

## Original Research Article

# The impact of occurrence of tinnitus in first degree relatives on the severity of disease among subjects

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## ABSTRACT

**Background:** The aetiology of tinnitus and the factors that contribute to the exacerbation from mild to severe tinnitus are poorly known. Particularly, a role of genetics has been proposed for tinnitus, although this has not been conclusive. In order to establish a possible role for heritability in our population, we explored the history of tinnitus among first degree family members of those suffering from tinnitus using cross-sectional community-based strategy.

**Methods:** There were 300 subjects with idiopathic tinnitus with mean ( $\pm$ SD) age of 51.88 ( $\pm$ 15.11, range=19-80 years) comprising 169 males and 131 females.

**Results:** Tinnitus was severe in 37.9% and bilateral in 65.1% while 26.6% reported having family members with history of tinnitus. Tinnitus was significantly more severe ( $p<0.001$ ) and more frequent ( $p<0.001$ ); and the psychological distress related to tinnitus ( $p<0.001$ ) measured by the mini-TQ was worse among those with family history compared to those without. Bivariate analysis reveals that the presence of tinnitus in other family members, occurrence of tinnitus for more than 3 months ( $p=0.003$ ), increasing age (0.001) and higher mean mini-TQ scores (0.001) showed significant association with severity of tinnitus. Logistic regression reveals that presence of tinnitus in other family members increases the odds of frequency of tinnitus by 5.08 (95% CI=1.70-15.12), elevates the mean scores of the mini-TQ by 1.31 (95% CI=1.20-1.44) while increasing age greater than 50 years increases the odds of severity of disease by 2.81 (95% CI=1.59-4.94).

**Conclusions:** We conclude that the findings of significant correlation between presence of tinnitus in first degree relatives and severity of tinnitus among the subjects provides an empirical evidence to explore a possible genetic aetiology for severe tinnitus in our population.

**Keywords:** Correlation, First degree relatives, Tinnitus

## INTRODUCTION

Tinnitus is defined as “the perception of sound that results exclusively from activity within the nervous system without any corresponding mechanical, vibratory activity within the cochlea, and not related to external

stimulation of any kind”.<sup>1,2</sup> It is estimated that approximately one third of the population experiences tinnitus at least once per lifetime, and approximately 1-5% develop serious psychosocial complications.<sup>3</sup> The incidence of tinnitus in the adult population of the United States is 10-15%, as approximately 50 million US adults

reported having tinnitus.<sup>4</sup> Various epidemiological studies reported a prevalence of 10-16% for chronic tinnitus in the adult population; the prevalence of tinnitus increases with age.<sup>3-5</sup> While the majority of the population is unaffected by tinnitus, 0.5-3% of the adult population develop severe distress and experience impairment in everyday life, sleep, mood, concentration, and daily work.<sup>5-7</sup> In Nigeria we have reported a prevalence of 14% among the elderly above 65 years.<sup>8</sup>

No effective treatments are currently available for severe tinnitus, which affects 1% of the population and lowers the quality of life. The aetiology of tinnitus and the factors that contribute to the exacerbation from mild to severe tinnitus are poorly known. Particularly, a role of genetics has been proposed for tinnitus, although this has not been conclusive, as is the case for other emotional processing disorders.<sup>1,9,10</sup> The thrust of this study is to determine the history of tinnitus among first degree family members of those suffering from tinnitus and find the correlation, if any, with the severity of disease among the subjects with tinnitus. This will form the basis to investigate and establish further a possible role for genetics in the aetiology and severity of tinnitus among an African population. We therefore examine whether clinically significant tinnitus is associated with familial occurrence of tinnitus using cross-sectional community-based strategy.

## METHODS

### *Study design*

This was a cross-sectional study of the community dwelling adult subjects above 18 years with complaint of tinnitus of unknown cause. In order to have subjects from diverse educational and socioeconomic background, participants were selected from both the urban and rural communities in Ibadan interior. The urban population consisted of participants drawn from the Centre for Aged, University College Hospital, Ibadan, while the rural population included Agodi, Mokola, Moniya and Basorun community, already tagged to an out-reach programme organized for the detection and prevention of illnesses, specifically, these communities have been used for study of hearing impairment among the elderly people in the past. All adult men and women above 18 years of age who have tinnitus without any known medical condition were included in the study while the exclusion criteria included those people with history of diabetes, stroke, hypertension, ear diseases, exposure to noise and ototoxic drugs such as aminoglycosides antibiotics, diuretics in the last 4 weeks; ear trauma or ear surgery.

