{3,4} and two US studies^{5,6} found an increased risk in children of smoking parents, and a South African study found that parental smoking increased the risk of meningococcal disease in the presence of a recent respiratory infection.⁷ The adjusted relative risks for maternal smoking in the US studies were 3.8 (1.6–8.9)⁵ and 2.9 (1.5–5.7)⁶; in the more recent British study, passive smoking in the home was associated with an odds ratio of 7.5 (1.5–38.7).⁴ Our results are consistent with these studies.

We have used several markers for parental smoking. The largest relative risk (more than eightfold) was observed in the children of parents who both smoked. This may be an overestimate, as families where both parents smoke are likely to have multiple social disadvantage which would not be taken into account by adjusting for the socioeconomic factors in the questionnaire. A rate ratio of 2.6 per 20 cigarettes smoked at home daily seems a conservative estimate of the real effect of passive smoking in children, but it indicates a relatively strong effect.

Smoking is a major source of indoor air pollution. We have included two other indirect measures of indoor pollution previously linked with respiratory symptoms and disease in children: type of heating (particles are a byproduct of coal burning) and cooking (burning gas generates nitrogen dioxide). Spending weekends out of town may also be related to lower indoor exposures, in addition to being a socioeconomic indicator. However, the numbers of children in individual categories were small and the estimates were imprecise; the results do not allow firm conclusions on indoor environment and meningococcal disease.

Existing data suggest that socioeconomic disadvantage increases the risk of meningococcal disease. In Brazil, the incidence of meningococcal disease was about two times higher in deprived areas than in more affluent areas.⁸ In both US studies, low maternal education and other social characteristics were associated with increased risk of the disease.^{5,6} In the UK, crowding and several other social indicators were related to meningococcal disease.^{3,4} Our results are consistent with these reports, and confirm our previous findings that maternal education is a powerful predictor of children's health.^{13,24} Some of the association between maternal education and meningococcal disease was (statistically) mediated by maternal smoking, but the fully adjusted rate ratios, despite the loss of statistical significance, suggest that a part of the effect may be independent from parental smoking. The effects of the father's education were largely eliminated in multivariate analysis. The observation that the effects of ownership of a car and a weekend house remained relatively unchanged in multivariate

models indicates that material conditions may also contribute to the risk of the disease.

The socioeconomic factors measured in our study represent different aspects of living conditions relevant to the Czech situation. Education appears the best predictor of individual health behaviours of adults in Czech Republic,²⁵ and available evidence suggests that maternal education is the best predictor of child health in the Czech population.^{13,24,26} The distribution of income in the Czech Republic is still relatively equitable, despite the increase in income inequality since 1992.²⁷ Crowding, ownership of a car, and a weekend house or a cottage may be better indicators of the material circumstances than official income in post-communist societies. In particular, car and weekend house (or cottage) are both sufficiently desirable and common to be used as proxies for material circumstances. Because of the limited housing market, crowding is probably a poor measure of financial situation; it rather measures the housing conditions per se. Weekends spent outside of the town are mostly those spent in the weekend house but they also include trips, holidays, and visits to relatives and friends. The number of siblings were included as a possible indicator of both socioeconomic circumstances and, possibly, the risk of contacts with the infectious agent.

The findings on meningococcal disease are similar to other infections. For example, social deprivation and crowding was found to be associated with bacterial meningitis.²⁸ Maternal smoking during pregnancy increased risk for sudden infant death syndrome and childhood infections.²³ Passive smoking and low socioeconomic status now appear to be established as risk factors for invasive meningococcal disease. Although the exact mechanisms are not known, improving social conditions and reducing parental smoking seem appropriate interventions, not only with respect to meningococcal disease.

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Neutralising enterotoxin

The verotoxin (Shiga toxin) of Shiga toxin producing organisms—such as *Escherichia coli* 0157:H7, binds to specific carbohydrate containing receptors on intestinal epithelial cells and on renal and vascular endothelial cells. Treatment aimed at preventing this binding should be effective. Work in California (Adrienne W Paton *et al. Nature Medicine* 2000;6:265–70; see also commentary *Ibid*: 257–8) may have made this possible.

Theoretically, the enterotoxin could be bound by administering synthetic carbohydrate which mimics the natural enterotoxin receptor, but the problem with this approach is that such synthetic carbohydrate binds only small amounts of enterotoxin and very large doses would be needed. The Californian workers have apparently overcome this difficulty in an ingenious way. They took a strain of *E coli* which lacked the enzymes responsible for lipopolysaccharide production (glycosyl transferases) and inserted into it two new galactosyl transferase genes, one from a meningococcus and one from a gonococcus. The *E coli* then produced lots of lipopolysaccharide with the same end units as the enterotoxin receptor. The dried bacteria were 10 000 times more effective at binding enterotoxin than was the synthetic carbohydrate previously available, and a live or dead preparation of the transformed *E coli* given orally to mice protected them against a lethal dose of verotoxin.

Another recent report, in *Nature* (PI Kitov *et al.* 2000;403:669–72) described the stereochemical synthesis of a complex trisaccharide containing molecule (called STARFISH because of its configuration) with high affinity for verotoxin. It is suggested that oral administration of the bacterial preparation might bind verotoxin in the gut and intravenous administration of the STARFISH complex might deal with systemic verotoxin.

The hope, of course, is that these new preparations can be given at the right time and in sufficient quantity to influence the course or development of the haemolytic uraemic syndrome.

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