A small number of prior epidemiologic studies of occupational noise exposure based on self-report have suggested an association with acoustic neuroma. The goal of the present study was to further examine the association between noise exposure and acoustic neuroma by using an objective measure of exposure in the form of a job exposure matrix. A total of 793 acoustic neuroma cases aged 21–84 years were identified between 1987 and 1999 from the Swedish Cancer Registry. The 101,756 controls randomly selected from the study base were frequency matched to cases on age, sex, and calendar year of diagnosis. Occupational information, available for 599 of the cases and 73,432 of the controls, was obtained from censuses and was linked to a job exposure matrix based on actual noise measurements. All risk estimates were close to unity, regardless of noise exposure level or parameter. The overall odds ratio for exposure to ≥85 dB of noise was 0.89 (95% confidence interval: 0.64, 1.23). Contrary to previous study results, the present findings did not demonstrate an increased acoustic neuroma risk related to occupational noise exposure even after allowing for a long latency period. The effect of nondifferential misclassification of exposure must be considered a potential cause of the negative findings.

Acoustic neuroma, also referred to as vestibular schwannoma, constitutes 6–10 percent of all intracranial tumors, with an incidence of 1–20 per million per year (1–3). The sex ratio (females/males) has been reported to be greater than 1 (1, 4–6), and the tumor occurs mainly in individuals aged 50 years or older (1). Although benign, the tumor can cause significant morbidity because of its location on the vestibular division of the eighth cranial nerve in the internal auditory canal (4, 7, 8). In the present study, we examined unilateral sporadic acoustic neuroma, which comprises 90–95 percent of all acoustic neuromas (1, 9).

The only well-established exogenous risk factor for acoustic neuromas is ionizing radiation. A link between acoustic neuroma and mobile phone use has been suggested, although the increased risk, if real, seems to be associated with longer duration of use, generally 10 or more years of use prior to diagnosis (10, 11). In the present study, we focused on occupational noise exposure as a potential risk factor for acoustic neuroma. Two previous studies have examined occupational noise and its relation to acoustic neuroma, with consistent results (12, 13). In the first study, elevated risks of acoustic neuroma were found for occupational noise exposure based on self-reported occupational histories reviewed by an occupational hygienist (13). In the second study, elevated acoustic neuroma risks were detected for self-reported regular exposure to occupational and nonoccupational noise (12). In both studies, a dose-response effect was evident with increasing years of noise exposure (12, 13). Limitations of the prior studies include their use of self-reported exposure; both studies analyzed participant interview data.

The purpose of the present study was to investigate exposure to objectively measured occupational noise and...
acoustic neuroma risk in a large, register-based case-control study. Doing so would facilitate further examination of the role of noise in acoustic neuroma etiology.

**MATERIALS AND METHODS**

**Study design and population**

A register-based case-control study was conducted in which the source population included all residents of Sweden between 1987 and 1999 gainfully employed according to any census performed between 1975 and 1990. The study was approved by the Ethics Committee at the Karolinska Institutet.

**Acoustic neuroma case ascertainment**

Eligible cases included all patients diagnosed with acoustic neuroma (International Classification of Diseases, Ninth Revision, code 1920 and histopathologic code 451, classified according to WHO/HS/CANC/24.1 histology code) between 1987 and 1999 (14). We identified 793 acoustic neuroma cases reported to the national Swedish Cancer Registry who met these criteria. In Sweden, physicians and pathologists must notify the Cancer Registry of every case of acoustic neuroma. In our study, reference year was defined as the year of acoustic neuroma diagnosis.

**Controls**

Controls were randomly selected from the continuously updated Swedish Population Registry from among individuals never diagnosed with acoustic neuroma or other intracranial tumors, pancreatic cancer, or hematologic malignancies (controls were selected simultaneously for studies of the latter two tumor types as part of another larger case-control study). On December 31 of each year of the study, controls were frequency matched on age and sex to cases with acoustic neuroma, pancreatic cancer, and hematologic malignancies diagnosed during that year. The year in which a control was selected was used as the reference year for the control. Controls could be selected only once, and cases could not be selected as controls. Registry information necessary for the analysis was readily available because all study participants could be linked to other Swedish registers by means of the national registration number unique to each individual in Sweden (15). In our study, the entire set of controls (n = 101,756) was used.