### *Sample size*

The minimum sample size required to have a 90% power among the adult people is 336 subjects. However, a sample size of 300 constituting a power of 80% was adjudged adequate for the conclusion from the study.

### *Participant's recruitment*

Following approval of the study protocol by the University of Ibadan/University College Hospital Joint Ethical Review Committee, consented participants were recruited and history of feeling of noise in the ear were confirmed. The participants were then taking through an already prepared questionnaire aimed at eliciting otological and general medical conditions. The participants were also asked about history suggestive of allergy and use of some notable medications that are toxic to hearing function such as: aminoglycosides, diuretics and 4-amino-quinolines antimalarial drugs. History of exposure to excessive noise such as working (as)/living clear (to) blacksmith shop, radio room/disco room, welding shop etc. for at least 2 hours per day for at least 5 days a week were also obtained. The educational status of each subject was determined using the number of years spent in formal education and the economic status was based on the estimated annual income which included the salary from work and other services rendered by the subjects.

The family pedigree was probed to ascertain the occurrence of tinnitus in the parents, grandparents, siblings or children. This was followed by physical examinations and routine clinical investigations including arterial blood pressure, blood glucose and urinalysis to rule out common conditions which could cause tinnitus. The severity of the tinnitus was determined using the visual analogue scale and perceived stress questionnaire (PSQ) and the mini tinnitus questionnaire (mini-TQ) were administered by trained assistant.<sup>11</sup>

### *Measures*

Tinnitus was assessed by asking respondents whether they had a perception of ringing, swishing, humming or other type of noise in the ear or head without an external source of sound. In addition, questions were asked about tinnitus-related problems. Specifically, respondents were also asked: 1) "difficulty hearing clearly"; 2) "recurrent pus discharge from the ear in the past"; 3) "recurrent nasal congestion and rhinorrhea"; and 4) "any previous head injury." Respondents were required to give a yes or no answer to each of these questions. Blood pressure was measured using sphygmomanometer and recorded in mmHg. Diabetes was assessed as present if the respondent answered in the affirmative to a question about whether they had ever been told by a doctor that they had diabetes. Hypertension was defined as an elevated blood pressure beyond 140/90 mmHg. Respondents were asked if they had ever smoked or been a frequent alcohol drinker. All respondents were assessed for functional limitations

### *Study instruments*

*Perceived stress questionnaire (PSQ)*: This is a 30-item pencil and paper questionnaire that assesses subjective

experience of stress. The items are scored on a four-point Likert scale; 1- almost never, 2- sometimes, 3-often, 4- usually. The total score is derived by adding the scores of each item with higher scores denoting higher stress level. Scores on items 1, 7, 10, 13, 17, 21, 25, 29 are however deducted from 5 before summing with others because they are reverse coded. The total score is then converted to an index score which gives a score between 0-1 by using the formula: PSQ-Index = (raw score-30)/90.<sup>11,12</sup>

**Mini Tinnitus Questionnaire (Mini-TQ):** The mini-TQ is a short 12-item questionnaire developed from the tinnitus questionnaire with 52 items.<sup>11</sup> It assesses subjective psychological distress related to tinnitus, responses on each item are scored, 2-true, 1-partly true and 0- not true. The sum of all items gives the total score of 24 and higher score denotes higher distress.

**Statistics**

The main outcome variable was presence of tinnitus in first degree family members and the severity of tinnitus, which was graded 1-10 on the visual analogue scale as mild, grade 5 or lower; and severe, grade >5. The data was analysed using the SPSS version 22 initially explored using the stata software and Spearman’s correlation was utilized to determine the correlation between the severity of tinnitus and the other variables. To adjust for the effect of age and gender on the tinnitus, a linear regression model was used. Level of statistical significance was put at p<0.05 for all the analyses.

