INSOMNIA, ANXIETY AND DEPRESSION IN ADULT COCHLEAR IMPLANT USERS WITH TINNITUS

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ABSTRACT

Objective: Determine the prevalence of clinical insomnia and its associations with anxiety, depression and tinnitus in adult CI users.

Design: Self-reported information on tinnitus, sleep and demographic variables were collected from adult cochlear implant users (n = 127). Tinnitus presence, its persistence, related emotional distress, and difficulties with sleep were assessed using questions from the UK Biobank study (www.ukbiobank.ac.uk). Tinnitus-related handicap was assessed using the Tinnitus Handicap Inventory. Clinical insomnia symptoms were characterized using the Insomnia Severity Index (ISI), and clinical anxiety and depression symptoms using the Hospital Anxiety and Depression Scale (HADS). Regression models were used to compare the data from cochlear implant users with and without tinnitus, and to test the associations between clinical insomnia, anxiety, depression and tinnitus handicap.

Results: About a half (53%) of cochlear implant users reported tinnitus, of whom 54% described it as persistent, 41% as emotionally distressing and 73% reported having difficulties with sleep based on the UK Biobank questions. The ISI suggested that clinically abnormal insomnia symptoms were more likely to occur with tinnitus (Odds Ratio (OR) = 2.60, 95% confidence interval 1.04 to 6.45; $p = 0.040$) and were found in 41% of cochlear implant users with tinnitus. Post-hoc exploratory analyses on the ISI suggested that cochlear implant users with tinnitus experienced greater levels of difficulty falling asleep, lower satisfaction with sleep patterns, greater interference of sleep problems with daily activities, and a greater impact on their quality of life. The HADS scores suggested that those with tinnitus were also more likely to have clinically abnormal anxiety (42%; OR = 3.50, 1.49 to 8.22; $p = 0.004$) and depression symptoms (14%; OR = 6.18, 1.17 to 32.82; $p = 0.032$). The clinical insomnia observed in cochlear implant users with tinnitus was associated with tinnitus handicap ($p = 0.028$), and the levels of clinical anxiety ($p = 0.012$) and depression ($p < 0.001$).

Conclusions: Clinically abnormal insomnia symptoms are prevalent, potentially affecting over 40% of cochlear implant users with tinnitus. The associations between clinical insomnia, anxiety and depression symptoms, and tinnitus-related handicap suggests that all of these symptoms should be considered when assessing the tinnitus-related burden and its impact on the quality of life after cochlear implantation. The present findings also have potential implications for the clinical management of cochlear implant recipients with tinnitus, in whom it may be advisable to monitor sleep problems so that they can be addressed where appropriate. Further research is needed to investigate the mechanisms and causal links behind insomnia and tinnitus-related symptoms in this population. Future studies should also investigate the feasibility and effectiveness of night-time use of cochlear implants to alleviate tinnitus-related insomnia. The potential impact of insomnia on the quality of life of cochlear implant user with tinnitus highlights the importance of including sleep measures in future evaluations of the effectiveness of cochlear implantation for the alleviation of tinnitus.

INTRODUCTION

Tinnitus is a perception of sounds in the ears or head that do not come from an external source (National Institute for Health and Care Excellence 2017; Tunkel et al. 2014). The management of tinnitus in people who are profoundly deaf has been identified by patients and clinicians as one of priorities for further research (Hall et al. 2013). Tinnitus appears to be highly prevalent in individuals with severe-profound hearing loss. Recent epidemiological data suggest that at least 50% of people who are eligible to receive a cochlear implant (CI) experience tinnitus (Pierzycki et al. 2016), but the prevalence reported across different studies suggests it can be as high as 80% on average (Amoodi et al. 2011; Andersson et al. 2009; Baguley & Atlas 2007; Pan et al. 2009). While the primary clinical purpose of cochlear implantation is to improve the ability to understand speech, recent systematic reviews suggest that cochlear implantation can be also associated with the alleviation of tinnitus and the burden it imposes (Ramakers et al. 2015; Zenner et al. 2017).

