Exposure to cold and draught, alcohol consumption, and the NS-phenotype are associated with chronic bronchitis: an epidemiological investigation of 3387 men aged 53–75 years: the Copenhagen Male Study

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Abstract

Objectives—This study was performed to estimate the strength of association between chronic bronchitis and lifetime exposure to occupational factors, current lifestyle, and the NS-phenotype in the MNS blood group among middle aged and elderly men.

Methods—The study was carried out within the frameworks of the Copenhagen Male Study. Of 3387 men 3331 men with a mean age of 63 (range 53–75) years could be classified by prevalence of chronic bronchitis. As well as the completion of a large questionnaire on health, lifestyle, and working conditions, all participants had a thorough examination, including measurements of height and weight and blood pressure and a venous blood sample was taken for the measurement of serum cotinine and MNS typing; 16.5% of the men had the NS-phenotype. Chronic bronchitis was defined as cough and phlegm lasting 3 months or more for at least 2 years; 14.6% had chronic bronchitis.

Results—Smoking and smoke inhalation were the factors most strongly associated with prevalence of chronic bronchitis. There were three major new findings: (a) long term (>5 years) occupational exposure to cold and draught was associated with a significantly increased prevalence of chronic bronchitis; compared with others, and adjusted for confounders, the odds ratio (OR) with 95% confidence interval (95% CI) was 1.4 (1.1 to 1.7), p=0.004; (b) a significant J shaped association existed between alcohol use and bronchitis, p<0.001, with the lowest prevalence found among moderate users; (c) a significant gene by environment association existed between smoking and the NS-phenotype in the MNS blood group; only among smokers was the NS-phenotype associated with a significantly decreased risk of chronic bronchitis, OR 0.67 (0.47-0.97), p=0.02. Other well known associations between dust, fumes, and even exposure to solvents and bronchitis were confirmed.

Conclusion—The results emphasise the multifactorial nature of chronic bronchitis, and show some hitherto unrecognised associations between cold and draught exposure, alcohol consumption, and the NS-phenotype and chronic bronchitis.

Keywords: alcohol; chronic bronchitis; cold; draught; genetic marker; MNS; occupational exposure

Based on results from studies of non-selected populations1–7 and occupational cohorts,8–11 it has been established that smoking, exposure to dust, and exposure to fumes and solvents are associated with risk of chronic bronchitis; the literature on lifestyle factors and environmental exposures has been reviewed by Higgins12 and by Garshick et al.13

Genetic factors also have been implicated in the aetiology of chronic bronchitis. In a recent review article, Sandford et al stated that only a few genes have been investigated as potential risk factors for chronic bronchitis.7 Homozygosity for the Z allele of the α1-antitrypsin gene has been established as a risk factor, and heterozygotes for the Z allele may be at increased risk. Other mutations affecting the structure of α1-antitrypsin or the regulation of gene expression have been identified as risk factors. Genes, including those for 1-antitrypsin or the regulation of D binding protein, and blood group antigens have been associated with the development of bronchitis—for example, in the Copenhagen Male Study.14 Among more than 3000 middle aged and elderly men there was a significant, heterogenous association between the MNS phenotypes and prevalence of chronic bronchitis, with the lowest prevalence found in men with the NS-phenotype.

The strength of the association between lifestyle and environmental factors and chronic bronchitis may depend on genetics. Despite this, the importance of the interplay of genetic and environmental factors has not, to our knowledge, previously been studied in non-selected populations. This study of middle aged and elderly men was performed to (a) estimate the relative strength of association between chronic bronchitis and occupational and lifestyle factors and the NS-phenotype; and, (b) to test if the risk associated with identified occupational and lifestyle factors was modified by the NS-phenotype.
Subjects and methods

The Copenhagen Male Study was set up in 1970 as a prospective cardiovascular cohort study of 5249 men with a mean age of 48 years (range 40–59). In 1985–6 a new baseline was established. All survivors from the 1970 study were traced through the Danish Central Population Register. Between June 1985 and June 1986 all survivors (except 34 emigrants) from the original cohort were invited to take part in this study: 3387 (75%) agreed and gave informed consent. Their mean age was 63 (range 53–74) years.

The 1985–6 study took place at Glostrup Hospital, University of Copenhagen. Each subject was interviewed (by HOH) about a previously completed questionnaire and then had a clinical examination.

Clinical examination

A clinical examination included measurement of peak expiratory flow with a Wright–McKerrow peak flow meter, and measurements of height, weight, and blood pressure measured with a radioimmunoassay (RIA) method at Medi-Lab, Copenhagen. As previously estimated by means of measurements of serum cotinine, the validity of tobacco reporting was high. The men classified themselves for leisure time physical activity as either sedentary, slightly active—less than 2 hours a week—or physically more active.