**Census data**

The study participants’ occupations were obtained from censuses performed by Statistics Sweden in 1975, 1980, 1985, and 1990. Census data, collected in September of each census year, provided the occupational codes and socioeconomic statuses for the study participants. Occupations were categorized by using a three-digit occupational coding system.

**Individual noise exposure assessment**

Instead of depending on self-reported noise exposure, as in prior studies, occupational exposure in the present study was based on knowledge of job titles (16, 17). Information regarding noise exposure for each study participant was assessed by linking the newly created job exposure matrix to each subject’s occupational code in each of four censuses. Exposure could be determined by the occupation at each census and by the noise measurement for each occupation during the pericensal time period. For each occupation, noise was measured for the 5-year periods preceding and following each of the four census years. Consequently, individual exposure data were not available for 1995–1999 (the last follow-up period) because 1990 was the last census from which occupational codes were available. In addition, only that exposure occurring prior to the reference date was considered in the analysis. Unfortunately, data on noise-induced hearing loss among study participants were not available for use as an indicator of noise exposure.

Although occupation was reported only every 5 years, if the noise measurement for an occupation was $\geq 75$ dB for the 5 years before the census, then a study participant reporting that occupation could be considered exposed during each of the 5 years prior to the census. Equivalently, if the noise measurement for the 5-year period was obtained after the census, the study participant could be assigned the noise measurement for that occupation for the 5 years including and following the census. However, exposure status for an occupation could not be based on an average of the years both preceding and following the census because combining exposure statuses for the years preceding and following a census might lead to further exposure misclassification.

All analyses were initially performed in two ways: first by assigning exposure before the census and then by assigning exposure for the period including and following the census. Differences in risk estimates and accompanying 95 percent confidence intervals between the two times of exposure assignment were negligible. Therefore, we arbitrarily selected the decibel measurement categories for the 5 years preceding each census to assess exposure in the final model.

In the present analysis, ever being exposed to low noise versus never being exposed was defined as ever holding an
occupation with exposure of 75–84 dB based on any census compared with never having an occupation with noise exposure. Ever being exposed to high noise versus never being exposed was similarly defined by using exposure of ≥85 dB.

To evaluate the impact of different latency periods, we examined the effect of time since first noise exposure on acoustic neuroma risk. Given the length of the observation period (1975–1990), the semidecadal censuses, and estimates of the latency period for acoustic neuroma reported in prior studies, latency periods of 5, 10, and 15 years were chosen (12, 18, 19). A 20-year latency period was not used because there were too few observations for meaningful analysis. In the analysis, risk estimates for low noise exposure as well as for high noise exposure were obtained for each of the three latency periods as well as for no latency period. The reference category for each comparison in this analysis included those whose first exposure occurred within the latency period as well as those never exposed. The latency period analysis implicitly assumes that exposure during the latency period has no effect on the developing tumor. Finally, the availability of occupational data from multiple consecutive censuses enabled us to assess exposure duration; that is, we investigated the effect of low noise exposure and high noise exposure at one, two, three, and four consecutive censuses prior to the reference year.

Statistical analysis

Unconditional logistic regression models adjusted for age, sex, and socioeconomic status were used to estimate odds ratios and their respective 95 percent confidence intervals with SAS, version 9.1, statistical software (SAS Institute, Inc., Cary, North Carolina) (20). The odds ratio was used as an estimate of relative risk in the analysis of the job exposure matrix data. Age was evaluated for inclusion in the model as both a categorical and a continuous variable. Because there was a negligible difference between these two representations of age, and to reduce the number of variables, age was included as a continuous variable in the final model. Socioeconomic status was categorized into eight groups, as shown in table 1. All statistical significance tests were two sided.

