Exposure-response analysis and risk assessment for silica and silicosis mortality in a pooled analysis of six cohorts

A ‘t Mannetje, K Steenland, M Attfield, P Boffetta, H Checkoway, N DeKlerk, R-S Koskela

Aims: To study the relation between exposure to crystalline silica and silicosis mortality. Although mortality is an important endpoint for regulators, there have been no exposure-response studies for silicosis mortality, because of the relative rareness of silicosis as an underlying cause of death, and the limited availability of quantitative exposure estimates.

Methods: Data from six occupational cohorts were pooled with good retrospective exposure data in which 170 deaths from silicosis were reported. Standard life table analyses, nested case-control analyses, and risk assessment were performed.

Results: The rate of silicosis mortality in the combined data was 28/100 000 py, increasing in nearly monotonic fashion from 4.7/100 000 for exposure of 0–0.99 mg/m³-years to 233/100 000 for exposure of ≥28.1 mg/m³-years. The estimated risk of death up to age 65 from silicosis after 45 years of exposure at 0.1 mg/m³ silica (the current standard in many countries) was 13 per 1000, while the estimated risk at an exposure of 0.05 mg/m³ was 6 per 1000. Both of these risks are above the risk of 1 per 1000 typically deemed acceptable by the US OSHA.

Conclusion: The findings from this pooled analysis add further support to the need to control silica exposure and to lower the occupational standards. Our estimates of lifetime silicosis mortality risk are probably underestimated as, in addition to exposure misclassification, our study might have suffered from outcome misclassification in that silicosis deaths might have been coded to other related causes, such as tuberculosis or chronic obstructive pulmonary disease.

Respirable exposure to crystalline silica has long been known to produce fibrotic nodules in the lungs. This crippling disease was named silicosis, after its causal agent. The disease can progress from “simple silicosis”, characterised by few symptoms and small lung impairment or disability, to progressive massive fibrosis (PMF), characterised by increasing impairment in lung function and disability, often leading to respiratory failure and death. PMF typically develops over many years of exposure to crystalline silica. A less common form of silicosis is “acute silicosis”, caused by inhalation of high concentrations of silica that can occur in very poorly controlled exposure conditions, and which has a high fatality rate.

Many workers are still exposed to crystalline silica in industries that involve the fragmentation or processing of silica containing rock or sand, such as mining, construction, stone and sand production, manufacture of clay and glass products, and foundries. There are an estimated 3 200 000 workers exposed in the European Union, and 1 700 000 in the United States. Many more workers are likely to be exposed in developing countries. The US Occupational Safety and Health Administration’s (OSHA) permissible exposure limit (PEL) is 0.10 mg/m³ for an eight hour time weighted average exposure to respirable crystalline silica. NIOSH has recommended an exposure limit of 0.05 mg/m³ as a time weighted average for up to 10 hours per day during a 40 hour work week.

Several studies have attempted to quantify the relation between exposure to crystalline silica and silicosis morbidity. A recent review of the literature by Greaves’ focuses on three studies with follow up extending after employment, because silicosis frequently occurs after leaving work. Greaves concludes that the risk of silicosis (ILO category 1/0 or more) following a lifetime of exposure at the exposure limit of 0.05 mg/m³ is likely to be 20–40%. Recent risk assessments for silicosis in tin miners’ and diatomaceous earth workers’ support Greaves’ conclusions.

The exposure-response relation between exposure and silicosis mortality is seldom studied because of the relatively small numbers of deaths for which silicosis is reported as an underlying cause on the death certificate. Some studies, for example Checkoway and colleagues, have considered exposure-response for the broader category of non-malignant respiratory disease mortality. Silicosis mortality, besides silicosis morbidity, is nonetheless an important endpoint for the purposes of regulation and risk assessment, which can complement findings on the relation between silica and silicosis morbidity. Another reason for looking at mortality besides morbidity is the often expressed concern that silicosis morbidity can be defined in different ways, and can include non-symptomatic silicosis only detectable through chest x-rays as well as clinical disease. Differential definitions of silicosis morbidity can cause heterogeneity between studies, while this is less the case for mortality.