The symptoms contributing to the perceived burden from tinnitus and the extent to which those symptoms are alleviated by CI use can vary between patients. However, a large proportion of CI users (about 75%) report difficulties with sleep which can be as prevalent in candidates for implantation and more likely to occur in those with tinnitus (Pierzycki et al. 2016). The alleviation of tinnitus resulting from CI use arises primarily when it is switched on and stimulating the auditory nerve (Zeng et al. 2011). Similarly, some CI users may experience difficulties with sleep due to the presence of tinnitus when their CI is switched off at night time (Chadha et al. 2009). This experience is illustrated clearly when CI users are asked to plot changes in the perceived severity of their tinnitus during the day relative to when their implant is switched on and off (Fig. 1).

There is a large body of evidence suggesting that sleep difficulties can be a significant contributor to the perceived emotional distress from tinnitus in general tinnitus population (Cronlein et al. 2007; Cronlein et al. 2016; Koning 2019; Langguth 2011; McKenna 2000; Tyler & Baker 1983). Recent reviews suggest that sleep difficulties may be prevalent in up to

80% of people with tinnitus (Asnis et al. 2018), consistent with the large prevalence of sleep difficulties found in CI users (75%) or potential candidates for implantation (82%) found in epidemiological studies (Pierzycki et al. 2016). However, the mechanisms behind tinnitus-related sleep difficulties are not well understood with recent studies suggesting the importance of psychological symptoms such as anxiety (Cronlein et al. 2016), or the intensity of the tinnitus percept itself as the factors affecting sleep in people with tinnitus (Koning 2019). Moreover, available evidence does not allow establishing the clinical importance of tinnitus-related sleep difficulties due to the large variability or inadequate use of insomnia assessments that do not allow a clinical diagnosis (Asnis et al. 2018). For example, while some studies suggest that tinnitus-related difficulties with sleep can be experienced in the absence of a sleep-related disorder (Cronlein et al. 2007), other suggest the presence of undiagnosed insomnia among tinnitus patients (Miguel et al. 2014). Therefore, the unanswered question about the sleep difficulties reported by adult CI users is whether these difficulties are of sufficient importance to reach a clinical diagnosis of insomnia and warrant clinical intervention.

*** PLEASE INSERT FIGURE 1 HERE (TINNITUS TIMECOURSE) ***

Tinnitus-related handicap has been found to be associated with increased anxiety and depression in CI users with tinnitus (Andersson et al. 2009; Kloostra et al. 2015; Olze et al. 2011). Prospective studies with patients undergoing cochlear implantation suggest only slight improvements in their anxiety and depression symptoms despite significant reduction of tinnitus-related distress as a result of implantation (Bruggemann et al. 2017; Olze et al. 2011). Similarly, the evidence from epidemiological studies suggests that the prevalence of emotionally distressing tinnitus among CI users, which may have been associated with anxiety and depression symptoms, could be as high as 41% compared to 63% among potential candidates to receive a CI (Pierzycki et al., 2016). However, anxiety and depression

are also major risk factors for developing insomnia (LeBlanc et al. 2009). Therefore, the reported emotional distress from tinnitus in CI users may have been also associated with the high prevalence of self-reported difficulties with sleep, which would be compatible with the known association between tinnitus distress and insomnia found in the general tinnitus population and recent cognitive-behavioral models of tinnitus distress (McKenna et al. 2014). Thus, not only is it important to explore the extent of clinical insomnia among CI users with tinnitus, but also the links between the insomnia, anxiety and depression symptoms in this population. The present study aimed to determine: (a) the prevalence and nature of insomnia symptoms; and (b) the associations between insomnia, anxiety and depression symptoms, and tinnitus handicap in adult CI users.

