Low Heritability of Tinnitus

Results From the Second Nord-Trøndelag Health Study

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Objective: To estimate the heritability of tinnitus.

Design: Self-report questionnaire data collected from August 1, 1995, through June 30, 1997, from individuals in the Nord-Trøndelag Hearing Loss Study (an integrated part of the Nord-Trøndelag Health Study) were used. The study also included information on first-degree family relationships, and age-corrected polygenic correlations of relatives’ tinnitus status were calculated. A structural equation model was fit to the data, and the relative contributions of genes and unique environmental effects were estimated. Models that included sex-specific effects were also tested.

Setting: Nord-Trøndelag County, Norway.

Patients: A population-based sample of 12,940 spouses, 27,607 parent-offspring, and 11,498 siblings was used. A total of 28,066 respondents were tested twice, yielding a test-retest correlation of 0.65 for the report of tinnitus.

Main Outcome Measure: Heritability of tinnitus.

Results: Correlations for parent-offspring ranged from 0.01 to 0.07 for the various sex combinations, sibling correlation ranged from 0.06 to 0.14, and the spouse correlation was 0.04. This family correlation pattern implies an upper limit for heritability of 0.11 with no sex differences in the heritability estimates.

Conclusions: This is the first large population-based family study, to our knowledge, to report on the heritability of tinnitus. In contrast to previous speculations in the literature, this low heritability indicates that additive genetic effects explain only a small proportion of the variance of tinnitus in the population.


Tinnitus, or the perception of sound without an external acoustic stimulus, is a common but poorly understood symptom. Although the list of factors associated with tinnitus is long, the causes of tinnitus onset and tinnitus maintenance are far from fully understood, and attempts to develop evidence-based therapies have been thwarted by a poor understanding of the pathophysiology of the condition.

The close relation of tinnitus to hearing impairment has suggested that tinnitus is caused by cochlear damage, but observation of tinnitus in persons in whom the auditory nerve has been severed implies that tinnitus can occur without involvement of the peripheral auditory system. The neurophysiologic model of tinnitus postulates that other systems in the brain, in addition to the auditory system, have to be involved in tinnitus. Buzzing or ringing in the ear itself is not the only source of tinnitus-related complaints; individuals who find tinnitus troublesome evaluate and perceive it as a threat or annoyance rather than as a sound of little or no consequence.

A significant familial aggregation of tinnitus has recently been reported. On the basis of same-sex siblings from the present data set, a significant familial association in tinnitus risk that could not be attributed to known risk factors for tinnitus has been found. With the exception of a report based on a small cohort of elderly Danish twins who reported a significant heritability of tinnitus for women, little is known about the relative importance of genetic effects in tinnitus susceptibility.

Heritability needs to be estimated through quantitative genetic studies, such as twin and family studies. Candidate gene studies of tinnitus may also be warranted, but only if quantitative studies can demonstrate a substantial heritability for tinnitus. The aim of the present study is to estimate the relative contribution of genetic effects to the susceptibility to tinnitus in a large population-based sample of nuclear families. The correlation structure among relatives is observed, and the heritability is estimated on the basis of these correlations.
From August 1, 1995, through June 30, 1997, the adult populations of the 24 municipalities of Nord-Trøndelag County, Norway, were invited to participate in a health screening survey, the second Nord-Trøndelag Health Study (HUNT 2). An integrated part of HUNT 2 is the Nord-Trøndelag Hearing Loss Study.11 and the populations of 17 of the 24 municipalities in the county were invited to participate in this hearing loss study. The invitation list was based on population files stored and continuously updated by Statistics Norway. The mean (SD) age of the participants was 50 (17) years (age range, 20-101 years). In one municipality, Levanger, individuals were reinvited to participate in the hearing examination after HUNT 2 was finished. The participation rate for all municipalities together (except Levanger) was 66.7%; for Levanger, the overall participation rate was 41.1%. Altogether, 51,574 people, including 5,114 from Levanger, participated in the hearing examination and signed an informed consent form. Information on first-degree relatives of the 24 municipalities of Nord-Trøndelag County, Norway, were included in the study sample.

