Respiratory disease and cardiovascular morbidity

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Background: Work related dust exposure is a risk factor for acute and chronic respiratory irritation and inflammation. Exposure to dust and cigarette smoke predisposes to exogenous viral and bacterial infections of the respiratory tract. A number of risk factors have been established for coronary artery disease. Experimental and epidemiological studies have shown a positive correlation between coronary atherosclerosis and a variety of infectious agents of both viral and bacterial origin.1 Atherogenesis can also be induced in animal models by microorganisms. The atherosclerotic lesion represents specific cellular and molecular changes that are no different from the “classical” inflammatory response.1,2 The frequently observed correlation between the incidence of atherosclerosis and the presence of a variety of infectious microorganisms including herpes viruses (particularly cytomegalovirus), Helicobacter pylori, and Chlamydia pneumoniae has suggested an infectious aetiology of coronary artery disease.3,5

Besides the involvement of inflammation in “active” coronary artery disease, chronic systemic infection may accelerate the clinical course of atherosclerosis.8 Increased coronary artery disease. Experimental and epidemiological infections of the respiratory tract. cigarette smoke predisposes to exogenous viral and bacterial infections that are no different from the “classical” inflammatory response.1,2 The frequently observed correlation between the incidence of atherosclerosis and the presence of a variety of infectious microorganisms including herpes viruses (particularly cytomegalovirus), Helicobacter pylori, and Chlamydia pneumoniae has suggested an infectious aetiology of coronary artery disease.3,5

METHODS

Study subjects and data collection

The study population comprised a sample of 6022 current and former workers from a total of 22 000 members of six cohorts variously exposed to dust. A cohort of granite workers consisted of 1026 men hired in quarries and processing yards in 1940–71.12 A cohort of foundry workers consisted of 931 men exposed for at least 4.2 years (hired in 1950–72 and still actively working in iron, steel, and non-ferrous foundries in 1972).14 A cohort of cotton mill workers comprised 1065 women exposed to raw cotton dust for at least five years (hired in 1950–71).15 The three other cohorts were derived from the metal industry: 1000 iron foundry workers, 1000 metal product workers (manufacture of fabricated metal products, machinery and equipment), and 1000 electrical workers (production of electrical devices and of electrical machinery, apparatus, appliances, and supplies) hired in 1950–76 and living in 1976. (A total of 400 current and 400 former male workers with the longest duration of employment and 200 with the shortest duration of employment were selected in each branch.) All cohorts were followed until the end of 1992.

The studies on these cohorts were based on an agreement with labour market organisations, and the research protocols were approved by the Research Committee of the Finnish Institute of Occupational Health. Register based data were collected with the consent of the legal authorities. Participation in the questionnaires was voluntary and was based on written information given previously to the respondents.

METHODS

Methods: The study comprised 6022 dust exposed (granite, foundry, cotton mill, iron foundry, metal product, and electrical) workers hired in 1940–76 and followed until the end of 1992. National mortality and morbidity registers and questionnaires were used. The statistical methods were person-year analysis and Cox regression.

Results: Co-morbidity from cardiovascular and respiratory diseases ranged from 17% to 35%. In at least 60% of the co-morbidity cases a respiratory disease preceded a cardiovascular disease. Chronic bronchitis, pneumonia, and upper respiratory tract infections predicted IHD in granite workers (rate ratio (RR) = 1.9; 95% CI 1.38 to 2.72), foundry workers (2.1; 1.48 to 2.93), and iron foundry workers (1.7; 1.16 to 2.35). Dust exposure was not a significant predictor of IHD or other CVD in any group. Dust exposure was related to respiratory morbidity. Thus, some respiratory diseases appeared to act as intermediate variables in the association of dust exposure with IHD.

Conclusion: Dust exposure had only a small direct effect on IHD and other CVD. IHD morbidity was associated with preceding respiratory morbidity. A chronic infectious respiratory tract disease appeared to play an independent role in the development of IHD.