Table 1

<table>
<thead>
<tr>
<th>NS-phenotype in MNS blood group:</th>
<th>Bronchitis n=485</th>
<th>No bronchitis n=2846</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall (%)</td>
<td>13.6</td>
<td>17.0</td>
<td>0.073</td>
</tr>
<tr>
<td>Among smokers (%)</td>
<td>12.7</td>
<td>17.4</td>
<td>0.033</td>
</tr>
<tr>
<td>Lifestyle factors:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol use:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abstinence (%)</td>
<td>12</td>
<td>11</td>
<td>0.532</td>
</tr>
<tr>
<td>Moderate (1–21 drinks/week) (%)</td>
<td>51</td>
<td>60</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>More than moderate (22–35 drinks/week) (%)</td>
<td>21</td>
<td>19</td>
<td>0.145</td>
</tr>
<tr>
<td>Heavy use (&gt;35 drinks/day) (%)</td>
<td>16</td>
<td>10</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Low physical activity, &lt;4 h/week (%)</td>
<td>52</td>
<td>47</td>
<td>0.088</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>80</td>
<td>51</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smokers only:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inhalation (%)</td>
<td>82</td>
<td>72</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Amount smoked (g/day)</td>
<td>17.2 (8.0)</td>
<td>14.9 (7.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Clinical or paraclinical variables:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak flow (l/min)</td>
<td>412 (125)</td>
<td>504 (87)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>173 (6)</td>
<td>174 (6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>76 (12)</td>
<td>78 (11)</td>
<td>0.009</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>118 (16)</td>
<td>122 (17)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>71 (13)</td>
<td>73 (12)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum cotinine (ng/ml)</td>
<td>327 (227)</td>
<td>197 (234)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Low social class (classes IV and V) (%)</td>
<td>59</td>
<td>51</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Retired (%)</td>
<td>54</td>
<td>47</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age (y, mean (SD))</td>
<td>63.2 (5.2)</td>
<td>62.8 (5.2)</td>
<td>0.175</td>
</tr>
</tbody>
</table>

Values are means (SD) or frequencies (%). p Values are of Student’s t test (for continuous variables other than peak flow), Mann-Whitney rank sum analysis (for peak flow), or Yates corrected χ² analysis (for categorical variables).

Table 2

<table>
<thead>
<tr>
<th>Smoking v not</th>
<th>OR (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking v not</td>
<td>2.5 (1.8 to 3.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Alcohol use, different categories referencing abstainers: Moderate use (1–21 drinks/week):</td>
<td>0.8 (0.6 to 1.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>More than moderate (22–35 drinks/week):</td>
<td>1.1 (0.7 to 1.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heavy use (&gt;35 drinks/week):</td>
<td>1.4 (0.95 to 2.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Retired v not</td>
<td>1.4 (1.1 to 1.7)</td>
<td>0.002</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg, risk associated with a one unit change)</td>
<td>0.99 (0.98 to 0.997)</td>
<td>0.002</td>
</tr>
<tr>
<td>Height (cm, risk associated with a one unit change)</td>
<td>0.98 (0.96 to 0.99)</td>
<td>0.004</td>
</tr>
<tr>
<td>NS-phenotype v others</td>
<td>0.7 (0.6 to 0.99)</td>
<td>0.038</td>
</tr>
</tbody>
</table>

Not in the final model (p>0.10): social class, weight, age. Variables are ordered according to statistical strength of association with bronchitis after multivariate adjustment in a logistic regression model with backward elimination of variables.

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The rationale of the method has been described by Kleinbaum et al. All risk factor covariates in the regression analyses were those measured in 1985–6. In the multivariate analyses we used the program default allowing variables with p values ≤0.10 to remain in the adjusted model.

Results

Table 1 shows the distribution of genetic, clinical, and sociodemographic characteristics in men with and without chronic bronchitis. Apart from lower peak flow values in men with bronchitis, the most pronounced differences were found for smoking, but also alcohol consumption was associated with the prevalence of bronchitis; moderate consumption had a lower prevalence and heavy consumption had a higher prevalence of chronic bronchitis. Men with bronchitis were less physically active, belonged to lower social classes, and were more often retired. The NS-phenotype was more often present in men without bronchitis, with a significantly stronger association among smokers. Moreover, men with bronchitis were of shorter stature, had a lower blood pressure, and weighed less than men without bronchitis.

Table 2 shows the results of a multivariate analysis including relevant factors presented in table 1. Positively associated with chronic bronchitis were current smoking, smoke inhalation, and being retired; negative associations were found with blood pressure, height, and the NS-phenotype, and a J shaped association was found with alcohol consumption. Social class, weight, and age were not in the final model.

Table 3 shows the association between potentially relevant occupational long term exposures to physical and chemical factors and prevalence of chronic bronchitis. All the listed factors were more prevalent among men with bronchitis. The factors were either of a chronic nature or related to exposure to dust, fumes, and organic solvents.

The relative strength of association between chronic bronchitis and long term occupational exposure to physical and chemical factors after multivariate analysis is shown in table 4. The strongest factor was long term exposure to cold and draughts, but also exposure to organic solvents and dust remained in the statistical model even when adjustment was made for social class. The odds ratios of occupational exposures associated with bronchitis in the adjusted multivariate model ranged between 1.3 and 1.5.

