Prevalence, Incidence Proportion, and Heritability for Tinnitus: A Longitudinal Twin Study

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Objectives: The purpose of this longitudinal twin study was to explore the effect of tinnitus on hearing thresholds and threshold shifts over two decades and to investigate the genetic contribution to tinnitus in a male twin cohort (n = 1114 at baseline and 583 at follow-up). The hypothesis was that participants with faster hearing deterioration had a higher risk for developing tinnitus and there is an underlying role of genetic influences on tinnitus.

Design: Male mono- and dizygotic twin pairs, born between 1914 and 1958 were included. Mixed models were used for comparison of hearing threshold shifts, adjusted for age. A co-twin comparison was made within pairs discordant for tinnitus. The relative influence of genetic and environmental factors was estimated by genetic modeling.

Results: The overall prevalence of tinnitus was 13.5% at baseline ($\bar{x}$ age 50) and 34.4% at follow-up ($\bar{x}$ age 67). The overall incidence proportion was 27.8%. Participants who reported tinnitus at baseline or at both time points were older. At baseline, the hearing thresholds differed between tinnitus cases and controls at all frequencies. New tinnitus cases at follow-up had the greatest hearing threshold shift at the high-frequency area compared with the control group. Within pairs, the tinnitus twin had poorer hearing than his unaffected co-twin, more so for dizygotic than monozygotic twin pairs. The relative proportion of additive genetic factors was approximately 0.40 at both time points, and the influence of individual-specific environment was 0.56 to 0.61. The influence of genetic factors on tinnitus was largely independent of genetic factors for hearing thresholds.

Conclusions: Our hypotheses were confirmed: The fastest hearing deterioration occurred for new tinnitus cases. A moderate genetic influence for tinnitus was confirmed.

Key words: Discordant twins, Genetic, Incidence proportion, Prevalence, Threshold shift, Tinnitus.

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INTRODUCTION

Tinnitus is defined as an auditory perception in the absence of an external source of sound (Møller 2007). It is a heterogeneous disorder and very commonly associated with hearing loss and ageing (Rosenhall & Karlsson 1991; Asplund 2003; Møller 2007). Headache, dizziness, anxiety, sleep disturbances, and duration could predict the severity of tinnitus (Scott et al. 1990; Sindhusake et al. 2004). The prevalence of tinnitus in adults (age 48 and above) varies between 8 and 39% depending on which population is studied (Parving et al. 1993; Nondahl et al. 2002; Shargorodsky et al. 2010; Nondahl et al. 2011). Among US adults, the overall prevalence was 25.3% for any tinnitus (daily) and 7.9% for frequent tinnitus in the past 12 months (Shargorodsky et al. 2010). The 5-year incidence of tinnitus varies between 5 and 18%, and may change with increasing age (Nondahl et al. 2002, 2010; Gopinath et al. 2010). Shargorodsky et al. (2010) found that those with hearing impairment had increased odds to report tinnitus. The association of tinnitus with age-related hearing problems (Gopinath et al. 2010) is greater in men than women.

Genetic factors have been considered as one possible cause of tinnitus (Sand 2011; Pawełczyk et al. 2012). The heritability of tinnitus has been documented in a few studies. A seven country European study (Hendrickx et al. 2007) found a familial correlation of 0.15 and a Norwegian family study reported a heritability of tinnitus of 0.11 (Kvestad et al. 2010). A candidate gene study (e.g., KCNE3, BDNF, SLC6A4(5-HTT)) found an association between disorders that can include secondary chronic tinnitus and gene mutations (Sand et al. 2007). Pawełczyk et al. (2012) found an association between polymorphisms in potassium recycling genes with the risk of developing tinnitus in a noise-exposed group of males.

Longitudinal studies make it possible to assess the influence of age and hearing loss on the incidence of tinnitus within a cohort. Twin studies provide an opportunity to investigate the relative influence of genetic factors on the prevalence and incidence of tinnitus. We found an increased prevalence of hearing loss across time, in male twins aged 52 to 96 years, especially in the high-frequency region, and a moderate genetic influence (53 to 65%) on hearing acuity in a male twin cohort (Bogo et al. 2015). The present study uses longitudinal data on tinnitus in the same cohort. The aim was to describe the prevalence of tinnitus at two time points, and accordingly the incidence proportion (IP) of tinnitus. The correlations between hearing thresholds, tinnitus, and the threshold shifts over two decades were investigated. The relative contribution of genetic effects to self-reported tinnitus was also estimated. We hypothesized that participants with faster hearing deterioration had a higher risk for developing tinnitus.

MATERIALS AND METHODS

Participants

The study population at baseline (1991 to 1995) consisted of male twins born between 1914 and 1958 (age 34 to 78), in total 1624 individuals from Stockholm and Uppsala counties (Karlsson et al. 1997). One thousand, one hundred and fourteen twins participated at baseline (68% response rate) and 583 of 895 possible participated at follow-up approximately 18 years later (65% response rate; Bogo et al. 2015).