Abbreviations: CI, confidence interval; CRP, C reactive protein; CVD, cardiovascular diseases; ICD, International Classification of Diseases; IHD, ischaemic heart disease; RR, rate ratio.
The vital statuses and addresses of the workers were traced through the Population Information System. Causes of death in 1940–92 were obtained from Statistics Finland. Causes of disability in 1969–92 were available from the Social Insurance Institution. The whole range of respiratory and cardiovascular diseases was available from the death and disability registers. Data on medicines for which special compensation (80–100%) is granted under the National Sickness Insurance Act were available for 1969–92 from the Social Insurance Institution. The cardiovascular diseases eligible for specially compensated medicines are coronary heart disease, cardiac insufficiency, cardiac arrhythmia, and hypertension. The only respiratory disease eligible for special compensation is bronchial asthma. Data on occupational history, smoking, angina pectoris, chronic bronchitis, and respiratory diseases diagnosed by a doctor were collected via questionnaire. The questionnaire was administered to the workers in 1980 (75%), to the electrical workers in 1980 (80%), and to the iron foundry workers in 1980 (79%), to the granite workers in 1986 (response rate 81%), to the electrical workers in 1980 (79%), to the cotton mill workers in 1985 (73%), to the iron foundry workers in 1980 (79%), to the metal product workers in 1980 (80%), and to the electrical workers in 1980 (75%).

The diseases were coded according to the eighth revision of the ICD. Each diagnosed disease entered in the registers or questionnaires was marked with the year of diagnosis in the questionnaires was included. Mild or severe angina pectoris and chronic bronchitis were included. All diseases obtained in the above manner were sorted by year of diagnosis to establish the earliest time point of each diagnosis for each cohort member and to determine the order of subsequent diseases.

**Statistical analyses**

Morbidity from cardiovascular and respiratory diseases was assessed by person-year analysis and Cox regression. The SAS system (version 8.1; SAS Institute, Inc., Cary, North Carolina) was used for statistical analysis.

In multivariate analyses the respiratory diseases were classified into five categories: chronic bronchitis (ICD 490.99–491.09), emphysema and asthma (ICD 492.01–493.09), pneumoconiosis (ICD 515.00–516.20), pneumonia (ICD 640.99–648.09), and other respiratory diseases (ICD 680.00–679.99, 500.99–514.99, and 517.01–519.98). In a separate analysis, these disease categories were used to predict the first subsequent occurrence of ischaemic heart disease (IHD) (ICD 410.00–414.99) and other cardiovascular diseases (CVDs) (ICD 390.97–458.99, excluding 410.00–414.99). The other variables in the models were age at entry to the work under study, lifelong smoking habits (smoker, ex-smoker, non-smoker), and dust exposure (defined as exposure years multiplied by dust concentration 10 mg/m³ or dust category, or as exposure years only). Dust exposure was treated in Cox regression as a time varying variable, and was calculated to estimate cumulative exposure at the time of the IHD event. The respiratory disease variables were also treated as time varying to establish whether or not the person had a certain type of respiratory disease before the time of the IHD event. In addition, carbon monoxide exposure was used as an explanatory variable for foundry workers. The effects of hypertension and congestive heart failure on IHD were controlled for as explanatory factors in the final analyses.

Respiratory diseases can be causal factors of IHD. Respiratory diseases, in turn, may be caused by dust exposure, smoking, and age, and are thus intermediate factors in the course of IHD (fig 1). Respiratory diseases as possible intermediate variables were studied by Cox regression analysis in two stages. First, the predictors of IHD and other CVDs were studied, with respiratory diseases and dust exposure as explanatory variables. Second, respiratory diseases were studied as response variables, with dust exposure as an explanatory variable. Rate ratios (RR) were used as the effect measures of the explanatory variables.

