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Tinnitus and Sleep Difficulties After Cochlear Implantation

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Objectives: To estimate and compare the prevalence of and associations between tinnitus and sleep difficulties in a sample of UK adult cochlear implant users and those identified as potential candidates for cochlear implantation.

Design: The study was conducted using the UK Biobank resource, a population-based cohort of 40- to 69-year olds. Self-report data on hearing, tinnitus, sleep difficulties, and demographic variables were collected from cochlear implant users (n = 194) and individuals identified as potential candidates for cochlear implantation (n = 211). These "candidates" were selected based on (i) impaired hearing sensitivity, inferred from self-reported hearing aid use and (ii) impaired hearing function, inferred from an inability to report words accurately at negative signal to noise ratios on an unaided closed-set test of speech perception. Data on tinnitus (presence, persistence, and related distress) and on sleep difficulties were analyzed using logistic regression models controlling for gender, age, deprivation, and neuroticism.

Results: The prevalence of tinnitus was similar among implant users (50%) and candidates (52%; p = 0.39). However, implant users were less likely to report that their tinnitus was distressing at its worst (41%) compared with candidates (63%; p = 0.02). The logistic regression model suggested that this difference between the two groups could be explained by the fact that tinnitus was less persistent in implant users (46%) compared with candidates (72%; p < 0.001). Self-reported difficulties with sleep were similar among implant users (75%) and candidates (82%; p = 0.28), but participants with tinnitus were more likely to report sleep difficulties than those without (p < 0.001). The prevalence of sleep difficulties was not related to tinnitus persistence (p = 0.28) or the extent to which tinnitus was distressing (p = 0.55).

Conclusions: The lack of association between tinnitus persistence and sleep difficulties is compatible with the notion that tinnitus is suppressed in implant users primarily during active electrical stimulation and may return when the implant is switched off at night time. This explanation is supported by the similar prevalence of sleep problems among implant users and potential candidates for cochlear implantation, despite differences between the groups in tinnitus persistence and related emotional distress. Cochlear implantation may therefore not be an appropriate intervention where the primary aim is to alleviate sleep difficulties.

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INTRODUCTION

Tinnitus, the perception of sound in the absence of an external stimulus, affects about 16% of the adult population (Dawes et al. 2014; McCormack et al. 2014). Hearing loss has been established as a major risk factor for tinnitus (Nondahl et al. 2011). It has been suggested that degraded auditory input due to cochlear damage can trigger aberrant neuronal activity that is interpreted as tinnitus (Preece et al. 2003; Eggermont & Roberts 2014). The burden imposed by tinnitus is complex and extends beyond the persistence of the percept itself. The overall perceived handicap can include hearing difficulties, anxiety, depression, inability to relax, and sleep difficulties (Tyler & Baker 1983; Langguth 2011; McCormack et al. 2015). This heterogeneity in symptoms is reflected in the wide variety of proposed treatments, many of which are not supported by strong evidence for their effectiveness (Baguley et al. 2013).

Patients and clinicians agree that the management of tinnitus in those with profound hearing loss remains one of the top priorities for future tinnitus research (Hall et al. 2013). One potential device that has been proposed to manage tinnitus in the profoundly deaf is the cochlear implant (CI), which is an established intervention to restore useful aspects of hearing in these patients (Faulkner & Pisoni 2013). Cochlear implantation involves the surgical placement of an electrode array within the cochlea to stimulate spiral ganglion cells electrically to convey auditory information (Loizou 1998). On average, as many as 80% of candidates for cochlear implantation report experiencing tinnitus but the percept appears to subside in many after implantation (Baguley & Atlas 2007). As a result, it has been suggested that cochlear implantation should be considered as a treatment for tinnitus in the profoundly deaf (Tyler et al. 2008b). However, there remains a lack of comprehensive assessments of the burden of tinnitus and tinnitus-related symptoms after cochlear implantation (Baguley 2010) and therefore a lack of evidence for which symptoms may or may not be alleviated by implantation.