MATERIALS AND METHODS

Participants

A cross-sectional design was used to gather information about the prevalence of tinnitus, related clinical symptoms and patient demographic data among a population of adult CI users. The study was advertised to all adult patients managed by the Nottingham Auditory Implant Programme (N = 645), a large provider of cochlear implantation services in the United Kingdom. A cohort of 128 patients responded to postal invitations (response rate of 20%), of whom 127 gave information about the presence of tinnitus and were included in the study. The study obtained ethical approval from the South East Coast – Surrey National Research Ethics Service Committee.

Self-report measures of tinnitus and sleep difficulties

Table 1 shows the self-reported measures of tinnitus and sleep difficulties. All participants were asked about whether they experience tinnitus ('presence'). Those who reported having tinnitus were also asked to rate the frequency of occurrence of their tinnitus ('persistence'), and how much it worried, annoyed or upset them at its worst ('emotional distress'). All participants, regardless of tinnitus presence, were asked to report whether they had difficulties falling or staying asleep ('sleep difficulties'). The questions and response options about tinnitus and sleep difficulties were the same as those used in the UK Biobank study (Sudlow et al. 2015), and similar to assessments of tinnitus-related emotional distress and sleep problems included in many tinnitus questionnaires (Kuk et al. 1990; Meikle et al. 2012; Newman et al. 1996; Tyler et al. 2014).

The responses of participants identified as currently having tinnitus were used to categorize their tinnitus as 'infrequent' or 'frequent' in terms of persistence, and 'slight' or 'upsetting' in terms of tinnitus-related emotional distress (Table 2). All participants were also categorized as having difficulties with sleep that were either 'rare' or 'usual'. These

categories were the same as those used in our previous study characterizing tinnitus and sleep difficulties in adult CI users using the UK Biobank resource (Pierzycki et al. 2016).

Participants with tinnitus were also asked to complete the Tinnitus Handicap Inventory (THI) (Newman et al. 1996), a standard questionnaire used as a measure of tinnitus severity in clinical settings and tinnitus studies with CI users (Hoare et al. 2012; Ramakers et al. 2015). The THI consists of 25 items each asking the participant to rate the impact of their tinnitus on a specific aspect of daily function using a 3-point scale 'yes', 'no' and 'sometimes'. The participant's responses were used to compute a mean global score ranging from 0 to 100, and used as a validated measure of their tinnitus-related handicap (Andersson et al. 2009). The global score was used because it includes the contributions of THI items relating to anxiety, depression and sleep, and previous research suggests that the THI should be used as a unifactorial measure of tinnitus distress (Baguley & Andersson 2003).

*** PLEASE INSERT TABLE 1 HERE (UK BIOBANK QUESTIONS) ***

*** PLEASE INSERT TABLE 2 HERE (DEFINITIONS OF OUTCOMES) ***

Clinical measures of anxiety, depression and insomnia

All participants were asked to complete standard diagnostic questionnaires to assess the presence of anxiety and depression symptoms using the Hospital Anxiety and Depression Scale (HADS) (Zigmond & Snaith 1983), and the presence of insomnia symptoms using the Insomnia Severity Index (ISI) (Bastien et al. 2001). The ISI questionnaire was used due to its short timeframe for the assessment of symptoms (last two weeks) which was similar to that used in the assessment of the anxiety and depression symptoms in the HADS questionnaire (last week) and allowed to minimize potential recall bias in reporting the symptoms. The standard cut-off criteria (Table 2) for the respective summary scores on the HADS and ISI questionnaires were used to maximize the specificity when categorizing participants into those who either had normal or abnormal clinical anxiety or depressive symptoms, and those

with normal or abnormal clinical insomnia symptoms (Bastien et al. 2001; Zigmond & Snaith 1983).

