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Is it exposure to cigarette smoke or to smokers which increases the risk of meningococcal disease in teenagers?

Pietro G Coen,1* Joanna Tully,1 James M Stuart,2 Deborah Ashby,3 Russell M Viner4 and Robert Booy1

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Background Passive smoking appears to increase the risk of meningococcal disease (MD) in adolescents. Whether this effect is attributable to exposure to cigarette smoke or contact with smokers is unknown.

Methods We conducted a prospective population-based case–control study with age, sex matched-controls in 1:1 matching. Participants were 15–19 year old with MD recruited at hospital admission in six regions (65% of the population of England) from January 1999 through June 2000, and their matched controls. Data on potential risk factors were gathered by confidential interview, including seven passive smoking variables. Factor analysis was performed to assess the dimensionality of the passive smoking exposure variables. The data were analysed with univariate and multivariate conditional logistic regression.

Results 144 case–control pairs were recruited (51% male; median age 17.6). Factor analysis identified two independent factors representing passive smoking (P<0.01), one associated with ‘exposure to smoke’, the other with ‘smoker contact’. Only smoker contact was a significant risk factor for MD (OR = 1.8; 95% CI 1.0–3.3; P = 0.05). In multivariate analysis this factor was still associated with MD independently of potential confounders such as active smoker status and household crowding.

Conclusion Contact with smokers is associated with increased risk of MD in adolescents. This is more likely to be due to higher carriage rates in smokers than to exposure to smoke and emphasizes the importance of public health measures to stop smoking. In epidemiological studies that assess risk from passive smoking, exposure to smoke should be differentiated where possible from contact with smokers.

Introduction

Meningococcal disease (MD) is a life-threatening illness with peaks of incidence in young children and teenagers.1 Despite successful immunization programmes against serogroup C meningococci, MD remains a significant problem; the majority of cases are caused by serogroup B and there is no efficacious vaccine to protect the population from these bacteria. The study of risk factors may help identify other forms of preventive action against MD.

Passive smoking increases the risk of many human diseases including heart and lung disorders,2–9 independently of the effects of active smoking. Passive smoking is the exposure to ‘sidestream’ smoke (SS). SS evolves from the smouldering end of a cigarette while the smoker is not puffing, and contributes substantially (85%, the rest being mainstream smoke, MS) to passive smoke exposure. Since puffing increases air flow through the burning cone of the cigarette, MS results from tobacco combustion at a higher temperature than that which results in SS and thus the major chemical components of the two types of smoke are qualitatively distinct.10 Several in vitro experiments have demonstrated the disruptive effect of passive smoke on the epithelial cell lining of the upper respiratory tract and on the
mucosal immune system. Tobacco smoke has been shown to impair the function of monocytes and macrophages, to enhance bacterial adherence of the epithelial lining of the upper respiratory tract, to suppress immunoglobulin production, and to disrupt the ciliary activity of epithelial cells of the upper respiratory tract. Passive smoking was also shown to impair the proper functioning of the circulatory system.

Studies carried out in Greece, Norway, the USA, and the UK have demonstrated a significant correlation between active and passive smoking with asymptomatic meningococcal carriage, in both adults and children. The association between MD and passive smoking was also clearly established in young children and Kriz et al. demonstrate a dose-response relationship. Few studies have investigated the effect of passive smoking on MD in teenagers and adults. Stuart et al. detected an effect in adults aged >20 years but no effect in teenagers. Fisher et al. detected an association between passive smoking in and/or out of the home and MD in those aged <18 years. Interpretation of these studies remains controversial. In particular, as active smoking was shown to be associated with carriage, it is not clear whether passive smoking could increase risk of MD via a direct effect of smoke on the depression of the mucosal immune system or through an indirect effect of infectious contact with a smoker or both.

Epidemiological studies of the effects of passive smoking on the risk of disease have a fundamental problem. There is no universally agreed working definition for the measurement of passive smoking. In theory, passive smoking is the exposure to SS, which is difficult to measure directly. Hence, the vast majority of epidemiological studies use indirect measurements of passive smoking that usually rely on the opinion of the study subject. Examples are parental smoking in the home, presence of ‘other’ smoker(s) in the household and number of smokers living in the household. Others have attempted to obtain a quantitative measure of passive smoke, such as the average daily number of cigarettes smoked in the house and the number of cigarette packs smoked daily in the household by each household member. Few studies enquired about the exposure to ‘smoke’ rather than smokers and their smoking behaviour. A problem with all these different measures is that they do not separate the effects of exposure to smoke and the exposure to the smokers who may themselves be sources of infection.