RESULTS

Basic demographic characteristics of cases and controls are presented in table 1. The total number of cases and controls in the study was 793 and 101,756, respectively. The ages of the cases ranged from 21 to 84 years. Differences among the demographic variable distributions between cases and controls can be seen for age and sex.
because controls were matched also on these variables to types of tumors other than acoustic neuroma. For all study participants, information on occupation was missing for fewer than 1 percent, and information on socioeconomic status was missing for approximately 2 percent. The job exposure matrix enabled 72 percent of the study participants to be assigned an exposure level, allowing 599 cases and 73,432 controls to be included in the final analysis. There were no meaningful differences in the distributions of sex, age, or socioeconomic status between all study participants and those for whom information on exposure was available.

Table 2 shows the most frequent occupations with high (≥85 dB) noise exposure according to case status and sex. Men were significantly more often employed in occupations with high noise exposure (14 percent of men and 3 percent of women) as well as in occupations with low (75–84 dB) noise exposure (63 percent of men and 43 percent of women).

In table 3, the odds ratio for ever being exposed to low noise and the odds ratio for ever being exposed to high noise were both slightly below unity, and the confidence intervals included the null. Odds ratios are presented for acoustic neuroma according to time since first noise exposure or latency period. All of the confidence intervals for the three latency periods for both low and high noise included the null.

Odds ratios for acoustic neuroma are presented in table 4 for exposure to occupational noise according to one, two, three, or four consecutive censuses closest in time prior to the reference year. The odds ratios for the four low noise exposure durations were slightly above unity, but all of the corresponding confidence intervals included the null. For the high noise exposure category, the odds ratios were generally at or close to unity and, again, all confidence intervals included the null. As part of the analysis, tables 3 and 4 were combined (i.e., duration of exposure stratified on latency period); however, the numbers of observations were too small for meaningful analysis.

**DISCUSSION**

Comparison of results to those from prior studies and strengths of the present study

To our knowledge, the present study is the third to examine the association between noise exposure and acoustic neuroma. We found no evidence of an increased acoustic neuroma risk among study participants working in occupations with noise exposure, regardless of exposure level, exposure duration, or latency period. This finding is in contrast to previous studies examining the role of noise exposure as a possible risk factor for acoustic neuroma that demonstrated...
an elevated risk of the tumor with exposure to occupational noise, nonoccupational noise, or both (12, 13).

In the first study to examine noise in the etiology of acoustic neuromas, by Preston-Martin et al. (13), controls were matched to cases aged 25–69 years diagnosed with acoustic neuroma. Self-reported occupational histories were reviewed by an occupational hygienist to determine whether significant noise exposure occurred. The study found an odds ratio of 2.2 (95 percent confidence interval: 1.12, 4.67) for ever having a job involving exposure to extremely loud noise. The authors also found a dose-response effect for years of employment in an occupation with noise exposure (p for trend = 0.02) (13).

In the second study, occupational and nonoccupational noise exposures were evaluated in a population-based case-control study of 146 men and women aged 20–69 years with acoustic neuroma (12). Type and duration of noise exposure were ascertained through self-report, with noise defined as ≥85 dB. Exposure to regular noise from machines, power tools, and/or construction was found to increase acoustic neuroma risk (odds ratio = 1.79, 95 percent confidence interval: 1.11, 2.89), as was regular exposure to loud music (odds ratio = 2.25, 95 percent confidence interval: 1.20, 4.23). When latency period was examined, an increased acoustic neuroma risk was found only with a latency of at least 13 years between first regular noise exposure and time of diagnosis, with an odds ratio of 2.12 (95 percent confidence interval: 1.40, 3.20) (12).