### QUESTIONNAIRE

A 1-page questionnaire was distributed to all participants and completed immediately before the hearing examination took place. A second questionnaire was distributed, usually a few months after the hearing examination, to individuals with a certain degree of hearing loss (n = 16,186) and to a control group (n = 17,785). Altogether, 28,066 persons (71.8%) returned questionnaire 2. Questionnaire 1 included questions about bothersome tinnitus (response categories: yes, no, and don’t know/maybe), tinnitus frequency (response categories: monthly, weekly, daily, and almost always), and typical duration of tinnitus attacks (response categories: a few minutes, 10 minutes to 1 hour, and longer than 1 hour). Questionnaire 2 included a slightly differently phrased question about the degree to which the respondent is bothered by tinnitus (response categories: not bothered, a little bothered, and strongly bothered). In the present study, data from questionnaire 1 were used in the estimation of the heritability, whereas both questionnaires 1 and 2 were used in the estimation of the test-retest correlation.

### STUDY SAMPLE

Records with missing values on all 3 items in questionnaire 1 were treated as not bothered by tinnitus. In cases with no information indicating the presence of tinnitus, that is, endorsing any of the 3 items, missing values for frequency and duration were imputed, using these 2 items as predictors for each other together with age and sex. Missing Values Analysis (option EM) using SPSS statistical software (SPSS Inc, Chicago, Illinois) was chosen as a tool for imputation. Responses on all items were plotted on the z-scale and summed to create an index. When information from all 3 items was included, 40,795 of the respondents (79.1%) reported no signs of tinnitus. The remaining 10,779 who reported tinnitus symptoms (20.9%) were split into 4 groups each containing approximately 5%, yielding an index with 3 response categories. This index was used as input in the heritability analyses.

### MODEL AND ESTIMATION

Structural equation modeling is well established and widely used for the analysis of family data to disentangle the relative contribution of genetic and environmental effects on complex traits. Information about genetic relation (siblings, parent-child) combined with information on family membership without genetic relation (spouses) can be used to quantify the relative importance of genetic and environmental effects in disease liability. Sex-specific genetic effect is indicated by a lower correlation between male and female sibling environmental effect; µ, correlation between spouses’ environment (social homogamy). Observed phenotypes in each relative are shown as rectangles, and latent variables are shown as circles. The value 0.5 denotes that parents each pass on half their genes to their children.

### Table 1. Age-Corrected Polychoric Correlations for Tinnitus Among Members of Nuclear Families

<table>
<thead>
<tr>
<th>Family Relation</th>
<th>Polychoric Correlation (95% CI)</th>
<th>No. of Observationsa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mother-son</td>
<td>0.052 (0.010 to 0.094)</td>
<td>7970</td>
</tr>
<tr>
<td>Mother-daughter</td>
<td>0.068 (0.023 to 0.112)</td>
<td>7855</td>
</tr>
<tr>
<td>Father-son</td>
<td>0.060 (0.013 to 0.106)</td>
<td>5907</td>
</tr>
<tr>
<td>Father-daughter</td>
<td>0.012 (−0.038 to 0.061)</td>
<td>5875</td>
</tr>
<tr>
<td>Sisters</td>
<td>0.074 (−0.007 to 0.148)</td>
<td>2739</td>
</tr>
<tr>
<td>Brothers</td>
<td>0.141 (0.077 to 0.207)</td>
<td>3137</td>
</tr>
<tr>
<td>Different-sex siblings</td>
<td>0.062 (0.010 to 0.144)</td>
<td>5622</td>
</tr>
<tr>
<td>Spouses</td>
<td>0.044 (0.011 to 0.075)</td>
<td>12,940</td>
</tr>
</tbody>
</table>

Abbreviation: CI, confidence interval.

a The same person can be included in more than 1 family relation.
According to convention, the observed phenotypes (tinnitus) in each relative are shown as rectangles and latent variables are shown as circles. Genetic effects that influence tinnitus are transmitted from the latent paternal (GF) and maternal (GM) genotypes to the latent genotypes of their children (GC1 and GC2). The phenotype is also influenced by environmental effects in the parents (Ea and Eb) and children (Ec1 and Ec2). Environmental sibling effects (Sc1 and Sc2) are shared fully by same-sex and partly by opposite-sex siblings.