We also present demographic and other correlates of the condition, derived via logistic regression analysis, as well as estimates of standard errors of the odds ratio. Bivariate analysis determined the significance of the differences in occurrence of the variables, comparing respondents with presence of tinnitus in family members and those without family members. The probability of occurrence of variables were determined using multivariate analysis. The mean total score for the mini Tinnitus and stress was determined for respondents with family history and those without, and the significance of any difference was determined using the student t-test. Using logistic regression analysis controlling for age and sex, we determined the significance of the association between severity of tinnitus and the total mean score of the mini tinnitus and stress. Statistical significance was set at 0.05 in two-sided tests.

**RESULTS**

There were 300 subjects with idiopathic tinnitus, the mean age of the participants was 51.88±15.11 with age range between 19 and 80 years. About 60% were above 50 years old. There were more males (59.9%) and a little over half (53.5%) have secondary level education while 6.7% attained postgraduate education. Trading was the most practiced occupation (53.5%) among them.

More than one-third (37.9%) adjudged their tinnitus to be severe and a little over quarter (26.6%) reported having family members with history of tinnitus. Majority (65.1%) had bilateral tinnitus, 25.1% had it on the left and the remaining 9.5% on the right. History in fathers was most common (37.9%) while least was among sisters (5.8%) (Table 1).

**Table 1: Descriptive (n=300).**

Variable	N (%)
<b>Age group (in years)</b>	
18-30	44 (13.5)
31-40	34 (10.4)
41-50	51 (15.6)
51-60	88 (26.9)
>60	110 (33.6)
<b>Gender</b>	
Male	169 (59.9)
Female	131 (40.1)
<b>Educational status</b>	
None	15 (4.6)
Primary	66 (20.2)
Secondary	175 (53.5)
Tertiary	49 (15.0)
Postgraduate	22 (6.7)
<b>Affected ear</b>	
Left	83 (25.4)
Right	31 (9.5)
Bilateral	213 (65.1)
<b>Unilateral/bilateral</b>	
Unilateral	114 (34.9)
Bilateral	213 (65.1)
<b>Severity (visual analogue scale)</b>	
Mild	203 (62.1)
Severe	124 (37.9)
<b>Tinnitus in family</b>	
Yes	87 (26.6)
No	240 (73.4)
<b>Family relationship</b>	
Father	33 (37.9)
Mother	14 (16.1)
Brother	14 (16.1)
Sister	5 (5.8)
Son	11 (12.6)
Daughter	10 (11.5)
<b>Frequency of occurrence</b>	
≤3 monthly	293 (89.6)
>3 monthly	34 (10.4)

Table 2 compares participants with family history tinnitus and those without. It shows the tinnitus was significantly more severe and more frequent, and the psychological distress related to tinnitus as shown by higher mean Mini-TQ among those with family history compared to those without.

**Table 2: Bivariate analysis between those with family history tinnitus and those without.**

Variable	Family history		Statistics
	Yes N (%)	No N (%)	
<b>Age group (in years)</b>			
≤50	53 (41.1)	76 (58.9)	$\chi^2=22.86$ ; df=1; p<0.001
>50	34 (17.2)	164 (82.8)	
<b>Gender</b>			
Male	54 (27.6)	142 (72.4)	$\chi^2=0.224$ ; df=1; p=0.636
Female	33 (25.2)	98 (74.8)	
<b>Education</b>			
None	0 (0)	15 (100.0)	$\chi^2=41.178$ ; df=4; p<0.001
Primary	11 (16.7)	55 (83.3)	
Secondary	41 (23.4)	134 (76.6)	
Tertiary	18 (36.7)	31 (63.3)	
Postgraduate	17 (77.3)	5 (22.7)	
<b>Affected ear</b>			
Unilateral	92 (80.7)	22 (19.3)	$\chi^2=4.786$ ; df=1; p=0.029
Bilateral	148 (69.5)	65 (30.5)	
<b>Frequency of occurrence</b>			
≤3 monthly	231 (78.8)	62 (21.1)	$\chi^2=42.78$ ; df=1; p<0.001
>3 monthly	9 (26.5)	25 (73.5)	
<b>Severity</b>			
Mild	133 (65.5)	70 (34.5)	$\chi^2=17.01$ ; df=1; p<0.001
Severe	107 (86.3)	17 (13.7)	
<b>Mini TQ (mean)</b>	8.68±3.34	4.09 ±3.97	t=-10.443**; df=325; p<0.001
<b>PSQ-index (mean)</b>	0.40±0.11	0.39±0.09	t=-0.517**; df=325; p=0.605