### Table 1  Age adjusted incidence rates per 100 000 person-years for respiratory and cardiovascular diseases

<table>
<thead>
<tr>
<th>Disease/workers</th>
<th>Incidence /100000</th>
<th>Rate ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>High dust†</td>
<td>Low dust†</td>
<td></td>
</tr>
<tr>
<td>All respiratory diseases</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Granite workers</td>
<td>1385.1</td>
<td>942.0</td>
<td>1.5</td>
</tr>
<tr>
<td>Cotton mill workers</td>
<td>550.1</td>
<td>130.3</td>
<td>4.0</td>
</tr>
<tr>
<td>Foundry workers</td>
<td>1181.7</td>
<td>1020.9</td>
<td>1.2</td>
</tr>
<tr>
<td>Metal workers (three industries)</td>
<td>885.3</td>
<td>577.6</td>
<td>1.5</td>
</tr>
<tr>
<td>All cardiovascular diseases</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Granite workers</td>
<td>2005.3</td>
<td>1877.2</td>
<td>1.1</td>
</tr>
<tr>
<td>Cotton mill workers</td>
<td>1029.6</td>
<td>863.8</td>
<td>1.2</td>
</tr>
<tr>
<td>Foundry workers</td>
<td>1832.2</td>
<td>1928.6</td>
<td>1.0</td>
</tr>
<tr>
<td>Metal workers (three industries)</td>
<td>1425.2</td>
<td>1199.5</td>
<td>1.2</td>
</tr>
<tr>
<td>Ischaemic heart disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Granite workers</td>
<td>943.2</td>
<td>769.7</td>
<td>1.2</td>
</tr>
<tr>
<td>Cotton mill workers</td>
<td>253.7</td>
<td>146.4</td>
<td>1.9</td>
</tr>
<tr>
<td>Foundry workers</td>
<td>882.8</td>
<td>973.1</td>
<td>0.9</td>
</tr>
<tr>
<td>Metal workers (three industries)</td>
<td>625.1</td>
<td>435.8</td>
<td>1.4</td>
</tr>
</tbody>
</table>

*Owing to small number of cases, the test was based on crude rates.
†Classification into high and low dust categories:
- Granite workers: high, >20 mg/m³; low, ≤20 mg/m³
- Cotton mill workers: high, >10 mg/m³; low, ≤10 mg/m³
- Foundry workers: high comprised floor and machine moulders and fettlers and the labourers assisting them; low comprised core makers, furnace men, casters, truck drivers, others
- Metal workers: high comprised iron foundry workers; low comprised metal product and electrical workers.
The potential violation of proportional hazard assumption was studied for the variables of age at entry, smoking, and dust exposure. The proportional hazard assumption was not fulfilled for the age at entry variable in any of the study groups. Consequently, all the results are based on the models including the interaction term between age and follow up time.

RESULTS
Person-year analyses of cardiovascular and respiratory diseases by dust exposure (table 1) showed that, in almost all study groups, morbidity from respiratory diseases was higher among workers with high exposure than among those with low exposure. Systematic, though mostly slight, differences were observed for all cardiovascular diseases and for IHD separately.

Co-morbidity from cardiovascular and respiratory diseases ranged from 17% to 35% in the study groups. In each study group, a respiratory disease preceded a cardiovascular disease in at least 60% of the co-morbidity cases. Respiratory diseases as possible predictors of CVDs were studied by multivariate analyses.

First, in the study of cardiovascular diseases, respiratory diseases and dust exposure were used as explanatory variables (table 2). For IHD, chronic bronchitis was a significant predictor for three occupational groups (granite workers, RR = 2.2, 95% CI 1.52 to 3.27; foundry workers, RR = 2.3, 95% CI 1.59 to 3.40; and iron foundry workers, RR = 2.0, 95% CI 1.41 to 2.96). Pneumonia showed a rate ratio of 1.4 (95% CI 0.86 to 2.27) among granite workers and of 2.0 (95% CI 0.93 to 4.27) among cotton mill workers. For other respiratory diseases (upper respiratory infections), the rate ratio among granite workers was 1.7 (95% CI 0.95 to 3.14). Emphysema and asthma did not prove to be predictors of IHD in any study group except electrical workers; among cotton mill workers the rate ratio was rather high (RR = 2.0; 95% CI 0.91 to 4.57). Pneumoconiosis had predictive value for granite workers only. Chronic bronchitis was also a significant predictor for foundry workers.