The effect of environmental transmission from parents to offspring and genetic effect (heritability) cannot be separated using data from nuclear families only. The heritability estimates presented in the following text are the upper limit of the heritability estimates and may also include environmental parent-offspring transmission.

Assortative mating is a tendency for individuals who mate to be similar for the trait being studied, generating a correlation between spouses. A significant spouse correlation may be expected in a population if the trait under study is heritable. The sibling correlation between spouses is a measure of the degree of similarity in behavior or traits between individuals who are compared as pairs. A significant spouse correlation may be expected in a population if the trait under study is heritable.

We used the age-corrected correlations as input in the structural equation model. The fit of each model was evaluated by the goodness-of-fit index AIC: goodness of fit is expressed by low values. The results of the model-fitting procedure, including model parameter estimates and model fit statistics, are listed in Table 2, starting with the least constrained model and subsequently adding constraints and comparing more parsimonious models with the full model. The parameter estimates correspond to the model illustrated in Figure 1.

Table 2. Parameter Estimates for the Full Model and Reduced Submodels Fit to Family Polychoric Correlations for Tinnitus

<table>
<thead>
<tr>
<th>Model No.</th>
<th>Constraints</th>
<th>s_M</th>
<th>s_F</th>
<th>g_M</th>
<th>g_F</th>
<th>σ</th>
<th>µ</th>
<th>df</th>
<th>Δχ²</th>
<th>P Value</th>
<th>AIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Full</td>
<td>0.33</td>
<td>0.15</td>
<td>0.30</td>
<td>0.33</td>
<td>0.30</td>
<td>0.05</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>g_M = g_F</td>
<td>0.32</td>
<td>0.17</td>
<td>0.32</td>
<td>0.32</td>
<td>0.27</td>
<td>0.05</td>
<td>1</td>
<td>0.09</td>
<td>.76</td>
<td>-1.91</td>
</tr>
<tr>
<td>3</td>
<td>s_M = s_F</td>
<td>0.27</td>
<td>0.27</td>
<td>0.34</td>
<td>0.29</td>
<td>0.21</td>
<td>0.05</td>
<td>1</td>
<td>1.62</td>
<td>.20</td>
<td>-0.38</td>
</tr>
<tr>
<td>4</td>
<td>s_M = s_F, σ = 1</td>
<td>0.21</td>
<td>0.21</td>
<td>0.35</td>
<td>0.28</td>
<td>0.1</td>
<td>0.05</td>
<td>2</td>
<td>3.50</td>
<td>.17</td>
<td>-0.50</td>
</tr>
<tr>
<td>5</td>
<td>Eliminate s_M and σ</td>
<td>0.33</td>
<td>0</td>
<td>0.30</td>
<td>0.35</td>
<td>0</td>
<td>0.05</td>
<td>0</td>
<td>0.35</td>
<td>.84</td>
<td>-3.65</td>
</tr>
<tr>
<td>6</td>
<td>Eliminate s from full model</td>
<td>0</td>
<td>0</td>
<td>0.39</td>
<td>0.31</td>
<td>0</td>
<td>0.05</td>
<td>0</td>
<td>6.86</td>
<td>.08</td>
<td>0.86</td>
</tr>
<tr>
<td>7</td>
<td>g_M = g_F, s_M = s_F</td>
<td>0.27</td>
<td>0.27</td>
<td>0.32</td>
<td>0.32</td>
<td>0.19</td>
<td>0.05</td>
<td>2</td>
<td>1.84</td>
<td>.40</td>
<td>-2.17</td>
</tr>
<tr>
<td>8</td>
<td>g_M = g_F, s_M = s_F, σ = 1</td>
<td>0.21</td>
<td>0.21</td>
<td>0.32</td>
<td>0.32</td>
<td>1</td>
<td>0.05</td>
<td>3</td>
<td>3.98</td>
<td>.26</td>
<td>-2.02</td>
</tr>
<tr>
<td>9</td>
<td>g_M = g_F, eliminate σ and s_F</td>
<td>0.32</td>
<td>0</td>
<td>0.33</td>
<td>0.33</td>
<td>0</td>
<td>0.05</td>
<td>3</td>
<td>0.60</td>
<td>.90</td>
<td>-5.40</td>
</tr>
<tr>
<td>10</td>
<td>Eliminate g from full model</td>
<td>0.38</td>
<td>0.27</td>
<td>0</td>
<td>0</td>
<td>0.61</td>
<td>0.04</td>
<td>2</td>
<td>18.66</td>
<td>&lt;.01</td>
<td>14.66</td>
</tr>
</tbody>
</table>