**MATERIALS AND METHODS**

Selection of the cohorts
We reviewed the literature to identify all occupational cohorts for which quantitative exposure assessment was available or for which quantitative exposure data could be developed. Thirteen cohorts were identified, of which 10 were included in a pooled analysis for lung cancer. For the analysis for silicosis presented here, we retained six cohorts, which are briefly described in the following paragraphs and table 1.

**Abbreviations:** ICD, International Classification of Disease; JEM, job-exposure matrix; OSHA, Occupational Safety and Health Administration; PEL, permissible exposure limit; PMF, progressive massive fibrosis

---

**References:**


---

**Note:** The above text is a natural representation of the document as if reading it naturally. Any footnotes, references, and abbreviations are included as part of the natural text for completeness.
(1) US diatomaceous earth workers. This is a historical cohort mortality study of 2342 male workers exposed to crystalline silica (predominantly cristobalite) in a diatomaceous earth mining and processing facility in California.10 Estimated exposure levels have been described by Seixas and colleagues,11 and were available for each worker from the original data.

(2) Finnish granite workers. This cohort consisted of 1026 workers hired between 1940 and 1971, in granite quarries and processing sites in three main granite areas of Finland.12,13 Koskela and colleagues14 have previously developed exposure estimates for subjects in nested case-control analyses of this cohort. For the purpose of this pooled analysis, the authors have applied the approach used in the case-control study to all members in the cohort. In addition they extended the mortality follow up from 1989 to 1993.

(3) US (Vermont) granite workers. This cohort consisted of 5408 workers from the Vermont granite industry including quarries, where the stone is cut, and sheds, where the stone is processed.15 Follow up for the pooled analysis was not extended beyond the original data of 1982, although some additional deaths prior to that were identified and added to the data. Attfield and Costello20 developed job and time specific quantitative exposures estimates for this cohort, using published data on the exposure to silica of the Vermont granite workers previously summarised by Davis and colleagues17 from six industrial hygiene surveys undertaken between 1924 and 1977.18,19

(4) US industrial sand workers. This cohort consists of 4027 workers in the industrial sand industry in the United States. Work in this industry consists of above-ground quarrying of ore with a high silica content, which is then ground and crushed, often into very pure and fine silica called silica flour.22 The authors developed quantitative job and time specific estimates of exposure based on extensive data from the 1970s and 1980s collected at all 18 plants in the study, as well as more limited data collected at a number of industrial sand plants in the 1940s.23

(5) US gold miners. This is a cohort of 3348 underground gold miners exposed to silica in South Dakota.24,25 For the pooled analysis, follow up was updated from 1990 to 1996. Quantitative job and time specific estimates of exposure (mg/m3 respirable silica) were available for this cohort,26,27 as were detailed work histories.

(6) Australian gold miners. This cohort consisted of 2213 underground gold miners in Kalgoorlie, Western Australia and was established from surveys of respiratory function and symptoms in underground gold miners.28,29 For this pooled analysis, the authors developed job and time specific exposure estimates (mg/m3 respirable silica). These estimates were based on industrial hygiene data collected since 1925 in the Australian gold mines.30

Four other cohorts, one from South Africa31 and three from China,32,33,34 for which quantitative exposure estimates of silica were available, were included in the pooled analysis for lung cancer. However, they were not included in this analysis because of a differential definition for silicosis in coding of causes of death: the three Chinese studies did not use the International Classification of Disease (ICD) system to code death certificates, and there is uncertainty regarding how to apply the original categories for silicosis, pneumoconiosis, and silicotuberculosis in the pooled analysis. Furthermore, the principal investigators of the Chinese cohorts are preparing their own report on silicosis and therefore preferred not to include their data on silicosis mortality in this pooled analysis.

In the case of the South African study,31 there were no deaths coded with silicosis as underlying cause, despite the documentation of high rates of silicosis in this cohort.1 Discussions with the principal investigator (personal communication, Eva Hnizdo) suggested that in South Africa silicosis was not generally considered an underlying cause of death. It is of note that we found in this cohort strong exposure-response related trends in mortality from related causes of death—that is, tuberculosis and non-specific chronic obstructive pulmonary disease.

In total, the pooled data set included 170 deaths with silicosis and unspecified pneumoconiosis as underlying cause, originating from a working population of 18 364 individuals. Table 1 lists the relevant studies with references and descriptive data.