Dust exposure was a weak predictor of IHD or of other CVDs in all the models presented here. Age and smoking had a high predictive value for IHD in each model (data not shown), whereas smoking did not predict other CVDs in any of the models.

Second, respiratory diseases were studied as response variables. The effect of dust exposure on each type of respiratory disease is presented in table 3. The effect of a particular respiratory disease on ischaemic heart disease is presented simultaneously (table 3).

Dust exposure predicted chronic bronchitis among granite workers. Dust exposure was associated with chronic bronchitis, and, further, chronic bronchitis was associated with IHD among granite workers. Dust exposure did not predict emphysema or asthma in any of the study groups; the only group in which respiratory diseases predicted IHD was that of electrical workers. Dust exposure predicted pneumoconiosis among granite workers. The results for pneumonia showed that dust exposure did not predict pneumonia in any
Table 3: Respiratory diseases as intermediate variables between dust exposure and ischaemic heart disease (IHD)

<table>
<thead>
<tr>
<th>Response variable (Explanatory variable)</th>
<th>IHD†</th>
<th>Emphysema, asthma*</th>
<th>Pneumoconiosis*</th>
<th>Pneumonia*</th>
<th>Other respiratory diseases*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Granule workers RR</td>
<td>1.0</td>
<td>2.2</td>
<td>1.1</td>
<td>1.0</td>
<td>1.2</td>
</tr>
<tr>
<td>Cotton mill workers RR</td>
<td>1.0</td>
<td>0.8</td>
<td>1.0</td>
<td>0.8</td>
<td>0.9</td>
</tr>
<tr>
<td>Foundry workers RR</td>
<td>1.0</td>
<td>2.3</td>
<td>1.4</td>
<td>1.1</td>
<td>1.3</td>
</tr>
<tr>
<td>Iron foundry workers RR</td>
<td>1.0</td>
<td>1.6</td>
<td>1.1</td>
<td>1.0</td>
<td>1.1</td>
</tr>
<tr>
<td>Metal products workers RR</td>
<td>1.0</td>
<td>0.8</td>
<td>1.1</td>
<td>1.0</td>
<td>1.1</td>
</tr>
<tr>
<td>Electrical workers RR</td>
<td>1.0</td>
<td>1.4</td>
<td>1.0</td>
<td>0.9</td>
<td>0.7</td>
</tr>
</tbody>
</table>

*Categorical variables in model: dust exposure, age, and smoking; interaction between age and follow-up time included.

†Only a few cases of this respiratory disease.

RR, rate ratio; 95% CI, 95% confidence interval.

DISCUSSION

In our study, IHD mortality was associated with preceding respiratory morbidity. The direct independent effect of respiratory disease on IHD is smaller, due to similar exposure of IHD and other CVDs. Dust exposure was associated with other respiratory diseases as explanatory variables and included respiratory diseases (mainly upper respiratory infections) and non-infectious respiratory diseases predicted IHD in more study groups than did chronic non-infectious respiratory diseases. Infectious respiratory diseases predicted IHD in the study groups of foundry workers, foundry workers, and foundry workers—those is groups with high dust exposure whereas chronic non-infectious respiratory diseases showed statistically significant associations among foundry workers.

In the above-mentioned facts, the statistical significance of the five respiratory disease categories or other respiratory disease categories did not change the statistical significance of the IHD and other CVDs. The rate ratio ranged from 1.3 (95% CI 0.42 to 3.90) to 2.8 (95% CI 1.3 to 6.0) in all the study groups except those of the foundry workers. Dust exposure was associated with other respiratory diseases only among electrical workers, a group with low exposure to dust.
variables, each reducing the effect of dust. Further, since smoking was significant it also reduced the effect of dust exposure. Moreover, health selection of persons with juvenile asthma, emphysema, or chronic bronchitis to jobs with low dust exposure (electrical work) resulted in high rates of these diseases in occupations with low dust exposure, thus reducing the differences between the disease rates for low dust and high dust occupations.