Many studies that have evaluated the impact of cochlear implantation on tinnitus have assessed outcome in terms of relief from the percept, for example, the reduction in tinnitus loudness (for a review see Baguley & Atlas 2007; Arts et al. 2012). Other studies have focused on designing and optimizing electrical stimulation strategies to suppress the percept (Chang & Zeng 2012; Arts et al. 2015). The assumption is that the suppression of tinnitus will alleviate its intrusiveness and reduce overall burden. However, although the number of profoundly deaf patients reporting tinnitus decreases following implantation, clinical observations suggest that a large proportion of CI recipients still experience some degree of tinnitus-related

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handicap (Pan et al. 2009; Bovo et al. 2011; Kloostra et al. 2015; Ramakers et al. 2015). A review of studies that have assessed the levels of tinnitus-related handicap following implantation suggested that about 25% of CI users experience a clinically significant tinnitus, that is, a degree of tinnitus-related handicap that may warrant intervention (Baguley 2010).

The presence of tinnitus after implantation may be explained by the finding that tinnitus is suppressed mostly when the implant is stimulating the auditory nerve and often reverts back to its original loudness (or becomes louder) soon after stimulation is turned off (Zeng et al. 2011; Vlastarakos et al. 2014). Therefore, it is plausible that tinnitus could be still bothersome in CI users at night time if the CI is switched off before going to sleep (Chadha et al. 2009), and consequently that they would not experience a reduction in the occurrence of tinnitus-related insomnia. However, despite the decades of research and converging evidence that sleep difficulties are one of the most common tinnitus-related complaints (Tyler & Baker 1983; Langguth 2011), the treatment of tinnitus-related insomnia remains an outstanding uncertainty for both clinicians and patients (Hall et al. 2013).

Few studies have assessed the association between tinnitus and sleep difficulties in CI users, or whether the presence of tinnitus leads to sleep difficulties after patients turn their CI off at night time. One observational study on a small sample of adult CI users has suggested that implant use may reduce sleep difficulties in some, but not all, patients (Di Nardo et al. 2007), but the factors that contribute to that reduction remain unclear. The aims of the present study were therefore to (i) estimate the prevalence of sleep difficulties among adult CI users and those who may be candidates for implantation and (ii) examine the associations between sleep difficulties, tinnitus characteristics, and tinnitus-related emotional distress.

METHODS

Participants

The data were obtained from the UK Biobank resource. The UK Biobank baseline health data were collected in 2007 to 2010 from over 500,000 people aged 40 to 69 years who were invited to participate based on their residence proximity to a UK Biobank Assessment Center (Allen et al. 2014). The present study included data from participants who reported using a CI and those identified as candidates for cochlear implantation (see section "Comparison Group"). The UK Biobank has ethical approval from the North West Multi-centre Research Ethics Committee. Associated research using the resource within the UK is monitored and licensed by the UK Biobank Ethics and Governance Council.

Self-Reported Measures

UK Biobank participants completed a touchscreen questionnaire. All participants were asked questions on sleep problems, hearing device use, hearing difficulties, and tinnitus. The selected questions and response options are listed in Table 1. The responses characterized when participants reported experiencing tinnitus

Question	Response Options	Category/Rating
"Do you have trouble falling asleep at night or do you wake	Never/rarely	Rare
up in the middle of the night?"	Sometimes	Usual
	Usually	Usual
	Prefer not to answer	-
"Do you use a hearing aid most of the time?"	Yes	Yes
	No	No
	Prefer not to answer	-
"Do you have a cochlear implant?"	Yes	Yes
	No	No
	Prefer not to answer	-
"Do you have any difficulty with your hearing?"	Yes	Yes
, , , , , ,	No	No
	I am completely deaf	-
"Do you find it difficult to follow a conversation if there is	Yes	Yes
background noise (such as TV, radio, children playing)?"	No	No
	Do not know	-
	Prefer not to answer	-
"Do you get or have you had noises (such as ringing or	Yes, now most or all of the time	Current/Frequent
buzzing) in your head or in one or both ears that lasts for	Yes, now a lot of the time	Current/Frequent
more than five minutes at a time?"	Yes, now some of the time	Current/Infrequent
	Yes, but not now, but have in the past	Past
	No, never	Never
	Do not know	-
	Prefer not to answer	-
"How much do these noises worry, annoy or upset you	Severely	Upsetting
when they are at their worst?"	Moderately	Upsetting
	Slightly	Slight
	Not at all	Slight
	Do not know	-
	Prefer not to answer	-

("tinnitus presence") and its frequency of occurrence ("tinnitus persistence"). Participants who indicated that they have experienced tinnitus at some point also judged the level of "tinnitus distress" similar to the assessment of tinnitus-related emotional distress in standard tinnitus questionnaires (Kuk et al. 1990; Meikle et al. 2012). The self-report question on sleep difficulties was the same as that often included in standard tinnitus questionnaires (Kuk et al. 2012; Tyler et al. 2014). However, it was asked before the tinnitus assessments in the UK Biobank study and therefore responses on sleep difficulties may not be related specifically to tinnitus.