Clearly these characteristics of passive smoking mean that the definition of this exposure remains necessarily arbitrary. In this study we aim to describe the methodology for improving the interpretation of many of these passive smoking measures, within the context of a case–control study, in order to help decide what components of ‘passive smoking’ may be considered to be risk factors for MD in teenagers. We introduce factor analysis as a novel method of interpretation of passive smoking data, with particular reference to the question: is smoke or contact with a smoker the true exposure of MD risk?

**Methods**

**Data collection**

We conducted a prospective population-based case–control study covering six contiguous regions of England representing ~65% of the population of England. Data were collected from January 5, 1999 until June 9, 2000, covering two winter MD peaks. Teenagers from 15 to 19 years of age admitted to hospital with a primary clinical diagnosis of meningococcal infection (signs of septicaemia and/or meningitis in association with haemorrhagic rash) were recruited between January 1999 and June 2000. The study population comprised 144 survivors of MD and 144 respective age-matched, sex-matched, and geographically-matched controls. Recruitment details have been previously described. Cases and controls were interviewed with a structured questionnaire and questioned on the occurrence of risk-taking behaviours (e.g. active and passive smoking, alcohol and illicit drug consumption, intimacy, and other behaviours). To minimize recall bias, all controls and cases were questioned about the 2 week period immediately preceding the interview and disease onset, respectively. The list of relevant variables for our analysis is displayed in Table 1.

**Statistical methods**

Analytical methods are summarized by the flow chart in Figure 1. All analyses were carried out in STATA 8.0. We used factor analysis with the maximum-likelihood option for the estimation of factor loadings. The maximum likelihood algorithm was iterated from 50 random starting values in order to maximize the chances of obtaining the ‘global’ maximum likelihood estimates. ‘Varimax’ rotation was applied to the matrix of factor loadings.

**Table 1** Variable list

<table>
<thead>
<tr>
<th>Passive smoking variables</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of smoker household guests ()</td>
</tr>
<tr>
<td>Number of close contacts who smoke ()</td>
</tr>
<tr>
<td>Number actually smoking in the household ()</td>
</tr>
<tr>
<td>Exposure to smoke at work</td>
</tr>
<tr>
<td>Case/control status O</td>
</tr>
<tr>
<td>Sniffing glue or exposure to illegal drugs 2</td>
</tr>
<tr>
<td>Attendance of pubs or bars 2 weeks prior interview 2</td>
</tr>
<tr>
<td>Occupation (including student status) 1, 2</td>
</tr>
<tr>
<td>Meningococcal vaccination status 1, 2</td>
</tr>
<tr>
<td>Attendance of religious ceremonies in the 2 weeks prior interview 2</td>
</tr>
</tbody>
</table>

Age and sex are not included because cases were matched to controls by age and sex. Passive smoker variables hypothesized to be more associated with smoker contact () or with smoke exposure (). Multivariate model usage: O = outcome variable; 1 = included in the first multivariate model, and 2 = included in the second multivariate model (see Figure 1 for more details).
Factor analysis, full data set, with 6 household crowding association including socioeconomic status, occupation, and passive smoking. We used factor analysis based on Krzanowski’s guidelines to the resulting matrix of coefficients, \( \hat{B} \), was then applied for the estimation of factor Z-scores. The dimensionality of the passive smoking data were established with the Chi-square tests for the null hypotheses of \( x \) factors vs no factors, and \( x \) factors vs more factors (\( x \) an integer), as output by the STATA factor command. After interpretation of the meaning of the estimated ‘passive smoke’ factors, we used multivariate conditional logistic regression to assess their association with MD. We used a seasonal variable of MD incidence to account for delay in control interview. We controlled for variables that might confound the association including socioeconomic status, occupation, and household crowding.

**Factor analysis and the a priori hypothesis for passive smoking**

We used factor analysis based on Krzanowski’s guidelines to investigate the true dimensions (or ‘latent variables’) of the passive smoking variables, and we subsequently tested their association with risk of MD. Latent variables (factors) are Z-scores (with expectation of zero mean and standard deviation 1) and are calculated from the expression:

\[
F_k = \sum_{i=1}^{7} s_{ki} \cdot z_i,
\]

where \( F_k \) refers to the \( k \)th factor, \( z_i \) is the Z-score of the \( i \)th passive smoking variable, and \( s_{ki} \) is the scoring coefficient. The latter shows the relative ‘importance’ or ‘influence’ played by each of the seven passive smoking variables on the magnitude of each factor.

Our a priori hypothesis was that some variables are more associated with contacts with smokers (number of overnight guests, household residents, close contacts, partner who smokes), others are more associated with exposure to smoke (number of household members actually smoking in the house, number of cigarettes smoked per day in the house), and smoke exposure at work could be associated with either manifestation of passive smoking. The hypothesis, therefore, predicts that we would detect at least two latent passive smoking variables, one tracking the degree of contact with smokers and the other tracking exposure to smoke (Table 1).