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The present study was based on this closed cohort of 1114 individuals from 557 twin pairs; $\bar{x}$ age 49.5 (34 to 78) at baseline. Out of the 1114 participants, 30 participants did not fill in the tinnitus questions at baseline, resulting in 1084 twins. Of these, 128 monozygotic (MZ) pairs, 111 dizygotic (DZ) pairs, and 105 singletons ($\bar{x}$ age 66.6 [52 to 95]) participated at follow-up, and 7 twins did not fill in the tinnitus questions. Complete audiometric and questionnaire data were collected at both time points (n = 1084 at baseline and n = 576 at follow-up).

The project received approval from the Regional Ethical Review Board in Stockholm, Sweden (registration number 2009/378-31), and Karolinska University Hospital, Huddinge, Sweden (registration number 18/92).

Audiometry

Pure-tone audiometry at 10 frequencies (125 to 8000 Hz), in both ears, was performed by licensed audiologists using the national standardized method (ISO 8253-1 2000) and standardized calibrated clinical audiometers. The hearing thresholds in the left and right ears were used to divide the ears into the better and worse ear (Bogo et al. 2015). The longitudinal change in hearing (threshold shift in dB) was calculated as the difference between the baseline and follow-up measurements for each frequency.

Tinnitus Questions

The persistence and the impact of tinnitus among the participants were measured by self-reported questions. Questions regarding tinnitus and tinnitus annoyance (Klockhoff & Lindblom 1967) were included at both time points.

> *"Are you annoyed by tinnitus: buzzing or ringing in the ears?" ("yes" or "no").*
> *"If you have tinnitus, how annoying is that?" ("mild" or "moderate" or "severe").*

Complete questionnaire data regarding tinnitus were available from 1084 participants at baseline and 576 at follow-up.

For the longitudinal comparison, the participants with tinnitus were stratified into different groups depending on how they reported tinnitus at both time points. Group 1 (n = 361) never reported tinnitus and was used as the reference. Group 2 (n = 24) reported tinnitus only at baseline. Group 3 (n = 139) reported tinnitus only at follow-up. Group 4 (n = 52) reported tinnitus at both time points.

Twin Zygosity

Zygosity was determined in 90% of the population based on comparisons of 47 single nucleotide polymorphism markers distributed across the genome (Hannelius et al. 2007). When no DNA was available, zygosity was based on questions regarding similarity, a method that has over 98% accuracy (Lichtenstein et al. 2002).

Statistical Analysis

Self-reported tinnitus prevalence and confidence intervals accounting for the twin correlation were computed for both time points. Because this is a closed cohort with longitudinal data, we calculated IP and confidence interval accounting for the twin correlation of tinnitus (Rothman & Greenland 2014) as the number of new tinnitus cases (n = 139) divided by the number initially at risk (participants without tinnitus at baseline who also participated at follow-up; n = 500). The IP was also calculated for 3 age groups (50 to 59 years old; 60 to 69 years old; 70 years old and above).

Each frequency of the hearing thresholds was compared between tinnitus cases and controls using a mixed model adjusted for age and the correlation within twin pairs; a similar model was fit to compare hearing threshold shifts. Generalized estimating equations with logit link were used to analyze the effect of age on tinnitus at baseline and follow-up separately. Generalized estimating equation with multinomial responses was used to analyze the effect of age on the combined levels of tinnitus at baseline and follow-up.

A co-twin analysis was performed in twin pairs discordant for a trait, that is, one twin within the pair reported tinnitus and the other twin did not. Paired *t* test was used to compare hearing thresholds at each frequency between tinnitus cases and controls within the discordant twin pairs. Finding a significant difference in MZ pairs indicates that tinnitus is associated with hearing loss beyond genetic reasons, and in DZ pairs, beyond shared environmental reasons.

P values adjusted for multiple tests from the mixed models and from the paired *t* tests are reported in each of the figures. The *p* values were adjusted for multiple tests through the false discovery rate (FDR) approach (Benjamini & Hochberg 1995)

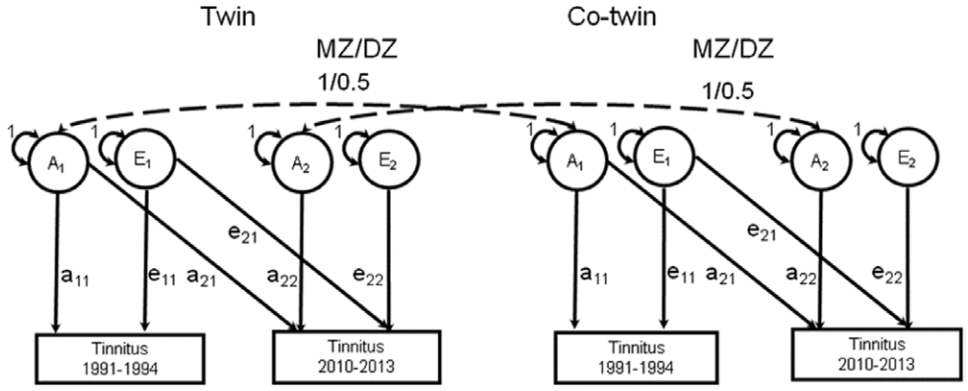

Fig. 1. Path diagram of the bivariate Cholesky model of additive genetic (A) and individual-specific environmental (E) components at baseline and follow-up. A1 indicates additive genetic effect at baseline; A2, additive genetic effect at follow-up; E1, individual-specific effects at baseline; Co-twin, within-pair; DZ, dizygotic; E2, individual-specific effects at follow-up; MZ, monozygotic.