Confounding by other occupational exposures was not probable. The granite workers were employed outdoors and were exposed to relatively pure silica. Only 3% had obvious confounding exposure to other dusts or chemicals. The cotton mill workers were exposed to raw cotton dust over an average of 28 years. During their total occupational history only 6.5% of the workers were exposed to other dusts or chemicals. The workers in iron, steel, and non-ferrous foundries were exposed to sand dust. Total exposure to dust, including quartz dust, was highest in iron foundry workers and among floor moulders, machine moulders, and fettlers. The follow up of foundry workers until 1987 controlled for potential confounding exposure to polycyclic aromatic hydrocarbons and heat but found no dose-response correlation between exposure and CVDs. The effect of carbon monoxide was controlled for in the analyses conducted for the present study. The same potential confounding exposures as in the foundry cohort were found in the cohort of iron foundry workers. In the cohort of metal product workers, only a relatively low number of workers were exposed to potential confounding exposures: 10% were welders exposed to welding fumes, and 4% were painters, metal platers, and coaters exposed to solvents. Among the electrical workers, relevant confounding exposure to solvents, colophony, or resins was shown for sodelling workers (0.5%), exposure to solvents for metal platers and coaters (1.2%), and exposure to welding fumes for welders (1.3%).

In our study, respiratory morbidity (chronic bronchitis, pneumoconiosis) was associated with dust exposure, and IHD morbidity was associated with preceding respiratory morbidity. Infectious respiratory diseases—that is, chronic bronchitis, pneumonia, and upper respiratory infections, predicted IHD in more study groups than did chronic non-infectious respiratory diseases (asthma, emphysema, and pneumoconiosis). Experimental and epidemiological studies have shown a positive correlation between coronary atherosclerosis and a variety of infectious agents of both viral and bacterial origin, and the cellular and molecular responses of atherosclerotic lesions resemble the ‘classical’ inflammatory response. An association between atherosclerosis and the presence of certain infectious microorganisms has been reported for herpes viruses (particularly cytomegalovirus), _Helicobacter pylori_, and _Chlamydia pneumoniae_. Dust and cigarette smoke exposure may also predispose to viral and bacterial infections of the respiratory tract.

Local or systemic low grade infections have been suggested as inducers of inflammatory reactions in atherosclerotic lesions, and chronic systemic infection may accelerate the clinical course of atherosclerosis. Among chronic infections, chronic bronchitis caused by inhalation of industrial dusts is associated with ischemic heart disease. Respiratory infection may thus act as a synergistic risk factor together with classical risk factors in the development of atherosclerosis. Other potential pathophysiological links between respiratory infection(s) and coronary artery disease include direct arterial wall damage, the effect on blood lipids, and the production of acute phase reactants, for example, fibrinogen and C reactive protein (CRP). It has been shown that the baseline values of acute phase reactants, CRP included, are associated with the risk of coronary heart disease; chronic infections that cause a rise in circulating levels of CRP also yield a higher risk of CVD.

Respiratory diseases are associated with local and systemic inflammatory activity of different intensities. Patients with chronic bronchitis are more susceptible to bacterial bronchial infections than to infections at the emphysema or asthma ends of the spectrum. Bacterial infections are the main culprit in acute flares of the disease. Respiratory inflammatory diseases are associated with increased levels of acute phase reactants, including CRP levels. Despite a lack of diagnostic specificity, CRP levels reflect the presence and intensity of an inflammatory process. Even considering the co-morbidity of different respiratory diseases, inflammatory activity is generally agreed to be more intense in pneumonia, exacerbated chronic bronchitis, and acute upper respiratory infections than in bronchial asthma and emphysema. The different humoral, cellular, and immunological responses and mediators in these diseases may explain the different associations with and development of IHD.

In conclusion, our study found that dust exposure had only a small direct effect on IHD and other CVDs. IHD morbidity was associated with preceding respiratory morbidity, and respiratory morbidity, in turn, was associated with dust exposure. Infectious respiratory diseases (chronic bronchitis, pneumonia, and upper respiratory infections) appeared to play an independent role in the development of IHD. Thus, efforts to prevent IHD should include the prevention of respiratory diseases and the control of dust exposure.

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