The Preston-Martin et al. study (13) contained a relatively small number of cases (n = 86) and was restricted to men. In the second study of both men and women (12), data for 146 acoustic neuroma cases were analyzed, although the number of men in the study was in fact smaller than in the first study. It is important to note that while the total number of cases in the second study (n = 146) was considerably lower than in the present study (n = 599), the statistical power of the second study was in fact higher because of the larger number of cases (n = 74 or 51 percent) exposed to ≥85 dB compared with the present study (n = 67 or 11 percent). The negative findings of the present study may therefore be due to lack of statistical power.

The strengths of our present study include the high quality of data available for analysis. Coverage and accuracy of the data obtained from the Swedish Cancer Registry are high. In excess of 98 percent of histologically confirmed cancers in Sweden are reported to the Cancer Registry (15). Of all cases of cancer reported to the registry, including both malignant and benign tumors, close to 80 percent are histologically confirmed (15). Of the acoustic neuromas reported to the Cancer Registry, 99 percent are histologically confirmed (Swedish Cancer Registry). Although the quality of the registry is high, it should be acknowledged that acoustic neuroma is a benign tumor and may therefore be diagnosed many years after the tumor has developed, or it may never be diagnosed at all.

The census registries cover the whole population; therefore, the information collected on occupation was remarkably complete. The risk of selection bias was minimized through the random selection of controls from the population, and the potential for recall bias was eliminated by using objectively collected occupational data obtained from censuses. In addition, the job exposure matrix included a large number of different occupations and was based on actual measurements of noise.

### Comparison of results to those from a prior study of self-reported noise exposure and potential for recall bias

The present study was conducted, in part, to replicate the results of the second study of self-reported noise exposure and acoustic neuroma through the use of a job exposure matrix and census data collected independently of disease (12). Accordingly, the first explanation for the negative findings of the present study was the effect of recall bias in the second study. The tendency for patients with a tumor to focus on the reasons that they may have developed the disease was a potential source of recall bias. At the time of the interview, 91 percent of the cases in the second study reported unilateral hearing loss. This factor may have made the cases more aware of past noise exposures prior to their diagnosis compared with the controls, of whom only 29 percent reported hearing loss (12).

### Table 4. Odds ratios and 95% confidence intervals for exposure to occupational noise at any time (ever) for one, two, three, or four consecutive censuses closest in time prior to the reference year, Sweden, 1987–1999

<table>
<thead>
<tr>
<th>Exposed according to</th>
<th>Cases</th>
<th>Controls</th>
<th>OR†</th>
<th>95% CI†</th>
<th>Cases</th>
<th>Controls</th>
<th>OR†</th>
<th>95% CI†</th>
</tr>
</thead>
<tbody>
<tr>
<td>One census</td>
<td>250</td>
<td>23,740</td>
<td>1.13</td>
<td>0.86, 1.49</td>
<td>25</td>
<td>2,578</td>
<td>0.94</td>
<td>0.58, 1.52</td>
</tr>
<tr>
<td>Two censuses</td>
<td>183</td>
<td>16,711</td>
<td>1.18</td>
<td>0.88, 1.58</td>
<td>15</td>
<td>1,496</td>
<td>1.02</td>
<td>0.56, 1.83</td>
</tr>
<tr>
<td>Three censuses</td>
<td>131</td>
<td>11,955</td>
<td>1.21</td>
<td>0.88, 1.66</td>
<td>10</td>
<td>1,026</td>
<td>1.00</td>
<td>0.88, 1.66</td>
</tr>
<tr>
<td>Four censuses</td>
<td>100</td>
<td>10,006</td>
<td>1.15</td>
<td>0.81, 1.63</td>
<td>9</td>
<td>796</td>
<td>1.17</td>
<td>0.81, 1.63</td>
</tr>
</tbody>
</table>

* The reference category includes 178 cases and 16,761 controls never exposed to occupational noise (i.e., exposure of <75 dB).
† OR, odds ratio derived from unconditional logistic regression analysis; adjusted for age, sex, and socioeconomic status.
‡ CI, confidence interval.
Diagnostic delay and the healthy worker survivor effect