TABLE 1. Prevalence (%) and incidence proportion for twins with tinnitus status

	Baseline		Follow-Up	
Zygosity	MZ	DZ	MZ	DZ
(n=)	494	590	285	291
Prevalence (%)	12.1 (9.5–15.4)	14.3 (11.7–17.5)	31.9 (26.8–37.6)	34.4 (29.1–40.0)
Participants with tinnitus status (n=)	1084		576	
Overall prevalence (%)	13.5 (11.6–16.6)		33.5 (29.7–37.4)	

	Baseline	Follow-Up	
Zygosity		MZ	DZ
(n=)		248	252
Incidence proportion (%)		27.8 (22.6–33.7)	27.8 (22.6–33.6)
Tinnitus-free participants at baseline (n=)		500	
Overall incidence proportion (%)		27.8 (24.1–31.9)	

95% confidence intervals are within the parentheses.
DZ, dizygotic; MZ, monozygotic.

with a FDR at 0.05 and the number of tests set to be equal to the number of tests in each figure. Unlike a family-wise error rate approach such as the Bonferroni correction, which controls the probability of committing a type I error for a set of tests, the FDR approach tolerates a certain number of tests determined by the FDR to be incorrectly discovered.

Genetic modeling is based on the fact that MZ twins share 100% of their genes while DZ twins share on average half of their segregating genes, resulting in a greater similarity in MZ pairs compared with DZ pairs. Thus, the impact of the genetic component can be calculated. Both MZ and DZ twins are assumed to share the same family environment when they grow up.

To estimate the magnitude of additive genetic (A), shared environmental (C), and individual-specific environmental variance (E) to the total phenotypic variation, structural equation modeling was used, a general statistical model in classical twin studies to estimate genetic and the environmental effects. The measured trait, tinnitus, was treated as a dichotomous variable. The genetic and environmental components of tinnitus were estimated in both univariate and bivariate (longitudinal) liability threshold models, as well as in bivariate models with PTA4 and HPTA4 in the better ear. For description of PTA4 and HPTA4, see Bogo et al (2015). According to liability threshold model, the observed trait is a representation of an imprecise measurement of a trait with an underlying continuum. The resemblance of twin pairs was computed as a tetrachoric correlation. Cross-trait, cross-twin tetrachoric correlations, and probandwise concordance rates in MZ and DZ pairs were used to assess the contribution of A, C, and E to the total variation initially. In bivariate Cholesky

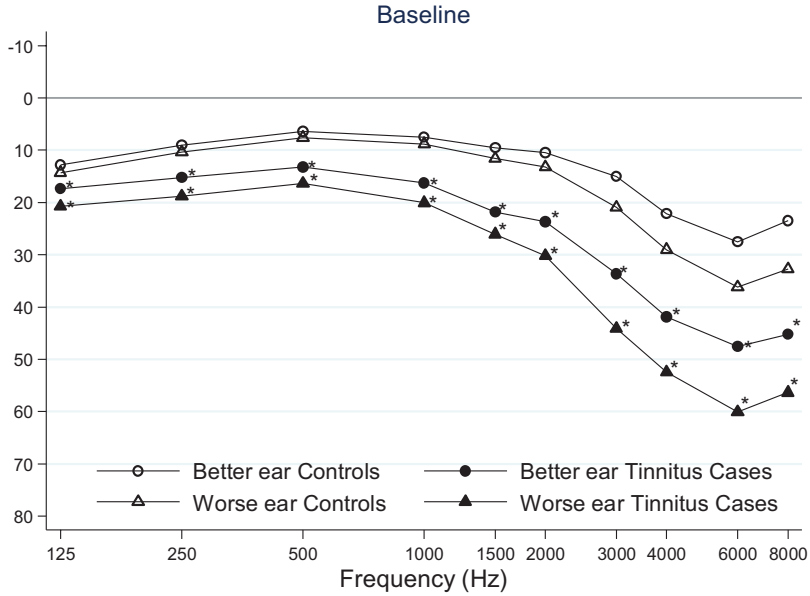

Fig. 2. Mean hearing thresholds (*y* axis, dB HL; *x* axis, frequencies 125 to 8000 Hz) in 1084 twins for the better (open circle, filled circle) and worse (open triangle, filled triangle) ear. Self-reported tinnitus status at baseline in tinnitus cases (n = 146; filled circle, filled triangle) and controls (n = 938; open circle, open triangle). *Statistically significant difference for better or worse ear compared with controls (FDR-adjusted $p < 0.05$). FDR indicates false discovery rate.