Speech in Noise Test

Participants completed a shortened version of the Digit Triplets Test (DTT, Dawes et al. 2014) at the UK Biobank assessment center after completing the touchscreen questionnaire. The DTT was not administered to any participant reporting CI use, regardless of whether they also reported using a hearing aid (HA) or not. Participants who did not use a CI but who wore HAs did complete the DTT but were asked to remove their aids for the assessment. The stimuli were presented separately to each ear via circumaural headphones (Sennheiser D25) at a comfortable level set by the participant. Fifteen monosyllabic digit triplets (e.g., 1-3-9) were presented in noise that was spectrally shaped to match the complete set of nine digits (0 to 9, excluding 7). The level of the noise was varied adaptively to estimate the signal to noise ratio at which the participant could report all three digits in the triplet correctly on 50% of the trials. The mean signal to noise ratio from the last eight triplets was used as a measure of hearing disability and is referred to as the speech reception threshold (SRT).

Comparison Group

A "candidate" group for cochlear implantation was selected by relating the available data in the UK Biobank to the UK candidacy criteria for cochlear implantation in adults. The criteria not only require impairment to hearing sensitivity (i.e., unaided pure-tone thresholds >90 dB at 2 and 4 kHz) but also an impaired speech perception (only able to report less than 50% of words in sentences in the best-aided condition, National Institute for Health and Clinical Excellence 2009). As the UK Biobank did not assess hearing sensitivity directly, self-reported use of a HA "most of the time" was assumed to be an indicator of a clinically diagnosed hearing loss. In addition, only those HA users with SRTs ≥ 0 dB on the DTT were included in the candidate group because it would be atypical for cochlear implantation candidates to have a negative SRT in an unaided speech in noise test such as the DTT (Donaldson et al. 2009). Participants with an SRT of +8 dB (the maximum possible value) were excluded to avoid the inclusion of any participants whose DTT results could possibly be attributed to noncompliance or equipment failure.

Data Analysis

Descriptive statistics were used to summarize participant characteristics. Specific hypotheses were analyzed by applying logistic generalized linear modeling methods. Responses "prefer not to answer" or "do not know" to any questions were treated as missing data. Missing data were accounted for by multiple imputations by chained equations with 100 imputed datasets (Sterne et al. 2009). This method was used, as missing data could not be assumed missing completely at random due to the use of the response option "prefer not to answer." The data were analyzed using R 3.1.0 and the package mice (van Buuren & Groothuis-Oudshoorn 2011). Results were considered statistically significant if p < 0.05.

The models controlled for age (banded into 5-year-age groups), gender, the interaction between age and gender, and deprivation-a measure of socioeconomic status based on the national quintiles for the Townsend deprivation index score. These factors are known to be associated with the prevalence and severity of tinnitus (Dawes et al. 2014; McCormack et al. 2014). The level of neuroticism, known to be associated with both tinnitus and sleep difficulties (Hintsanen et al. 2014; McCormack et al. 2014), was included as a covariate in the model to account for a potential confound when testing associations between tinnitus-related distress and sleep difficulties. The neuroticism score was constructed by assigning a score of 1 to all "yes" answers resulting in a range of scores from 0 to a maximum score of 13 if participant responded "yes" to all questions in the neuroticism assessment. The level of neuroticism was built into the model as a 4-level factor based on score intervals of 0 to 2 (low), 3 to 5 (low-medium), 6 to 9 (mediumhigh), and 10 to 13 (high) (McCormack et al. 2015).

RESULTS

Participant Characteristics

Table 2 lists the characteristics of the participants and Table 3 lists their self-reported difficulties. About 1.4% of all HA users (n = 211) were included in the candidate group, which is similar to the proportion of the UK population with severe to profound