Table 1 Description of the six studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Reference</th>
<th>Number of workers</th>
<th>End of follow up</th>
<th>Number of deaths</th>
<th>Number of silicosis deaths†</th>
<th>Median duration (y)</th>
<th>Median average (mg/m³)</th>
<th>Median cumulative (mg/m³·y)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. US diatomaceous earth workers</td>
<td>Checkoway et al (1997)</td>
<td>2342</td>
<td>1994</td>
<td>749</td>
<td>15</td>
<td>4.3</td>
<td>0.18</td>
<td>1.05</td>
</tr>
<tr>
<td>3. US granite workers</td>
<td>Costello et al (1988)</td>
<td>5408</td>
<td>1982</td>
<td>1762</td>
<td>43</td>
<td>18.0</td>
<td>0.05</td>
<td>0.71</td>
</tr>
<tr>
<td>5. US gold miners</td>
<td>Steenland et al (1995)</td>
<td>3348</td>
<td>1996</td>
<td>1925</td>
<td>39</td>
<td>5.4</td>
<td>0.05</td>
<td>0.23</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>18364</td>
<td>7065</td>
<td>170</td>
<td>10.4</td>
<td>0.07</td>
<td>0.62</td>
<td></td>
</tr>
</tbody>
</table>

*Follow up extended beyond original publication (see text).
†Those with underlying cause of death silicosis (ICD9 502) or unspecified pneumoconiosis (ICD9 505).

### Exposure data

The original data were obtained from each investigator. All exposure estimates were either originally in terms of milligrams of respirable silica per cubic metre of air, or were converted to this unit. We have reported details on the exposure data as well as the process of creating a common exposure metric.35 Job-exposure matrices (JEMs) for all six cohorts permitted exposure estimation of plant specific, job specific, and calendar-time specific exposure levels. The JEMs were typically based on a large number of actual measurements, supplemented by opinions from experts with extensive knowledge of the industries concerned.

### Analyses

For all six cohorts, silicosis deaths were defined for the pooled analysis as those with underlying cause of death silicosis (ICD9 502) or unspecified pneumoconiosis (ICD9 505). This definition of outcome was conservative; it is likely that some
silicosis was coded to other causes such as tuberculosis or chronic obstructive pulmonary disease with no mention of pneumoconiosis. Of the 170 silicosis deaths in our analysis, 150 were from silicosis and 20 were from unspecified pneumoconiosis.

We conducted standard life table analyses of silicosis mortality of the combined data, using 10 categories of cumulative exposure. This was chosen by dividing the cumulative exposure of the 170 silicotics deceased into deciles. Poisson regression was used to calculate rate ratios using the lowest exposure category as referent, including age, calendar period, and study in the model as potential confounders.

More detailed analyses of the exposure-response were conducted via a nested case-control analysis. The cases were defined again as those with underlying cause of death silicosis (ICD9 502) or unspecified pneumoconiosis (ICD9 505). For each case (n = 170), a risk set was assembled composed of those who had survived to an age at least as great as the case, and which was matched for race (relevant only for US studies), sex, date of birth (within five years), and study to the index case. One hundred controls were randomly drawn from each risk set to be compared to the index case, sufficient to assure good statistical precision and a point estimate very close to the point estimate that would have been obtained using full risk sets. The pooled case-control analysis was conducted using conditional logistic regression (in which the likelihood is equivalent to Cox regression), using the PHREG procedure of SAS. This analysis permitted flexible modeling of different exposure metrics and lags, and avoided the inherent categorisation of Poisson regression. We considered cumulative exposure (mg/m³-years), average exposure over working period (mg/m³), peak exposure over working period (mg/m³), and duration of exposure (years), and logarithmic transformations of these variables. We also considered lags of 0, 3, 10, 15, and 20 years. A priori there was no reason to believe that a lag was necessary, in that at least some types of silicosis can develop rapidly after exposure. However, we nonetheless investigated whether the data could be modelled better using a lag, since we knew that in many cases silicosis develops years after exposure ceases. Constants of 1.0 and 0.005 were added to cumulative exposure or average exposure respectively, when taking the logarithms, to avoid taking the logarithm of 0 in lagged analyses. We also ran some analyses using a cubic spline model with five knots (5%, 25%, 50%, 75%, 95% of the distribution); this is a very flexible exposure-response model, free from the usual parametric restraints inherent in many of the models specified above. Heterogeneity of exposure effect between the studies was considered via assessment of interaction terms between study and exposure. Heterogeneity by age was considered by stratifying by age (<65 years and ≥65 years) and including an age-exposure interaction term.