Abbreviations: AIC, Akaike information criterion; F, female; g, genetic effects; M, male; s, environment effects common to same-sex siblings; σ, correlation between male and female sibling effect; µ, correlation between spouses’ environment (social homogamy); Δχ², difference in χ² values compared with the full model.

We used the age-corrected correlations as input in the structural equation model. The fit of each model was evaluated by the goodness-of-fit index AIC: goodness of fit is expressed by low values. The results of the model-fitting procedure, including model parameter estimates and model fit statistics, are listed in Table 2, starting with the least constrained model and subsequently adding constraints and comparing more parsimonious models with the full model. The parameter estimates correspond to the model illustrated in Figure 1.

Model 1 is the full model that includes genetic and environmental factors that influence tinnitus in parents and children and a common environmental sibling effect in children. In model 2, the genetic effects are constrained to be equal across sexes with a minimal loss in fit. The sibling effect could not be constrained to be equal across sexes without significant loss of fit (models 3, 4, 7, and 8), but the sibling effect for women could be eliminated from the model without any substantial loss of fit (models 5 and 9). The

RESULTS

CORRELATIONS AND PREVALENCE

Test-retest polychoric correlation for 28,066 persons tested twice was 0.65 (95% CI, 0.63-0.66), indicating relatively high reliability for our tinnitus measure. The prevalence of tinnitus was 15.1% using only respondents with a positive report on the 1 item on bothersome tinnitus (“Are you bothered by ringing in your ears?”) as case patients. The index used for the heritability estimation includes information from records with missing data or a “maybe” report of bothersome tinnitus that also had valid data on either tinnitus duration or frequency. On the basis of this index, 20.9% of the sample reported symptoms of tinnitus. Polychoric correlations for tinnitus (Table 1) are small, yet all, except for the father-daughter and sister correlations, are statistically significant.

MODEL FITTING
high AIC value for model 10 illustrates that the genetic effect is small but significant. The best-fitting model (model 9), which included equal genetic effects for men and women, unique environmental effects, and sibling effect for men, is illustrated in Figure 2. Heritability of 0.11 was found in men and women. Environmental effects shared by siblings were found only in men.

**COMMENT**

This study addressed the importance of genetic factors in tinnitus using a large population-based cohort of Norwegian nuclear families. We found a heritability of 0.11, meaning that the relative importance of genetic factors in tinnitus is low.

When interpreting these findings, the following limitations should be taken into consideration. To date, most traits studied with quantitative population genetic methods have shown moderate to high heritability. High heritability has been taken as evidence for high validity, or at least high reliability. Reversing this reasoning, low heritability could raise suspicion of low measurement precision. However, our questions about tinnitus are straightforward and appear to have face validity; also, the test-retest reliability is satisfactory. Our prevalence is comparable with those of similar studies from other countries. Even if our measure should only be moderately valid and, for example, capture only half the population variance in tinnitus, the true heritability would only be double our estimate (0.22 for men and women), which is still low.