Data Analysis

Descriptive statistics were used to summarize participant characteristics in the tinnitus and no tinnitus groups. Responses 'Prefer not to answer' or 'Do not know' to any questions were treated as missing data. Linear regression models were used to compare the groups on their HADS anxiety and depression, and ISI scores. A multivariable model was used to test for associations between the THI, HADS anxiety and depression, and ISI scores in the tinnitus group, and the interaction between the HADS anxiety or depression score and the ISI score. The relationships between the binary categories defined by the UK Biobank questions and the standard clinical diagnostic tools (HADS, ISI) were analyzed using logistic regression models. All regression models controlled for sex, age and their interaction. Multivariable regression models were used to test the relative influence (marginal effects) between the tinnitus handicap and anxiety, depression and insomnia symptoms because these symptoms may have occurred together and be related to each other in a given patient. The use of regression models also allowed estimating the marginal effects while controlling for age, sex and their interaction. Group differences in HADS and ISI item scores were explored using post-hoc independent samples t-tests. Correction for multiple comparisons was performed using the Holm-Bonferroni method at 0.05 level. The data were analyzed using R statistical package. Results were considered statistically significant if $p < 0.05$.

RESULTS

Participant Characteristics

Table 3 lists the characteristics of participants in the tinnitus and no tinnitus groups. About 53% of CI users (n = 67) reported experiencing tinnitus, a similar proportion to that found in the UK Biobank population (50%) (Pierzycki et al. 2016). The majority of participants with tinnitus reported tinnitus onset before cochlear implantation surgery (84%), and smaller proportions reported tinnitus onset after the surgery and some time before (5%) or after (11%) the first CI activation. The average THI score in the tinnitus group was 21.14 (Standard Deviation = 21.51), with about 79% of participants having scores indicative of no or mild tinnitus handicap and 21% indicative of moderate or severe tinnitus handicap (Newman et al. 1998). Nearly all participants (96%) were unilateral CI users. The sample comprised participants who were predominantly users of Cochlear Ltd. (71%) and Advanced Bionics Corp. CIs (27%), and several participants used devices from Med-El Corp. (2%). However, the distribution of device makes was almost identical between the tinnitus and no tinnitus groups (Table 3). These two groups were also similar in terms of their sex ($p = 0.37$), age ($p = 0.29$), duration of deafness ($p = 0.49$) and duration of CI use ($p = 0.99$).

*** PLEASE INSERT TABLE 3 HERE (SAMPLE DEMOGRAPHICS) ***

Self-report Measures of Tinnitus and Sleep Difficulties

Table 4 lists the outcomes on the self-report measures. The UK Biobank self-report measures suggested that about 54% of participants had persistent tinnitus and 41% reported emotional distress due to their tinnitus. A large proportion of all CI users (63%) reported experiencing difficulties with sleep. Logistic regression showed significant associations between tinnitus persistence and tinnitus-related emotional distress ($p = 0.015$; Odds ratio (OR) = 4.19, 95% Confidence interval (conf. int.) = 1.33 to 13.22). Sleep difficulties were not significantly associated with tinnitus persistence ($p = 0.37$) or emotional distress

($p = 0.10$), but were more likely to occur in CI users with tinnitus than those without ($p = 0.01$; $OR = 2.84$, 95% conf. int. 1.28 to 6.27).

*** PLEASE INSERT TABLE 4 HERE (SELF-REPORT MEASURES) ***

Impact of Tinnitus on Clinical Symptoms

Table 4 shows the prevalence of clinical symptoms in the tinnitus and no tinnitus groups. Table 5 shows descriptive and statistical comparisons between the groups in terms of their mean scores on the HADS and ISI, and the proportions with abnormal clinical anxiety, depression, and insomnia symptoms. About 42% of CI users with tinnitus reported abnormal anxiety symptoms on HADS, and were significantly more likely to have abnormal anxiety symptoms compared to those without tinnitus (19%; $p = 0.004$; Figure 2). Abnormal depression symptoms were also significantly more likely to occur in those with tinnitus (14%) than in those without (4%; $p = 0.032$). Clinical insomnia was found in 41% of CI users with tinnitus, and was significantly more likely to occur compared to those without tinnitus (21%; $p = 0.040$; Figure 3). The results of the regression models also showed that the scores on the HADS anxiety and depression questionnaire and the ISI questionnaire were significantly different between the tinnitus and no tinnitus groups (Table 5).