Diagnostic delay is the period between the appearance of the first symptom and the time that medical attention is first sought. Because the majority of acoustic neuroma tumors grow slowly, it is likely that many of the cases had the tumor for several years before a clinical diagnosis was made (19, 21). According to one study, the delay from the first symptom of acoustic neuroma until diagnosis averaged more than 5 years, with a range of 2–30 years (18). In addition, study participants working in high noise exposure occupations may have developed hearing loss or tinnitus and consequently may have left their occupation or transferred to an occupation with lower noise exposure. This potential source of bias is termed the healthy worker survivor effect (22). Such a situation could possibly explain the observed odds ratios below unity when no, or a very short, latency period was used in our analyses (23).

Additionally, the slow growth of acoustic neuromas may have resulted in the inclusion in the exposure assessment of a time period during which the tumor was already present, in contradiction to study methodology whereby etiologically relevant exposures are considered only those prior to disease onset. However, the latency calculation was assigned to address the issue of time between disease onset and diagnosis; furthermore, this method of estimating exposure also eliminates bias that results when workers leave their occupations because of noise exposure or symptoms of a tumor (the healthy worker survivor effect).

Misclassification of exposure and confounding

Another concern is nondifferential misclassification of exposure, whereby exposure is misclassified similarly among study participants with and without disease (24, 25). Job exposure matrices are often suspected of producing greater nondifferential misclassification than do questionnaires (17). When individuals who perform different tasks in different work environments are grouped under the same occupational title and are classified as exposed or unexposed depending on whether the probability of exposure exceeds a given threshold (i.e., either 74 or 84 dB), misclassification will inevitably occur (17, 26, 27). If present, misclassification may lead to underestimation of the effect estimate with associated loss of statistical power (16, 24, 27). In addition, in our study, nonoccupational noise exposure was not considered. If a true association between noise and acoustic neuroma exists, then nonoccupational noise contributes to the risk burden and to exposure misclassification.

Nevertheless, misclassification may in fact be less than anticipated when defining exposure as occupations with noise levels of ≥85 dB. Occupations with this noise exposure level are relatively uncommon, with only 13 percent of controls so classified, corresponding to a high specificity. Therefore, even in the unlikely event that a majority of study participants classified as exposed are misclassified, most participants classified as unexposed are most likely classified correctly.

It is possible that imprecision of the job exposure matrix may be a result of the noise measurements being taken later than the time of the actual exposures, since the noise exposures related to each occupation may have changed over time (28). In addition, census data on occupation were obtained every 5 years and reflect the occupational status at only one point in time; therefore, they may not accurately reflect the occupational exposure between the censuses or if more than one job was held at the same time (27, 29, 30). There were also a limited number of measurements taken for each occupation. Another limitation of the study includes the potential for reporting of acoustic neuromas to the Cancer Registry as unspecified tumors. However, such misclassification of cases should be unrelated to exposure.

Finally, because exposure in the present study was assessed by using a job exposure matrix, data on the use of hearing protection were not available. In the second study of occupational and nonoccupational noise and acoustic neuroma risk, the odds ratio for study participants exposed to noise while using hearing protection was close to the null; thus, these individuals were categorized as unexposed (12). The observed odds ratios in the present study that were close to or below the null in the high noise exposure analysis may be attributable, in part, to the use of hearing protection. At an occupational noise exposure level of ≥85 dB, and during the years of our study, the use of hearing protection would have been commonplace. This, and the aforementioned issues, may contribute to the imprecision inherent in assigning exposure according to occupational categories in a study such as ours that may ultimately attenuate a true effect.

Conclusion

In summary, the overall results of the study do not support the hypothesis that occupational noise exposure is a risk factor for acoustic neuroma. In the present study, we used an objective measure of noise exposure in the form of a job exposure matrix. Yet, because we had no direct measure of each individual’s exposure to noise but rather used occupational categories to estimate this exposure, the effect of nondifferential misclassification of exposure must be considered as a potential cause of the negative findings.

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