decomposition of an AE model (Fig. 1), the first genetic (A_1) and individual-specific environments (E_1) factors load on all variables from baseline, but the second genetic (A_2) and individual-specific environments (E_2) factor A_2 load on variables from follow-up. The goodness of fit of reduced models against nonconstrained models was evaluated with likelihood ratio χ^2 test and the Akaike information criterion. To evaluate if the bivariate model could be reduced to a univariate model, two separate AE models with the parameters a_{21} and e_{21}, respectively, fixed to 0 were compared against the full AE model. Heritability, the contribution of A to the total variance in univariate model is computed by the ratio $a^2/a^2 + e^2$. In the bivariate case, the corresponding value of A is obtained as the ratio $a^2_{11}/a^2_{11} + e^2_{11}$ at baseline and at follow-up as $a^2_{21} + a^2_{22}/a^2_{21} + a^2_{22} + e^2_{21} + e^2_{22}$. Similarly, the corresponding values for E in the univariate model is $e/a + e$, and in the bivariate case, the corresponding value of E is obtained as the ratio $e^2_{11}/a^2_{11} + e^2_{11}$ at baseline and at follow-up as $e^2_{21} + e^2_{22}/a^2_{21} + a^2_{22} + e^2_{21} + e^2_{22}$ (Neale & Cardon 1992).

RESULTS

Prevalence and Incidence Proportion

Participants with tinnitus were older than participants without tinnitus ($p < 0.05$). The overall tinnitus prevalence of the entire cohort was 13.5% (146/1084) at baseline and 33.4% (191/576) at follow-up (Table 1). The prevalence of self-reported tinnitus among the 531 twins who did not participate at follow-up was higher at baseline (17.5%) than the overall prevalence at baseline. No statistically significant difference in

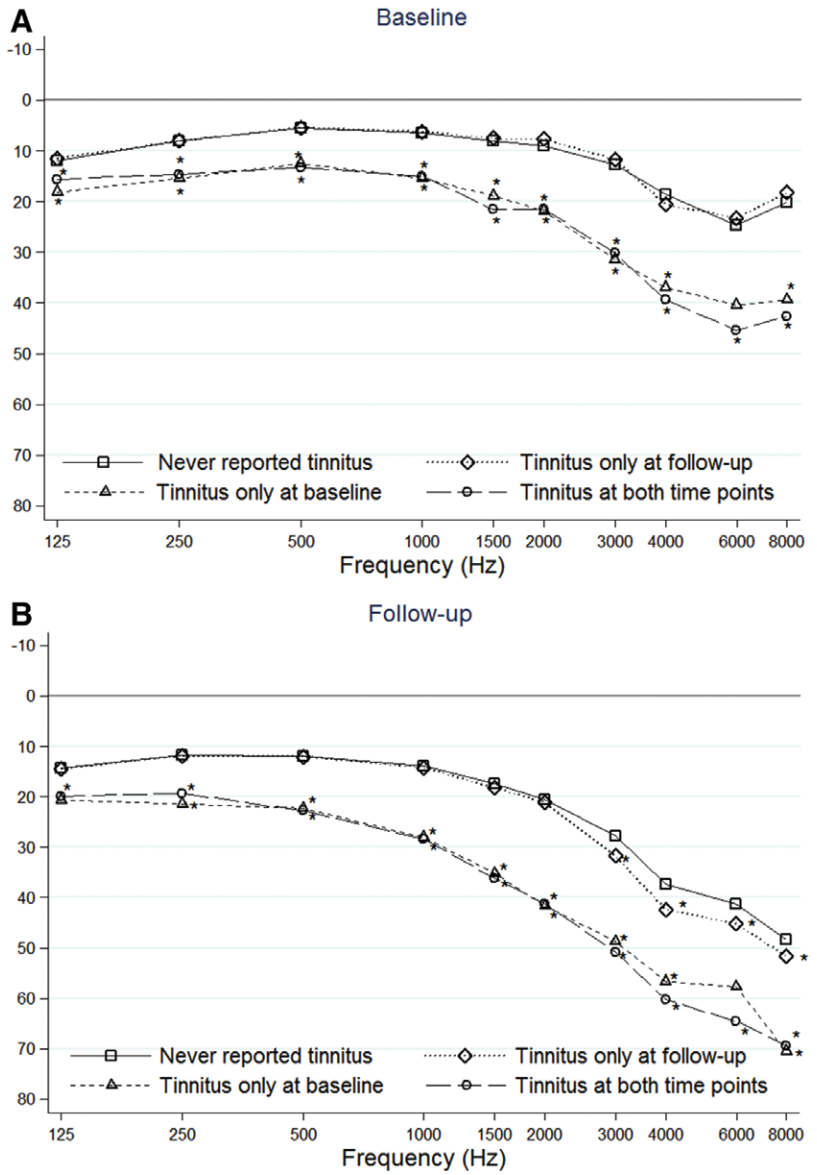

Fig. 3. A and B, Mean hearing thresholds for the better ear (*y* axis, dB HL; *x* axis, frequencies 125 to 8000 Hz) by tinnitus groups at baseline (A) and follow-up (B). Never reported tinnitus (rectangle); tinnitus only at baseline (triangle); tinnitus only at follow-up (diamond); tinnitus at both time points (circle). *Statistically significant difference (FDR-adjusted $p < 0.05$) to the reference group (never reported tinnitus). FDR indicates false discovery rate.

tinnitus prevalence was found between MZ and DZ twin pairs at any of the time points.