**Role of the funding source**

The Meningitis Research Foundation, who funded this study, played no role in the design, data collection, analysis, and the write-up of this paper.

**Results**

During the study period 319 statutory notifications of MD in teenagers aged 15–19 years were made to public health units in the study regions. Of these, 244 were referred to the study centre and full questionnaire data were collected from 144 cases and their matched controls (51% male; median age 17.6 years). Correlation and variance-covariance matrices (data not shown) show that all passive smoking variables were correlated with each other to varying degrees of significance. Univariate matched analyses for the passive smoking variables are presented in Table 2.

Factor analysis of the seven passive smoking variables revealed that the dimensionality of the data was 2. The \( P \)-values for the tests for the null hypotheses that there should be more than 0, 1, and 2 factors are <0.001, <0.001, and 0.45 for controls and <0.001, 0.004, and 0.55 for the full data set. This strongly suggests that there are likely to be two latent variables (no more, no less) that may have ‘passive smoking’ relevance. This conclusion is supported by the eigenvalues (\( \lambda \)) associated with each factor both using a ‘scree-plot’ and because only the first two have values greater than unity (\( \lambda_1 = 1.62, \lambda_2 = 1.38, \) and \( \lambda_3 = 0.33 \)).

Scoring coefficients, \( s_{ki} \), are displayed in Table 3. Cronbach’s alphas are low (0.164 for S1 and C1; 0.0868 for S2 and C2; 0.197 for S3 and C3), which indicates low correlation between the two ‘passive smoking’ factors; consistent with these being independent of each other. The correlation coefficients are: 0.089 (for S1 and C1), 0.045 (for S2 and C2), and 0.109 (for S3 and C3). Using only control data results in very similar coefficients (Table 3a) as using the full data set (Table 3b).

Coefficient magnitudes imply that the first latent variable, \( S \), tracks ‘exposure to smoke’ (Factors S1, S2, and S3 of Table 3).
This may directly be evaluated as the standard transformation of the number of smokers that actually smoke in the household, as this has a coefficient of unity and other coefficients approach zero. The second latent factor, C, most likely tracks ‘contact with smokers’ (Factors C1, C2, and C3 of Table 3). The number actually smoking in the household inversely ‘influences’ this second factor (the coefficient is negative) suggesting that factors S2 and C2 as those that represent exposure to ‘smoke’ and ‘smokers’, respectively. The univariate distribution of these variables is shown in Table 4. Factor S2 correlated significantly with attendance at a pub or a party (r = 0.19; P = 0.05) and with having a job in a pub (r = 0.19; P = 0.001). S2 did not correlate with these behaviours.

Univariate conditional logistic regression revealed that C2 is directly correlated with MD status [odds ratio (OR) = 1.6; 95% confidence interval (95% CI) 1.1–2.5; P-value = 0.03].
In contrast, S2 is not significantly associated with case/control status (OR = 1.2; 95% CI 0.9–1.6; P-value = 0.26). Analysis of the first multivariate model (Figure 1) revealed that factor C2 (smoker contact) remained significant (OR = 1.8; 95% CI 1.1–3.0; P = 0.01) and S2 (smoke exposure) remained insignificant (OR = 1.3; 95% CI 0.9–1.8; P = 0.16). This trend remained true for the second multivariate model, where factor C2 was significant (OR = 1.8; 95% CI 1.1–3.3; P = 0.05) and factor S2 was not significant (OR = 1.3; 95% CI 0.8–2.1; P = 0.35; 132 case–control pairs). The form of the relationship between MD risk and passive smoke exposure is shown graphically in Figure 2.

**Discussion**

Univariate analysis showed that not all seven passive smoke variables were associated with MD risk. These differences can be explained by the suggestion that these variables represent not one but two independent (latent) measures of the effects of passive smoke. Our interpretation is that the first latent variable measures exposure to smoke (number actually smoking and number of cigarettes smoked in the household), which was not associated with MD, whereas the second one measures exposure to smokers (the number of smoking overnight guests, of household smokers, of close contacts who smoke, a partner who smokes), which was associated with MD. This is the first study to explicitly examine the mechanism of passive smoking in relation to MD risk, using factor analysis. Although the seven passive smoking variables in our study were correlated with each other, and although factor analysis requires an a priori hypothesis, we were able to identify two distinct independent groups of variables that were consistent with our stated hypothesis.