Risk assessment was based on the absolute rates of silicosis by cumulative exposure (adjusted for age, calendar time, and study). Cumulative lifetime risk of death from silicosis through age 65 was calculated by standard formulas for converting rates to risks (risk = 1−exp(−[time*rate]), where time is divided in intervals of one year). In these analyses, risk was calculated from age 20 to age 65, and assumed to be constant after leaving work and ending exposure. For each year from age 20 to 65, cumulative exposure increased depending on what exposure intensity was assumed (we considered 0.1 mg/m³ and 0.05 mg/m³), and the rates over time increased correspondingly (for example, at an intensity of 0.1 mg/m³ after 10 years (age 20–29) the cumulative exposure was 1.0 mg/m³-years, and the rate increased in that year from 4.7/100 000 to 233 per 100 000 person years for the whole cohort). The first level considered (0.1 mg/m³) is currently used as the permissible level for crystalline silica (quartz) in a number of countries in the world; the second (0.05 mg/m³) is the NIOSH recommended exposure limit.

RESULTS
The age of death for the 170 silicosis deceased ranged between 32 and 91 years, with a mean of 68.7 (SD 9.65). Of all silicosis deaths, 9% (n = 16) had occurred within one year after leaving the job. Fifteen of these 16 workers had a long duration of exposure prior to leaving the job, suggesting the development of a chronic disease rather than acute silicosis. Overall, those who died of silicosis had a median duration of exposure of 28 years and a median cumulative exposure of 7.15 mg/m³-years (compared to respectively 10 years and 0.62 mg/m³-years for the whole cohort). The median average exposure of the 170 silicosis deceased was 0.26 mg/m³, compared to 0.07 for the whole cohort.

Life table analysis and Poisson regression

The silicosis mortality rate was 28.8 per 100 000 person years for the whole cohort (table 2). The mortality rates for each decile of cumulative exposure to crystalline silica, increased from 4.7 per 100 000 person years for the lowest exposure category (less than 1 mg/m³-years), to 233 per 100 000 person years in the highest exposure category (more than 28 mg/m³-years). When adjusted for age, calendar period, and study, a rate ratio of 64 (95% CI 19.87 to 203.8) was found for the highest exposure category compared to the lowest. The increase of rate ratio by increasing cumulative exposure was almost monotonic.

Table 2 Exposure specific mortality rates and mortality rate ratios from silicosis

<table>
<thead>
<tr>
<th>Cumulative exposure to crystalline silica (mg/m³·py)</th>
<th>Person years (&gt;100000)</th>
<th>Silicosis mortality rate (per 100000 py)*</th>
<th>Adjusted† silicosis mortality rate (per 100000 py)</th>
<th>Adjusted† rate ratio</th>
<th>RR</th>
<th>(95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.00–0.99</td>
<td>3.634</td>
<td>4.7</td>
<td>4.7</td>
<td>1.00</td>
<td></td>
<td>(referent)</td>
</tr>
<tr>
<td>0.99–1.97</td>
<td>0.631</td>
<td>26.9</td>
<td>15.9</td>
<td>3.39</td>
<td>1.42 to 8.08</td>
<td></td>
</tr>
<tr>
<td>1.97–2.87</td>
<td>0.291</td>
<td>58.4</td>
<td>29.2</td>
<td>6.22</td>
<td>2.56 to 15.12</td>
<td></td>
</tr>
<tr>
<td>2.87–3.83</td>
<td>0.252</td>
<td>67.4</td>
<td>44.2</td>
<td>4.90</td>
<td>3.71 to 23.80</td>
<td></td>
</tr>
<tr>
<td>3.83–4.83</td>
<td>0.276</td>
<td>61.1</td>
<td>64.3</td>
<td>13.69</td>
<td>3.04 to 37.18</td>
<td></td>
</tr>
<tr>
<td>4.75–5.78</td>
<td>0.188</td>
<td>90.6</td>
<td>112.6</td>
<td>22.64</td>
<td>7.85 to 65.10</td>
<td></td>
</tr>
<tr>
<td>5.78–6.85</td>
<td>0.204</td>
<td>83.2</td>
<td>116.2</td>
<td>23.97</td>
<td>5.03 to 71.32</td>
<td></td>
</tr>
<tr>
<td>6.85–7.95</td>
<td>0.118</td>
<td>144.7</td>
<td>189.2</td>
<td>40.25</td>
<td>13.25 to 122.3</td>
<td></td>
</tr>
<tr>
<td>7.95–8.97</td>
<td>0.231</td>
<td>73.6</td>
<td>118.0</td>
<td>25.11</td>
<td>8.09 to 77.91</td>
<td></td>
</tr>
<tr>
<td>&gt;28.10</td>
<td>0.073</td>
<td>233.6</td>
<td>299.1</td>
<td>63.63</td>
<td>19.87 to 203.8</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>5.903</td>
<td>28.8</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td></td>
</tr>
</tbody>
</table>