	TABLE 2. Par	ticipant characteristics	(missing data	excluded in %
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Group	CI	Candidate
n (total)	194	211
Gender		
Male	115 (59%)	130 (62%)
Age band in years		
40–44	17 (9%)	5 (2%)
45–49	15 (8%)	8 (4%)
50–54	19 (10%)	9 (4%)
55–59	28 (14%)	28 (13%)
60–64	47 (24%)	60 (29%)
65–69	68 (35%)	101 (48%)
Deprivation		
Quintile 1	46 (24%)	58 (28%)
Quintile 2	43 (22%)	46 (22%)
Quintile 3	37 (19%)	37 (18%)
Quintile 4	36 (19%)	41 (19%)
Quintile 5	30 (16%)	28 (13%)
Missing	2	1
Neuroticism score		
Mean (SD)	4.25 (3.60)	4.98 (3.37)
SRT in dB (SD)		
40–44	-	4.6 (3.4)
45–49	-	1.9 (1.6)
50–54	-	4.4 (2.7)
55–59	-	3.8 (2.4)
60–64	-	3.1 (2.2)
65–69	-	3.1 (2.5)

CI, cochlear implant; SD, Standard Deviation; SRT, speech reception threshold.

Characteristic	Category	Subcategory	CI	Candidate
Difficulty hearing	Yes		164 (87%)	210 (>99%)
	No		25 (13%)	1 (<1%)
	Missing		5	0
Difficulty hearing in noise	Yes		161 (87%)	20 (97%)
	No		24 (13%)	7 (3%)
	Missing		9	0
Tinnitus type	Current	Frequent	38 (21%)	78 (39%)
		Infrequent	47 (27%)	35 (17%)
	Past		25 (14%)	27 (13%)
	Never		67 (38%)	63 (31%)
	Missing		17	8
Tinnitus distress	Upsetting	Severely	13 (12%)	16 (11%)
		Moderately	27 (25%)	52 (37%)
	Slight	Slightly	43 (39%)	43 (31%)
	-	Not at all	26 (24%)	29 (21%)
	Missing		85	71
Sleep difficulty	Usual	Usually	50 (26%)	69 (33%)
		Sometimes	87 (46%)	105 (50%)
	Rare	Never/rarely	53 (28%)	37 (17%)
	Missing		4	0

TABLE 3. Self-reported measures of hearing, tinnitus type, and sleep difficulty (missing data excluded in %)

CI, cochlear implant.

hearing loss (Davis 1995). A comparison of the CI and candidate groups indicated that the gender balance did not differ significantly between the groups (p = 0.71) and that the CI group was characterized by a wider spread in age across bands (p = 0.001; Table 2). The groups did not differ on the measure of deprivation (p = 0.89). The geographical distributions of participants were very similar in both groups and clustered around major urban areas where large audiology and CI clinics are based (Supplemental Digital Content 1, http://links.lww.com/EANDH/A293).

The average SRT score in the candidate group was +3.5 dB (Standard Deviation SD = 2.4), with all but one participant reporting hearing difficulties and 97% reporting difficulties following conversations in noise (Table 3). In the CI group, a similar proportion of participants reported having hearing difficulties (87%) and experiencing difficulties with following conversations in noise (87%).

Tinnitus Profile and Sleep Difficulties

Figure 1 shows the self-reported tinnitus characteristics and sleep difficulties in the CI and candidate groups. Excluding those who had never experienced tinnitus, a similar proportion of the CI and candidate groups reported current tinnitus (p = 0.19; OR = 0.75, 95% confidence interval = 0.49 to 1.16; Fig. 1A). However, tinnitus in the CI group was significantly less persistent (p < 0.001; OR = 0.32, 95% confidence interval = 0.17 to 0.62; Fig. 1B) and less distressing (p = 0.02;OR = 0.44, 95% confidence interval = 0.23 to 0.86; Fig. 1C). Sleep difficulties were highly prevalent (≥75%) with no significant difference between the groups (p = 0.28; OR = 0.64, 95%) confidence interval = 0.29 to 1.44; Fig. 1D). A summary of the between-group comparisons is shown in Figure 2.

Figure 3 summarizes the results of testing specific associations between tinnitus characteristics and sleep difficulties. Tinnitus was more likely to be characterized as distressing when it was more persistent (p < 0.001; OR = 4.17, 95% confidence interval = 2.03 to 8.58). After controlling for persistence, the observed difference in tinnitus distress between the groups was no longer significant. The prevalence of sleep difficulties was not associated with either tinnitus persistence (p = 0.28) or distress (p = 0.55).