A majority of the participants with tinnitus rated it as mild (80% at baseline; 79.5% at follow-up), whereas moderate tinnitus was reported by 17.0% at baseline and 19.9% at follow-up and very few reported severe tinnitus (2.8% at baseline; 0.6% at follow-up). The prevalence of tinnitus excluding mild tinnitus cases was 2.6% at baseline and 7.1% at follow-up.

IP reported across age groups (new tinnitus cases at follow-up) was 27.8% (95% confidence interval, 24.5 to 32.0). No difference was found between MZ and DZ twins (Table 1). It was no statistically significant ($p > 0.05$), difference found between the different age groups.

Hearing Thresholds

The participants that reported tinnitus at baseline (n = 146) showed significantly (FDR-adjusted $p < 0.05$) poorer hearing thresholds at all frequencies in both the better and the worse ear compared with participants without tinnitus (n = 938). The difference in $\bar{x}$ hearing threshold was smaller (<10 dB) at the lower frequencies than the higher frequencies (approximately 20 dB; Fig. 2). Because hearing threshold and hearing threshold shifts were similar for the better and worse ear in most of the analyses, only results for the better ear are shown in the following figures and tables.

The $\bar{x}$ hearing thresholds for the better ear at baseline in the four groups are shown in Figure 3A. Significantly (FDR-adjusted $p < 0.05$) poorer hearing thresholds were found at all frequencies in those with tinnitus only at baseline and those with tinnitus at both baseline and follow-up, compared with the reference (never tinnitus; except at 6000 Hz for tinnitus only at baseline). Those with tinnitus only at follow-up did not differ in baseline thresholds from the reference group.

The $\bar{x}$ hearing thresholds at follow-up for the four groups are shown in Figure 3B. Those with tinnitus only at baseline and those with tinnitus at both times had significantly (FDR-adjusted $p < 0.05$) poorer hearing thresholds at all frequencies compared with never tinnitus. Tinnitus only at follow-up differed from the reference group above 2000 Hz.

The age distributions for the four groups are reported in Table 2. Participants with tinnitus only at baseline (group 2) and with tinnitus at both time points (group 4) were significantly older than the reference group without tinnitus (group 1). Participants with tinnitus only at follow-up (new cases; group 3) did not differ significantly from group 1.

The longitudinal hearing threshold shifts between 500 and 8000 Hz are also shown in Table 2. Those who never reported tinnitus (reference) had the mildest threshold shifts and those with tinnitus only at baseline did not differ from the reference. Those with tinnitus only at follow-up had significantly ($p < 0.05$) greater threshold shifts in the higher frequencies at and above 2000 Hz, whereas those with tinnitus at both occasions had significantly ($p < 0.05$) greater threshold shifts in the frequencies below 4000 Hz.

MZ twins with tinnitus had significantly (FDR-adjusted $p < 0.05$) worse hearing thresholds above 1000 Hz than their brothers without tinnitus at baseline (Fig. 4A). DZ twins with tinnitus had worse hearing thresholds than their brothers (FDR-adjusted $p < 0.05$) at all frequencies (except 125 Hz; Fig. 4A).

At follow-up, there were no significant (FDR-adjusted $p > 0.05$) differences in hearing thresholds in MZ pairs discordant for tinnitus (Fig. 4B). In DZ pairs, discordant for tinnitus at follow-up, greater hearing threshold (FDR-adjusted $p < 0.05$) differences were found at 500 Hz and above 1000 Hz (Fig. 4B).

Genetic Influences

Probandwise concordant rates at both time points were much higher for MZ pairs compared with DZ pairs, indicating that genetic effects are important: at baseline (MZ 0.46 [95% CI, 0.04 to 0.75%]; DZ 0.07 [95% CI, 0.01 to 0.41%]) and at follow-up (MZ 0.51 [95% CI, 0.22 to 0.80%]; DZ 0.32 [95% CI, 0.07 to 0.74%]). The tetrachoric and cross-trait cross-twin correlations among MZ pairs were also consistently higher than DZ pairs (Table 3), further indicating that genetic factors are of importance for tinnitus and for longitudinal continuity in tinnitus. The correlations among MZ pairs were more than twice as high as the DZ pairs, suggesting nonadditive genetic effects (D).

The AE model fitted better (AIC, −986.14; p value 0.71) than the ADE model. The removal of e_{21} resulted in a significant degradation of the model fit (AIC, −976.431; p value 0.00) but removal of a_{21} did not lead to any significant degradation (AIC −985.52; p value 0.11) of the model fit (Table 4), indicating that environmental, not genetic influences are important for continuity in tinnitus across time. The bivariate (two time point) model was retained. The proportion of additive genetic influences

TABLE 2. Age distribution and hearing threshold shifts for the better ear by tinnitus groups