*Each category includes 17 silicosis deaths (total 170).
†Adjusted for age in four categories, calendar period in eight categories, study in six categories, using Poisson regression.

n.a., not applicable.
Risk assessment
Cumulative risk of death from silicosis with an exposure of 0.10 mg/m³ from age 20 to 65 (4.5 mg/m³-years) was estimated to be 13 per 1000. At an exposure of 0.05 mg/m³ (2.25 mg/m³-years) the cumulative risk of death was estimated to be 6 per 1000.

DISCUSSION
The pooling of silica exposed cohorts with retrospective exposure data offered for the first time the opportunity to study in detail the quantitative relation between exposure to crystalline silica and silicosis mortality. Workers included in this study were exposed to crystalline silica in different occupational circumstances. To make the exposure estimate comparable between cohorts, respirable crystalline silica was used as the common unit of exposure. Differences in biological activity of different types of silica dust caused by their physical characteristics (for example, freshly cleaved silica, silica coated with clay) could not be taken into account in this pooled analysis. However, the exposure-response relation for log transformed cumulative exposure to crystalline silica (the metric that provided the best fit) was comparable between studies and no significant heterogeneity was found. We therefore think that our findings are relevant for different circumstances of occupational exposure to crystalline silica.

For all six cohorts, silicosis deaths were defined for the pooled analysis as those with underlying cause of death silicosis (ICD9 502) or unspecified or unknown pneumoconiosis (ICD9 505). This definition of outcome is specific but not sensitive, since deaths from silicosis might have been attributed to other causes such as tuberculosis or chronic obstructive pulmonary disease with no mention of silicosis or pneumoconiosis. Especially when only a singular underlying cause of death is available, an underestimation of the number of deaths caused by silicosis is likely to occur.

For the overall risk presented here (the estimation of 13 silicosis deaths per 1000 with lifetime exposure under the current standard), the under-report of silicosis deaths will have resulted in an under- rather than overestimation, irrespective of possible differences in exposure levels for unreported cases versus reported cases. The effect of under-reporting on the exposure-response curve is more difficult to predict, and would depend on the relative exposure levels of the unreported versus reported cases.

Misclassification of exposure status has inevitably occurred in this pooled analysis, but is not likely to be related to the disease status. A categorical analysis based on broad exposure groups should not be much affected by the resulting level of misclassification.