Table 5 shows the relative strength of association between chronic bronchitis and relevant genetic, lifestyle, clinical, and sociodemographic characteristics, and relevant occupational exposures after adjustment in the multivariate model. Smoking and smoke inhalation were the strongest discriminatory factors, but occupational exposure to cold and draughts, organic solvents and dust, and the NS-phenotype were also significant covariates of bronchitis. Other factors significantly characterising subjects with chronic bronchitis were blood pressure, age, height, and alcohol consumption. With the same factors as covari-
ates in analysis of smokers only, compared with
men with other phenotypes, the odds ratio
(95% confidence interval) of men with the
NS-phenotype was 0.67 (0.47 to 0.97), p=0.02
(not shown in table 5).

In an additional multivariate analysis we
included the same factors as in table 5 together
with interaction terms (between NS-phenotype
and the other factors which remained in the
final model in table 5 (not shown)). Of interac-
tion terms, only the interaction between
NS-phenotype and smoking was significantly
associated with bronchitis, p=0.02. The inter-
play of the NS-phenotype, current smoking,
and prevalence of chronic bronchitis is shown
in figure 1.

Figure 2 depicts the interplay of lifestyle fac-
tors, occupational exposures, and prevalence of
chronic bronchitis; occupational factors were
positively associated with the prevalence of
chronic bronchitis irrespective of the number
of adverse lifestyle factors characterising the
group.

Discussion
This study showed that occupational, lifestyle,
and genetic factors were independently associ-
ated with chronic bronchitis. There were three
major new findings: (a) an increased preva-
ence of bronchitis among men who had been
occupationally exposed to cold and draught for
more than 5 years, (b) a J shaped association
between alcohol consumption and prevalence
of chronic bronchitis, and (c) a significant gene
by environment association between smoking
and the NS-phenotype in the MNS blood
group. Established and less established inde-
pendent associations between smoking, expo-
sure to dust, and exposure to solvents and
chronic bronchitis were confirmed, as were the
well known inverse associations between sys-
temic arterial blood pressure and height and
chronic bronchitis.25 26

In cross sectional studies with retrospective
data it is necessary to consider potential bias, in
particular bias related to measurements, inad-
quate confounder control, and selection. Would such sources of bias be able to explain
the associations found?

Definition of chronic bronchitis was based
on conventional criteria of the British Medical
Research Council questionnaire for determin-
ing bronchitis. Recognised laboratory methods
were used to ascertain genetic markers, and the
distribution of MNS phenotypes was in agree-
ment with previous studies on Danes.27 Infor-
mation on smoking was validated by measuring
serum cotinine. Data on occupational exposure
were based on self assessment. However, previ-
ous studies in the Copenhagen Male Study
have shown a strong agreement between job
titles and exposures likely to be associated with
specific job functions.28 Despite this, impreci-
sion in the validity of exposure and outcome variables, and of potential confounders, cannot be excluded. It seems unlikely that this would be responsible for our findings, rather the strength of the associations found may have been underestimated. Selection bias is another potential problem. Chronic bronchitis is no rare cause of death, and severe bronchitis may further handicap a potential study participant, so that he would be less likely to attend the study. Measurement bias seems unlikely, but selection bias could not have been responsible for our findings, as selection phenomena would tend to obscure genuine associations. Finally, a comprehensive confounder control was carried out, so that inadequate control for the impact of major confounders also seems an unlikely explanation for our findings.

Are the new findings biologically plausible? Chronic bronchitis is primarily an inflammatory condition involving various immune responses. As reviewed by Shepard, exposure to various environmental stressors, including cold, may impair the human response to infections by modifying various components of immune function such as T cell count, natural killer cell counts, cytotoxic activity, cytokine secretion, lymphocyte proliferation, and immunoglobulin concentrations. An immunological mechanism caused by exposure to cold and draught therefore seems likely.

An immunological mechanism related to the MNS blood group is also likely. The MNS phenotypes are involved in the function of immunoglobulins, and is therefore at least one biologically plausible mechanism for the association found between the NS-phenotype blood group and chronic bronchitis. The finding is furthermore interesting in the light of findings made in the field of carcinogenesis that individual susceptibility to carcinogens may be particularly important at low environmental exposures. This agrees with the finding that, in this study, the apparently protective effect of the NS-phenotype vanished at high exposures to tobacco. The J-shaped association between alcohol consumption and bronchitis is interesting in the light of the well known association between bronchitis and risk of ischaemic heart disease, and the well known J or U shaped association between alcohol consumption and risk of ischaemic heart disease. Previous studies on lung function and haemostatic factors have shown an increased concentration of plasma fibrinogen in subjects with bronchitis, and one of the mechanisms whereby alcohol is supposed to lower risk of heart disease is through its lowering of fibrinogen.

In conclusion, the results of this study emphasise the multifactorial nature of chronic bronchitis, and show some hitherto unrecognised associations between exposure to cold and draughts, alcohol consumption, and the NS-phenotype and chronic bronchitis.


20 Hansen EJ. *Socialgrupper i Danmark* Copenhagen: The Institute of Danish Social Science, 1984. (Study no 48.)


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