\*\*Independent t-test

**Table 3: Bivariate analysis of clinical correlates between those with mild and severe tinnitus.**

Variable	Severity		Statistics
	Mild N (%)	Severe N (%)	
<b>Age group (in years)</b>			
≤50	101 (78.3)	28 (21.7)	$\chi^2=23.795$ ; df=1; p<0.001
>50	102 (51.5)	96 (48.5)	
<b>Gender</b>			
Male	120 (61.2)	76 (38.8)	$\chi^2=0.152$ ; df=1; p=0.697
Female	83 (63.4)	48 (36.6)	
<b>Education</b>			
None	6 (40.0)	9 (60.0)	$\chi^2=20.283$ ; df=4; p<0.001
Primary	28 (42.4)	38 (57.6)	
Secondary	118 (67.4)	57 (32.6)	
Tertiary	33 (67.3)	16 (32.7)	
Postgraduate	18 (81.8)	4 (18.2)	
<b>Affected ear</b>			
Unilateral	74 (64.9)	40 (35.1)	$\chi^2=0.597$ ; df=1; p=0.440
Bilateral	129 (60.6)	84 (39.4)	
<b>Frequency of occurrence</b>			
≤3 monthly	119 (40.6)	174 (59.4)	$\chi^2=8.687$ ; df=1; p=0.003
>3 monthly	5 (14.7)	29 (85.3)	
<b>Family history</b>			
Yes	17 (19.5)	70 (80.5)	$\chi^2=17.011$ ; df=1; p<0.001
No	107 (44.6)	133 (55.4)	
<b>Mini-TQ (mean)</b>	6.52±4.17	9.01±3.34	t=-5.640**; df= 325; p<0.001
<b>PSQ-index (mean)</b>	0.39±0.99	0.40±0.92	t=-0.839**; df=325; p=0.402

\*\*Independent t-test

Table 3 shows the bivariate analysis of clinical correlates between those with mild and severe tinnitus. The presence of tinnitus in other family members, occurrence of tinnitus for more than 3 months, increasing age and higher mean mini-TQ scores showed significant association with severity of tinnitus.

Table 4 reveals the significance of the impact of family history among those subjects with tinnitus. It shows that presence of tinnitus in other family members increases the odds of frequency of tinnitus by 5.08 and mean scores of the mini-TQ by 1.31.

**Table 4: Significance of the impact of family history among those subjects with tinnitus.**

Variable	Odds ratio	95% CI	Standard error	P value
<b>Age group</b>				
>50 years	1.87	0.96-3.63	0.339	0.065
<b>Frequency of occurrence</b>				
3 monthly and above	5.076	1.70-15.12	0.557	0.004
<b>Severity</b>				
Severe	1.214	0.59-2.52	0.372	0.602
<b>Affected ear</b>				
Bilateral	0.672	0.34-1.34	0.353	0.260
<b>Mini-TQ</b>	1.313	1.20-1.44	0.046	<0.001

Table 5 shows the logistic regression analysis of the predictors of severity of tinnitus. This reveals that increasing age greater than 50 years increases the odds of severity of disease by 2.81 and higher mean scores of the mini-TQ increases the odds by 1.16.