### Table 3 Results of nested case-control analysis, relative risk models

<table>
<thead>
<tr>
<th>Continuous exposure measures</th>
<th>Model ( \chi^2 ), 1 df</th>
<th>RR*</th>
<th>(95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Log transformed cumulative exposure (log mg/m³-days)</td>
<td>By study</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. US diatomaceous earth workers</td>
<td>2.08</td>
<td>[1.23 to 3.52]</td>
<td></td>
</tr>
<tr>
<td>2. Finnish granite workers</td>
<td>2.76</td>
<td>[1.37 to 5.57]</td>
<td></td>
</tr>
<tr>
<td>3. US granite workers</td>
<td>1.76</td>
<td>[1.30 to 2.38]</td>
<td></td>
</tr>
<tr>
<td>4. US industrial sand workers</td>
<td>1.63</td>
<td>[1.03 to 2.57]</td>
<td></td>
</tr>
<tr>
<td>5. US gold miners</td>
<td>3.57</td>
<td>[1.90 to 6.69]</td>
<td></td>
</tr>
<tr>
<td>6. Australian gold miners</td>
<td>2.31</td>
<td>[1.34 to 3.97]</td>
<td></td>
</tr>
<tr>
<td>By age of death (of the cases)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65 years</td>
<td>2.70</td>
<td>[1.90 to 3.84]</td>
<td></td>
</tr>
<tr>
<td>≥65 years</td>
<td>1.81</td>
<td>[1.44 to 2.29]</td>
<td></td>
</tr>
</tbody>
</table>

Cases and controls were matched for age, race, sex, date of birth, and study.

*Rate ratio for increase of one unit of each exposure measure.
Main messages

- The pooling of six silica exposed cohorts enabled for the first time a detailed study of the quantitative relation between exposure to crystalline silica and silicosis mortality.
- The six cohorts showed similar patterns of exposure-response for the logarithm of cumulative exposure, without significant heterogeneity between studies.
- Cumulative risk of death from silicosis with an exposure of 0.1 mg/m³ from age 20 to 65 was estimated to be 13 per 1000.

Policy implications

- Results indicate that the current exposure standard for crystalline silica used by many countries (0.1 mg/m³), is not sufficiently protective against silicosis mortality.

The log of cumulative exposure provided the best fit to our data in regression analyses. Duration of exposure did not fit nearly as well as the log of cumulative exposure, suggesting that our estimation of exposure level was able to significantly add to simple duration in predicting silicosis, in turn lending some validity to our job-exposure matrices. The superior fit of the log of cumulative exposure compared with simple cumulative exposure suggests a flattening out of risk at high levels of exposure, a phenomenon which has been seen in occupational mortality studies for other agents, for example, studies of cancer mortality in relation to dioxin, or diesel fumes.

Including a lag for cumulative exposure did not improve the fit of the models or the risk estimates. While lagging is less important when the follow up time since cessation of exposure is long, in our study there was a wide heterogeneity of time since last exposure. Therefore the lack of improvement using a lag suggests that the whole exposure period was important, including recent periods. A similar finding has been made for silicosis morbidity by Chen and colleagues.

In this pooled analysis it was not possible to adjust for potential confounders, especially cigarette smoking. Some studies suggest that smoking increases the risk of silicosis in exposed workers, although no effect of smoking was detected in a study of Colorado miners.

Silicosis mortality rate was found to be 28 per 100 000 person-years for the pooled cohort, and 230 per 100 000 for the highest exposure category.

The estimated cumulative risk of silicosis death, assuming exposure at the current OSHA exposure standard (0.1 mg/m³ when dust is 100% silica) from age 20 to 65 was 13 per 1000 (1.3%). For silicosis morbidity (radiographic small opacity at the current OSHA exposure standard (0.1 mg/m³ when dust is 100% silica) from age 20 to 65 was 13 per 1000 (1.3%). For silicosis morbidity (radiographic small opacity from age 20 to 65 was 13 per 1000 (1.3%).

In conclusion, the findings from our pooled analysis add further support for the need to control silica exposure and to lower the occupational standards.

K Steenland, National Institute for Occupational Safety and Health (NIOSH), Department of Health and Human Services, Robert A Taft Laboratories, Cincinnati, Ohio, USA

M Attfield, National Institute for Occupational Safety and Health (NIOSH), Division of Respiratory Disease Studies, Morgantown, USA

H Checkoway, University of Washington, Department of Epidemiology, Seattle, USA

N DeKlerk, University of Western Australia, Department of Public Health, Perth, Australia

R-S Koskela, Finnish Institute of Occupational Health (FIOTH), Department of Epidemiology and Biostatistics, Helsinki, Finland

REFERENCES

37 Steenland K, Deddens JA. Increased precision using countermatching in nested case-control studies. Epidemiology 1997;8:238–42.