	Group 1	Group 2	Group 3	Group 4
n=	361	24	139	52
Age $\bar{x}$ at baseline	47.7 (46.8–48.6)	55.9 (52.1–59.9)*	47.3 (46.0–48.5)	50.6 (48.1–53.0)*
Age $\bar{x}$ at follow-up	66.2 (65.3–67.0)	73.9 (70.2–77.6)*	65.8 (64.6–66.9)	68.8 (66.5–71.2)*
Hearing threshold shift (Hz)				
500	6.4 (5.7–7.2)	9.8 (4.8–14.7)	6.6 (4.9–8.2)	9.5 (6.4–12.6)
1000	7.4 (6.6–8.3)	12.7 (7.3–18.1)	8.0 (6.1–9.9)	13.4 (9.4–17.5)*
1500	9.4 (8.4–10.4)	17.4 (11.4–23.4)	10.9 (8.7–13.1)	15.3 (11.4–19.2) *
2000	11.6 (10.5–12.7)	19.8 (13.5–26.1)	13.4 (11.4–15.4) *	19.7 (15.8–23.6) *
3000	15.2 (14.0–16.4)	17.3 (12.1–22.5)	20.1 (17.8–22.4)*	20.8 (16.7–24.9) *
4000	18.8 (17.5–20.1)	19.8 (14.6–25.0)	21.8 (19.2–24.4) *	20.9 (16.6–25.2)
6000	16.7 (15.2–18.2)	17.3 (11.2–23.4)	22.0 (19.1–24.9) *	19.2 (14.7–23.7)
8000	28.1 (26.4–29.8)	31.3 (24.6–38.0)	33.5 (30.5–36.5) *	26.9 (22.6–31.1)

Group 1, never reported tinnitus at any of the time point; group 2, reported tinnitus only at baseline; group 3, reported tinnitus only at follow-up; group 4, reported tinnitus at both time points.
**Statistically significant difference (p < 0.05) compared with the reference group (group 1), adjusted for age. 95% Confidence intervals are within the parentheses.*

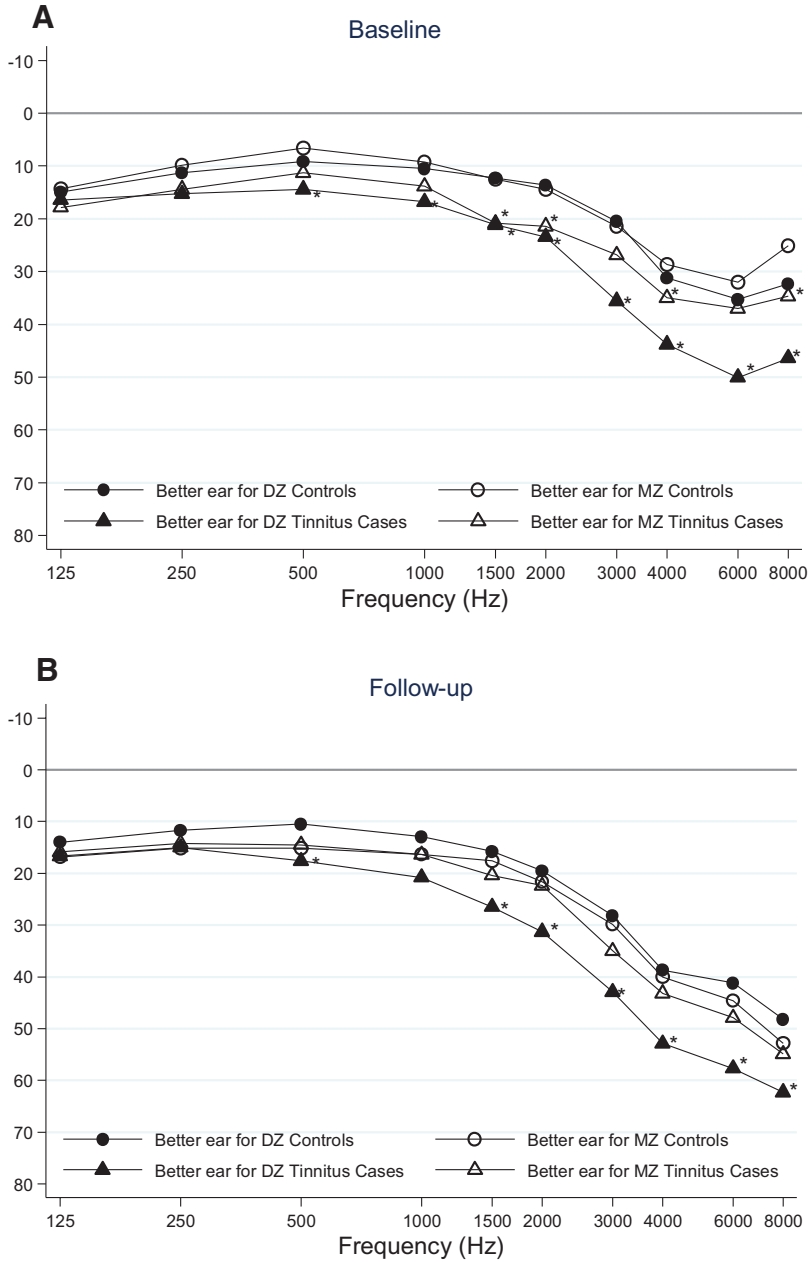

Fig. 4. A and B, Mean hearing thresholds for the better ear (*y* axis, dB HL; *x* axis, frequencies 125 to 8000 Hz) at baseline (A) in 35 monozygotic twin pairs (open circle, open triangle) and 70 dizygotic twin pairs (filled circle, filled triangle) discordant for tinnitus. Mean hearing thresholds for the better ear at follow-up (B) in 39 monozygotic twin pairs (open circle, open triangle) and 48 dizygotic twin pairs (filled circle, filled triangle) discordant for tinnitus. *Statistically significant difference (FDR-adjusted $p < 0.05$) compared with controls (unaffected brothers). Symbol triangles for tinnitus cases and symbol circle for controls. FDR indicates false discovery rate.