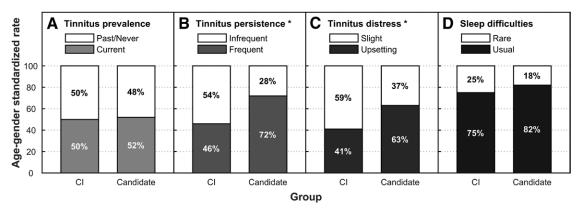


Fig. 1. Characterization of participants' tinnitus (A-C) and their sleep difficulties (D). Percentages represent the age-gender standardized rates with missing data excluded. Shaded areas represent the proportion of participants reporting the presence of tinnitus and relatively high tinnitus-related persistence and distress or sleep difficulties. An asterisk indicates a significant difference between the groups. CI, cochlear implant.

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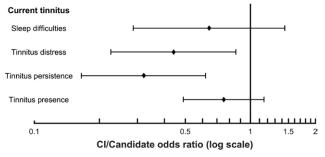


Fig. 2. Odds ratios for participants' tinnitus characteristics and their sleep difficulties in cochlear implant (CI) and candidate group, that is, CI/candidate. Error bars show 95% confidence intervals. Odds ratios less than 1 indicate that the effect was less likely to occur in CI users compared with potential candidates.

DISCUSSION

Tinnitus Persistence and Distress

An analysis of the UK Biobank resource found that tinnitus was reported as less distressing by a group of CI users compared with a group of HA users identified as potential candidates for implantation. Further analyses revealed that this group difference was driven by the lower persistence of their tinnitus (Fig. 3): participants who reported tinnitus as less persistent were more likely to report a lower level of emotional distress as a result of their tinnitus. These results are compatible with previous studies that have demonstrated the potential for electrical stimulation to reduce the percept of tinnitus (for a review, see Baguley & Atlas 2007).

Tinnitus still appears to cause considerable distress in a subset of implanted individuals. However, the data available in the UK Biobank were mostly retrospective and based on selfreport and may not accurately reflect participants' overall level of tinnitus-related distress. The self-reports of CI users might have been influenced by their experience of hearing restoration and/or by the hearing and speech therapy they received following implantation (Pan et al. 2009). However, the lack of general quality of life assessments did not allow for these or other potential psychological effects on well-being and reported tinnitus persistence or distress to be controlled for. While tinnitus can be experienced throughout the day, participants in the UK Biobank were only asked to judge their level of tinnitus-related

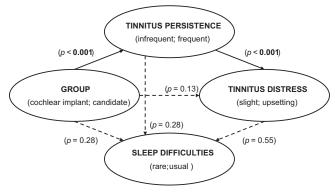


Fig. 3. Schematic associations between the groups with current tinnitus, their tinnitus persistence and emotional distress from tinnitus, and sleep difficulties. Lower emotional distress is driven by lower persistence of tinnitus in cochlear implant users.

distress during the periods when their tinnitus is at its worst, for example, when their CI is switched off. If so, the present results may overstate the overall level of distress experienced by CI users. If distress had been measured throughout the day, the difference in distress reported by the CI and candidate groups may have been even more pronounced.

One possible explanation for the lower level of tinnitus persistence among CI users is that they may have regained access to sound following implantation that could suppress or mask their tinnitus and/or reduce the extent to which they attend to their tinnitus. These effects could plausibly lead to a decrease in the perceived loudness of tinnitus and potentially give some relief from tinnitus-related emotional distress. However, neither suppression nor reduced attention to tinnitus may be fully effective or lasting if only due to the fact that currently CI stimulation is optimized for speech perception and may not be optimal for the suppression of tinnitus (Chang & Zeng 2012). Thus, many CI users will likely still experience periods of loud and distressing tinnitus as they did before implantation.

Sleep Difficulties

The overall prevalence of tinnitus and sleep difficulties was similar in both the CI and candidate groups. This observation is compatible with the notion that tinnitus loudness may build up and cause distress in CI users if the device is switched off at night time (Chadha et al. 2009). CI users may therefore report tinnitus as infrequent, but as still creating a substantial level of distress when at its worst, as observed in the present study.

Questions about sleep in the UK Biobank study were not asked in the context of tinnitus. Therefore, the reported difficulties with sleep may have been unrelated to tinnitus but related to other factors, for example, other age-related health problems. However, self-reported difficulties with sleep were highly prevalent in all participants reporting current tinnitus. This association between tinnitus presence and sleep difficulties was found even after controlling for neuroticism, a factor shown to be associated with both tinnitus (McCormack et al. 2014, 2015) and sleep problems (Hintsanen et al. 2014).