On the other hand, tinnitus is a symptom described in a heterogeneous group of diseases, and thus the heritability could differ substantially, depending on the biological nature of the underlying disease. The data available do not allow separation into different clinical subgroups of tinnitus, and our phenotype under study is also undoubtedly heterogeneous. Therefore, our results should be understood as average values across different types of tinnitus rather than valid for all types of tinnitus. However, if our measure represents both highly heritable and non-heritable forms of tinnitus, one would expect our heritability estimate to be at least moderate. The low heritability found in the present study does not suggest that any prevalent type of tinnitus is highly heritable.

Data from nuclear families do not allow separation of effect of environmental transmission from parents to offspring and genetic effect (heritability). The estimates presented are the upper limit of the heritability estimates and may be confounded by environmental parent-offspring transmission. If there is an effect of family environment, our heritability estimate is somewhat inflated.

Many participants in the data set are included in more than 1 family relation (eg, an individual could be a sister in one family and a mother in another), which introduces dependency among the observations. Somewhat inflated $\chi^2$ values in the testing of nested models have not affected our results, however, because all parameters except genetic effect and sibling environmental effects shared by brothers could be fixed at zero. These 2 effects were significant beyond doubt, with $\chi^2$ differences compared with nested models ($\chi^2 = 18.66, P < .001$ for genetic effects, and $\chi^2 = 6.51, P = .01$ for environmental effects on males).

The small but significant spouse correlation of 0.044 for tinnitus was modeled as social homogamy; mates assort because they belong to the same social groupings or strata, where the members are exposed to the same environmental risk factors (eg, noise exposure). This specification may not be entirely realistic, but the specification of this low partner correlation hardly matters for the parameter estimates.

We found a small but significant environmental sibling effect only present in men. This finding is consistent with results for noise-induced hearing loss in the same sample. Hearing impairment owing to occupational noise and noise from recreational sources, including from gunfire or shooting, could be demonstrated in men but not in women. This exposure in men is likely to aggregate in families to some extent and may well have contributed somewhat to tinnitus and hearing loss.

Our heritability estimate is lower than the heritability of 0.39 (95% CI, 0.03-0.75) for women in a previous report by Peterson et al. No significant genetic effect for men was found in this study. The result is based on a small sample of 478 twin pairs aged 70 to 100 years, with most individuals with tinnitus between 70 and 80 years old. The effect of age was not taken into account in the analysis. The correlations reported for men are low, indicating a negative heritability. However, if pooling the correlations across sex, which would seem reasonable in such a small sample, the correlation pattern indicates a much lower heritability estimate, which is in good agreement with the results from the present study.
In conclusion, we find a comparatively low heritability for tinnitus and a sibling environmental effect present only in men. This result needs to be replicated with other measures of tinnitus and other types of family data. Our results do not necessarily mean that genetic effects are unimportant for all forms of tinnitus, because this symptom can arise from a wide variety of underlying diseases. Considering the heterogeneous origin of tinnitus, rather than searching for the genes responsible for tinnitus in general, future investigators need to identify subgroups of individuals affected by tinnitus with specific causes. Our results do not support the spending of large amounts of time and resources to identify the genes that code for tinnitus in general.

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Author Contributions: All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Kvestad and Tambs. Acquisition of data: Hoffman and Tambs. Analysis and interpretation of data: Kvestad, Czajkowski, Engdahl, Hoffman, and Tambs. Drafting of the manuscript: Kvestad and Engdahl. Critical revision of the manuscript for important intellectual content: Kvestad, Czajkowski, Engdahl, Hoffman, and Tambs. Statistical analysis: Czajkowski, Hoffman, and Tambs. Obtained funding: Hoffman. Administrative, technical, and material support: Hoffman. Study supervision: Engdahl and Tambs.

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REFERENCES