(A) for tinnitus was found to be almost the same at baseline (0.40) and follow-up (0.44). The genetic correlation for tinnitus between time point 1 and time point 2 was 0.51 (Table 5).

Furthermore, the bivariate AE model between PTA4 and HPTA4 for better ear and tinnitus both at baseline and follow-up showed that proportion of the total variation due to genetic factors in common with either PTA4 or HPTA4 and tinnitus ranged from 7 to 11% and the proportion of the total variation unique to tinnitus was 40 to 43%. The genetic correlation, which measures the degree to which genetic influences are correlated between tinnitus and hearing thresholds ranged from 0.33 to 0.49, suggesting some overlap of genes affecting both tinnitus and hearing thresholds (see Tables 1 and 2 in Supplemental Digital Content, http://links.lww.com/EANDH/A322).

DISCUSSION

The present study characterized hearing thresholds and threshold shift differences between tinnitus cases and controls across 18 years. The prevalence of tinnitus was similar to other nonclinical studies with similar age groups and male participants. Our cohort of male twins provides new evidence indicating a moderate genetic influence for tinnitus (heritability overall

TABLE 3. Age-adjusted tetrachoric correlation for tinnitus by zygosity

	Monozygotic Twin Pairs (n = 126)		Dizygotic Twin Pairs (n = 108)	
	Baseline	Follow-Up	Baseline	Follow-Up
Baseline	0.46 (0.06–0.76)	0.22 (–0.05 to 0.48)	–0.04 (–0.46 to 0.42)	–0.05 (–0.34 to 0.25)
Follow-up	0.22 (–0.05 to 0.48)	0.47 (0.20–0.68)	–0.05 (–0.34 to 0.25)	0.10 (–0.21 to 0.40)

95% confidence intervals are within the parentheses.

40%, heritability independent of genetic effects for hearing thresholds 40 to 43%).

Prevalence and Incidence

The prevalence of tinnitus reported in this study (13.5% at baseline and 33.5 at follow-up) is similar to other population-based studies using self-reported tinnitus as an outcome. Parving et al. (1993) reported a 17% prevalence in a male cohort, which is similar to the prevalence at baseline in the present study. Both cohorts were unscreened for ear disease, noise exposure etc. and had approximately the same age span. Kvestad et al. (2010) found that 15.1% of their population reported bothersome tinnitus symptoms.

The present study found higher tinnitus prevalence at follow-up compared with baseline prevalence, which is probably due to aging ($\bar{x}$ age 50 at baseline; $\bar{x}$ age 67 at follow-up). Other older unscreened cohorts have found prevalences for tinnitus of 28.9% (Hendrickx et al. 2007), 30% (Gopinath et al. 2010), 31.4% (Shargorodsky et al. 2010), and 39% (Coles 1984), which are similar to this study's prevalence at follow-up. Coles (1984) also found a prevalence for severe tinnitus of approximately 1%, which is comparable with the present study. The above-mentioned cross-sectional studies, however, included both women and men. Even higher tinnitus prevalence has been shown (59%) in a clinical setting (Lindberg et al. 1984). Prevalence also depends on the criteria used for tinnitus annoyance. We found a prevalence of 7.1% at follow-up when including only moderate and severe tinnitus cases. This is similar to that found in several studies from the Beaver Dam cohort (Nondahl et al. 2002, 2010, 2011; Wilson et al. 2010).

Recently, Gallus et al. (2015) compiled data regarding prevalence rates of tinnitus from all continents. The populations in the Northern hemisphere have higher prevalence rates of tinnitus in comparison.

To our knowledge, this is the first longitudinal study extending as long as two decades. The overall IP for tinnitus was ~28%. Population studies with shorter follow-up periods show a lower tinnitus incidence (5.7 to 18%; Nondahl et al. 2002, 2010; Gopinath et al. 2010). The oldest participants (70 years old and above at follow-up) had a lower incidence, which may be explained by less likelihood to be exposed to occupational noise during follow-up period due to retirement.

Twenty-four out of 576 that reported tinnitus at baseline did not report tinnitus at follow-up. That tinnitus can cease is similar to Gopinath et al. (2010). We have no way of testing reasons for spontaneous remission of tinnitus. However, it could be that other severe diseases override tinnitus perception. Alternatively, spontaneous recovery may be due to, emotional state, coping strategies, or other rehabilitative actions, such as use of wearable devices, for example, hearing aids.

Hearing Thresholds and Threshold Shifts

Hearing thresholds among older participants with tinnitus were more elevated at both time points compared with participants without tinnitus. The threshold shifts differed significantly at frequencies at and under 2000 Hz for twins who reported tinnitus only at baseline and those who reported tinnitus at both time points. Those twins were the oldest participants at baseline. This confirms that hearing loss (Gopinath et al. 2010) and age are associated with tinnitus (Nondahl et al. 2002, 2010; Shargorodsky et al. 2010). Shargorodsky et al. (2010) show an increased risk to report tinnitus and an increased hearing deterioration with age in accordance with our previous study (Bogo et al. 2015).