**Table 5: Logistic regression analysis of the predictors of Severity of tinnitus.**

Variable	Odds ratio	95% CI	Standard error	P value
<b>Age group</b>				
>50 years	2.81	1.59-4.94	0.288	<0.001
<b>Frequency of occurrence</b>				
3 monthly and below	1.92	0.59-6.25	0.603	0.281
<b>Education</b>				
Primary	1.347	0.40-4.57	0.623	0.632
Secondary	0.393	0.12-1.24	0.587	0.111
Tertiary	0.485	0.13-1.78	0.663	0.275
Postgraduate	0.464	0.09-2.49	0.857	0.370
<b>Family history</b>				
Yes	0.856	0.41-1.78	0.374	0.677
<b>Mini-TQ</b>	1.159	1.08-1.25	0.038	<0.001

## DISCUSSION

The main findings in this study was that more than one-third of the subjects had severe tinnitus and there was significant correlation between the occurrence of tinnitus

in first degree relatives and severity of tinnitus. In addition, there was correlation between the self-assessed visual scale and the perceived stress score (PSQ) and the mini tinnitus (Mini-TQ) scores which are also measures of severity of tinnitus.

There is strong evidence from the literature that the clinical picture of tinnitus is not strictly limited to ontological considerations.<sup>1,13</sup> Psychological complications include concentration problems, depression, anxiety, sleep disturbances, and intense worrying among others. It is widely recognized that reliable and valid instruments are needed to describe these different facets and the degree of tinnitus-related distress.<sup>1</sup> The findings from this study have further validated the correlation between the visual analogue scale and the mini-TQ scores.

Our finding is similar to that of Cederroth et al, who reported a heritability of 32% with the transmission of tinnitus.<sup>14</sup> Their findings suggest that genetic factors are associated with the familial clustering of clinically significant tinnitus with no shared-environment association, revealing that the transition from negligible to severe tinnitus may be associated with genetic factors. In the same vein, Maas et al found that specific forms of tinnitus had greater heritability in a sex-specific manner.<sup>15</sup> In another work, bilateral tinnitus has been reported with a heritability of 0.41 in women and 0.68 in men; in contrast to unilateral, where heritability decreased to near 0.27.<sup>15</sup> Our finding showed that tinnitus was significantly more severe in those who have bilateral disease compared to unilateral disease. A key finding was that bilateral tinnitus had higher heritability than unilateral tinnitus.<sup>16</sup> The study was based on self-reported data from the Swedish twin registry, one of the largest twin registries in the world.<sup>17-19</sup> Of a total of 70,186 twins that answered questions related to tinnitus. 15% of them experienced tinnitus. 10,464 concordant or discordant pairs for tinnitus were identified, in which 6,990 subjects had tinnitus. When considering tinnitus as a whole, a moderate genetic contribution (near 40%) was found.<sup>20</sup> These findings open the possibility of specific forms of tinnitus being more genetically driven than others and pave the way for future genetic studies of tinnitus.

On the other hand, it has been proposed that the lack of evidence on a significant association with genetic factors is attributable to the large heterogeneity of tinnitus and that tinnitus should not be considered a single entity but an ensemble of multiple subtypes.<sup>16</sup> The selection of multiplex tinnitus families, in addition to unrelated cases and controls, for exome sequencing will be a potential strategy to be used for the discovery of genes involved in tinnitus. This strategy has been successful in the identification of DTNA, PRKCB, SEMA3D and DPT in autosomal dominant Meniere disease.<sup>21,22</sup> With tinnitus being a condition with highly unmet clinical needs, the identification of a high heritability may open door to exciting research.<sup>14</sup> Since it is likely that tinnitus is a

polygenic trait, optimizing their phenotyping by using high frequency audiometry and multivariate questionnaire will be a potent strategy in order to allocate a specific ICD-code for bilateral tinnitus, and start biobanking samples.<sup>16,23,24</sup> In addition, sex differences in familial aggregation and heritability of bilateral tinnitus suggest a potential sexual dimorphism in tinnitus inheritance.<sup>9</sup> Although our study did not find significant difference between the genders.

## CONCLUSION

We conclude that the findings of significant correlation between presence of tinnitus in first degree relatives and severity of tinnitus among the subjects provides an empirical evidence to explore a possible genetic aetiology for severe tinnitus in our population. The future goal of our research is to create guidelines to decipher the genetic basis of tinnitus and collect samples for DNA biobanking.

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