Epidemiological studies aiming to assess the effects of smoke exposure on the risk of air-borne infectious disease should control for the fact that smokers may be more infectious than non-smokers. This is probably true where smokers are more likely to be carriers such as is known for MD and other infections caused by *Staphylococcus aureus*, tuberculosis, *Streptococcus pneumoniae*, and group B beta-haemolytic streptococci. Numerous studies have reported passive smoke to be a risk factor for MD in children <5 years of age. These studies defined passive smoke in terms of smoking activity experienced in the household, implicitly assuming that no young children were smokers and exposure to smoke occurs mainly

<table>
<thead>
<tr>
<th>Exposure to smoke (Factor S2 [S1])</th>
<th>Exposure to smokers (Factor C2 [C1])</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cases</strong></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>0.06</td>
</tr>
<tr>
<td>SD</td>
<td>1.01</td>
</tr>
<tr>
<td>N</td>
<td>140</td>
</tr>
<tr>
<td><strong>Controls</strong></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>-0.07</td>
</tr>
<tr>
<td>SD</td>
<td>0.99</td>
</tr>
<tr>
<td>N</td>
<td>140</td>
</tr>
<tr>
<td><strong>Univariate OR</strong></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>1.18 [1.17]</td>
</tr>
<tr>
<td>SD</td>
<td>0.26 [0.27]</td>
</tr>
<tr>
<td>N</td>
<td>0.03 [0.01]</td>
</tr>
<tr>
<td><strong>Multivariate OR</strong></td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td>1.27 [1.27]</td>
</tr>
<tr>
<td>P-value</td>
<td>0.16 [0.17]</td>
</tr>
<tr>
<td><strong>Multivariate OR</strong></td>
<td></td>
</tr>
<tr>
<td>Model 2</td>
<td>1.34 [1.30]</td>
</tr>
<tr>
<td>P-value</td>
<td>0.19 [0.23]</td>
</tr>
</tbody>
</table>

See Figure 1 for an explanation of multivariate models 1 and 2.
within the household. These assumptions are justified in young children where household smokers are usually parents who are their only smoker contacts. Increased risk of MD could be caused by increased transmission from active smoker parents who are carriers as well as via exposure to smoke. Both mechanisms are plausible. The first is supported by the findings of our study, albeit in adolescents. The second is supported by the overwhelming evidence on adverse effects of passive smoke on physiological, developmental as well as behavioural well-being of young children. Disruption of a number of components of the mucosal immune system of the upper respiratory tract by SS has been demonstrated in vitro, this being consistent with the increased risk of meningococcal carriage in active smokers and passive smokers.

Similarly, exposure to smoke or smokers could both mediate risk of MD in adolescents. Furthermore, teenagers may also experience passive smoke outside the household and other measures of passive smoke are needed. Stuart et al., for example, defined passive smoking as non-smokers who lived with persons who ever smoked and found it significantly associated with increased risk of MD in young children <12 years and older adults (>20 years) but not in teenagers, a discrepancy that they explained with the suggestion that teenagers spend less time at home. These considerations justified the need to attempt alternative passive smoking measures for this study.

We decided to retain exposure to smoke at work in the factor analysis as it represents exposure to passive smoke outside the household. Exposure at work appears more indicative of having contacts with smokers than of the exposure to smoke (Table 3). Attendance at pub, bars, or parties may be additional correlates of passive smoke exposure outside the household, and we found them more associated with exposure to smokers than to smoke although these variables had no significant effect on multivariate results.

‘Exposure to smokers’ appears to be a risk factor for MD in teenagers in England although the relationship between this exposure and MD risk may not be necessarily linear. In contrast, ‘exposure to smoke’ was not a significant risk factor for MD, but as this point estimate is not much smaller than that for ‘exposure to smokers’, we could not exclude any effect of exposure to smoke. These results were independent of important potential confounders and effect modifiers such as active smoking, sniffing, or smoking illegal drugs, measures of social interaction (multiple intimate kissing contacts, attendance at pubs, bars, or parties), meningococcal vaccination, a preceding upper respiratory tract illness, attendance of religious ceremonies, socioeconomic status, occupation, and student status. We suggest that the effect of passive smoking on the risk of MD in teenagers could be mostly explained via increased contact with smokers, rather than by exposure to smoke. This work should encourage the measurement of more than one passive smoking variable in future epidemiological work and emphasizes the importance of the public health measures to stop smoking.

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Conflict of interest: R.B. has acted as a paid consultant for Wyeth, GSK, and Aventis Pasteur. DA has spoken on the methodology of adverse drug reactions in HIV at a scientific meeting attended by several pharmaceutical companies and sponsored by GSK. An honorarium was paid to her department. The other authors have no conflicts of interest to declare.

KEY MESSAGES

- Passive smoking has been linked with risk of MD in past literature. These results are ambiguous because contact with smokers can lead to (i) exposure to the aetiological agent (smokers are more likely to carry Neisseria meningitidis) and (ii) exposure to smoke.
- Factor analysis helped ‘summarise’ seven passive smoking variables into two ‘latent’ variables—one tracks contact with smokers, the other tracks contact with smoke.
- The ‘smoker’ latent variable is significantly associated with risk of MD while the ‘smoke’ latent variable is not.

References


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