Tinnitus and hearing loss are associated (Rosenhall & Karlsson 1991; Møller 2007; Gopinath et al. 2010), but looking at the association between tinnitus and hearing deterioration over time, that is, the mean threshold shifts, we found only small differences (5 dB) between tinnitus cases and controls. Statistically significant greater threshold shifts at high frequencies were found for the new tinnitus cases ($\bar{x}$ age less than 48 years at baseline) at follow-up, probably due to noise exposure (Pawełczyk et al. 2012). These findings were somewhat expected considering the opportunity for more frequent noise exposure that is present during 18 years of follow-up period, especially for gainfully employed.

A greater difference in hearing thresholds between tinnitus cases and controls were found among discordant DZ pairs compared with discordant MZ pairs at baseline and even more profound at follow-up. Thus, MZ twins discordant for tinnitus were more similar in hearing thresholds than discordant DZ twins, which can be partly explained by underlying genetic background.

TABLE 4. Model comparison for bivariate liability threshold model with Cholesky decomposition

Model	–2LL	df	AIC	Δ – 2LL	Δdf	Compared With Model	*p*
1. ADE	868.4907	925	–981.509				
2. AE	869.8583	928	–986.142	1.367466	3	1	0.713178
3. AE (a_{21} = 0)	872.4796	929	–985.520	2.621467	1	2	0.105427
4. AE (e_{21} = 0)	881.5688	929	–976.431	11.71042	1	2	0.000459

A, additive genetic effect; D, nonadditive genetic effect; E, individual-specific effect.

TABLE 5. Age-adjusted proportion of variance due to genetic (A) and individual-specific environment (E) affects for tinnitus by liability threshold model

Bivariate Model				
Baseline (n = 234)		Follow-Up (n = 234)		Genetic Correlation for Tinnitus Between Baseline and Follow-Up
A_1	E_1	A_2	E_2	
0.40 (0.10–0.69)	0.60 (0.30–0.98)	0.44 (0.18–0.65)	0.56 (0.35–0.82)	0.51 (0.00–1.00)

95% confidence intervals are within the parentheses.
A_1, additive genetic effect at baseline; A_2, additive genetic effect at follow-up; E_1, individual-specific effects at baseline; E_2, individual-specific effects at follow-up.

Genetics

The results of the present study support a moderate genetic contribution to tinnitus. Furthermore, we could quantify the extent to which genetic influences for tinnitus are independent of hearing thresholds. Indeed, a most of the genetic variation in tinnitus is unique to tinnitus, and only a small proportion shared with hearing thresholds.

Lower heritability estimates have been reported in studies using family data. In the Nord-Trøndelag study from Norway, Kvestad et al. (2010) reported a heritability of 0.11, with the highest correlation found between brothers and the lowest correlations between different-sex relatives. In a detailed analysis of European families, Hendrickx et al. (2007) found a significant heritable effect for tinnitus, with familial correlations as low as in the Norwegian study and brother correlation the highest. In the present study, the DZ twin correlation (which is comparable with siblings) was lower than that reported in those two studies.

The differences in results between twin and family studies, with the latter showing lower heritabilities, can be explained by the advantage of a cohort of same-sex twins such as used in the present study, in that twins are matched on age. On the other hand, if a trait is significantly associated with age, twin correlations can be elevated and appear as shared environmental variance if the models are not appropriately adjusted for age. Nevertheless, statistical power is a major concern in all twin and family studies and the present study is no exception. Hence, confidence intervals around parameter estimates are wide and overlap those reported by Kvestad et al. (2010).

The contribution of the individual-specific environmental factors to tinnitus was moderate but there was no evidence of a shared family environmental (C) influence. Kvestad et al. (2010) also found a statistically significant individual-specific environmental effect, but also a shared sibling environmental effect (only in men). Environmental influences on tinnitus should be expected, but not necessarily shared by family members. Occupational and recreational activities can entail noise exposure risks. Welch and Dawes (2008) suggests that personality affects the perceived tinnitus experience. We have not yet examined how noise exposure, other risk factors, or personality may affect the occurrence of tinnitus.

CONCLUSIONS

The prevalence of tinnitus (13.5%) was in accordance with other population-based studies and the increased prevalence in the ageing cohort at follow-up (33.4%) was also similar to data reported from other studies. The IP was approximately 28%, which is higher compared with other studies, probably due to a longer follow-up period, almost two decades.

Individuals with tinnitus have statistically significant greater threshold shifts compared with those without tinnitus. Threshold shifts differed significantly, depending on when the tinnitus was reported. More elevated hearing thresholds were found in older participants with tinnitus at baseline. Greater threshold shifts at high frequencies were found for those who are the new tinnitus cases.

Co-twin analyses of self-reported tinnitus show a moderate genetic importance as a cause of tinnitus. We found that approximately 40% of the phenotypic variation in tinnitus can be explained by genetic factors. Individual-specific environmental factors were shown to be the most important influence for the occurrence of tinnitus.

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