Sleep difficulties did not vary as a function of either tinnitus persistence or distress. This finding is consistent with the fact that participants were asked to rate distress based on how much the tinnitus "noises" upset them. Consequently, the reported distress was likely driven by hearing tinnitus persistently (Fig. 3) rather than sleep problems. Additional analyses also determined that the prevalence of sleep difficulties was not influenced by HA use or by poor speech perception (Supplemental Digital Content 2, http://links.lww.com/EANDH/A294). Thus, the presence of sleep difficulties appears to be predicated primarily on whether tinnitus is present or not, and would therefore be expected to occur in a majority of those who experience tinnitus. It is perhaps not surprising therefore that insomnia was identified by patients and clinicians as one of the outstanding priorities for tinnitus research (Hall et al. 2013).

Tinnitus Before and After Implantation

The present data cannot provide definitive estimates of the effect of implantation on tinnitus because it is not known whether tinnitus reported as occurring only in the past was abolished before or after implantation. If one assumes reporting moderately or severely distressing tinnitus as "significant" enough to consider additional tinnitus management options after implantation (Andersson et al. 2009), the estimate of 37% of CI users found in the present study (Table 3) would be somewhat higher than the 25% of "clinically significant" tinnitus estimated from data reported in other studies (Baguley 2010). If one also assumes that the candidate group was representative of those who are eligible to receive a CI in the UK, then the proportion of patients reporting current tinnitus of any kind (56%) was lower than the average estimate of 80% in CI candidates (lower limit of 67%) extrapolated from results of a number of studies (Baguley & Atlas 2007). One possible explanation for these discrepancies is that the UK Biobank study sampled from the middle-aged UK population (40 to 69 years old) and therefore excluded both younger and older adult CI users and candidates.

Clinical Implications

The absence of an association between tinnitus persistence, tinnitus distress, and difficulties with sleep reported here suggests that cochlear implantation may not be an appropriate intervention where the primary motivation is tinnitus suppression for the alleviation of tinnitus-related insomnia. Nevertheless, elevated sleep difficulties remain a significant contributor to perceived tinnitus-related emotional distress, and cases of undiagnosed insomnia may be present among tinnitus patients (Miguel et al. 2014). Insomnia management should therefore still be considered for any patient experiencing tinnitus, including CI users.

The results of the present study suggest that tinnitus is less persistent in those who use a CI compared with those identified as potential candidates for a CI despite similar prevalence of tinnitus in both groups. The results also suggest that the level of tinnitus persistence in CI users is similar to that observed in unaided participants with good speech perception in noise (Supplemental Digital Content 2, http://links.lww.com/EANDH/ A294). However, the limited information in the UK Biobank study on hearing loss and the type or number of devices used means that uncertainty remains as to whether (a) the difference in tinnitus persistence observed between CI users and potential candidates was a direct result of the devices used and (b) the subset of HA users identified as potential candidates were representative of those who are eligible to receive a CI in the UK. If the finding of lower tinnitus persistence among CI users compared with candidates is replicated in further observational and controlled studies, cochlear implantation could be considered as a potential treatment option for persistent and emotionally distressing tinnitus in those whose hearing loss may not otherwise make them a candidate. In those cases, implantation may have the potential to make tinnitus less persistent, possibly leading to a reduction in emotional distress.

The recognized breadth of observed symptoms among tinnitus patients has and continues to drive efforts toward delineating subtypes of tinnitus to provide tailored treatments and improve individual outcomes (Tyler et al. 2008a; Langguth 2011; COST Action BM1306: TINNET 2013). It is somewhat surprising therefore that, in the case of CI users, the focus appears to remain on suppressing the percept of tinnitus (Arts et al. 2012, 2015; Chang & Zeng 2012; Vlastarakos et al. 2014; Ramakers et al. 2015), with relatively less attention given to the characterization and management of other tinnitus-related symptoms. The present results suggest that CI users may experience a relief in tinnitus persistence, but not a complete abolition of tinnitus or tinnitus-related distress. Studies investigating other aspects of tinnitus handicap in CI users are encouraging (e.g., anxiety and depression; Andersson et al. 2009; Olze et al. 2011; Kloostra et al. 2015), but a more comprehensive characterization of tinnitus symptoms is still needed to understand the burden of tinnitus after cochlear implantation. It is only through such understanding that appropriate interventions for alleviating the burden of tinnitus in implant users can be identified and developed.

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RHP and PTK conceived the study and wrote the article, MEJ performed the analyses. All authors critically revised the manuscript.

This research has been conducted using the UK Biobank resource.

The authors have no conflicts of interest to disclose.

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