Comparison of single item scores on the HADS questionnaire showed significant differences between the groups on four items corresponding to anxiety symptoms ($p < 0.02$, significant after Holm-Bonferroni correction), excluding those reporting having worrying thoughts, frightened feelings of "'butterflies' in the stomach" or panic (Supplemental Digital Content Table S1). The groups also differed on one HADS item assessing depressive symptoms; i.e. being able to still enjoy things ($p = 0.005$, significant after Holm-Bonferroni correction; Supplemental Digital Content Table S2). Comparison of single item scores on the ISI questionnaire showed significant differences between the groups on four out of seven ISI items including self-reported difficulty falling asleep, but these differences were not

significant after correction for multiple comparisons (Supplemental Digital Content Table S3).

Figure 4 summarizes schematically the associations between tinnitus handicap measured with the THI, the HADS anxiety and depression scores, and ISI insomnia scores tested with the multivariable model in CI users with tinnitus. Tinnitus handicap scores were significantly associated with clinical depression scores ($p = 0.002$; $\beta = 4.20$, 95% conf. int. 1.67 to 6.74) but not with anxiety scores ($p = 0.080$; $\beta = –2.15$, 95% conf. int. –4.50 to 0.21). The clinical insomnia scores were also significantly associated with tinnitus handicap scores ($p = 0.028$; $\beta = 1.81$, 95% conf. int. 0.25 to 3.37) and significant interactions were observed between the ISI insomnia scores and both the HADS anxiety ($p = 0.012$; $\beta = 0.38$, 95% conf. int. 0.09 to 0.66) and depression scores ($p < 0.001$; $\beta = –0.53$, 95% conf. int. –0.80 to –0.25).

*** PLEASE INSERT TABLE 5 HERE (GROUP COMPARISON) ***

*** PLEASE INSERT FIGURE 2 HERE (ANXIETY AND DEPRESSION) ***

*** PLEASE INSERT FIGURE 3 HERE (SLEEP DIFFICULTIES AND INSOMNIA) ***

*** PLEASE INSERT FIGURE 4 HERE (SCHEMATIC ASSOCIATIONS) ***

DISCUSSION

The present study aimed to determine the prevalence of clinical insomnia among adult CI users, and to characterize associations between their clinical insomnia, anxiety, depression symptoms and their tinnitus-related handicap. Clinically abnormal insomnia symptoms were found in about 32% of CI users, but the prevalence of those symptoms in CI users with tinnitus (41%) was significantly higher and nearly double that found in those without tinnitus (21%). Clinically abnormal anxiety symptoms were more prevalent (31%) than those of depression (9%), but both were also more likely to co-occur with tinnitus. Tinnitus-related handicap was significantly associated with clinical insomnia and depression symptoms, and the effect of insomnia on the level of perceived handicap varied based on the level of clinical anxiety and depression (Fig. 4).

Domains of Tinnitus Burden in Cochlear Implant Users

About a half of CI users (53%) experienced tinnitus consistent with previous findings suggesting that complete suppression of tinnitus occurs in only about a half of CI recipients (Kloostra et al. 2015; Pan et al. 2009; Ramakers et al. 2015; Tyler 1994), and with the population-based prevalence of 50% found in CI users in the UK Biobank resource estimated using the same definition of tinnitus (Pierzycki et al. 2016). This finding also suggests that the prevalence of tinnitus in CI recipients is slightly higher than that found in the general population (34.3%) estimated using a similar question about the presence of tinnitus lasting >5 min at a time (McCormack et al. 2016). The prevalence estimates for persistent tinnitus (54%) and distressing tinnitus (41%) were relatively high, and the significant association between these characteristics suggests that tinnitus is more likely to be distressing when it is persistent. Difficulties with sleep were more likely to occur with tinnitus and a large proportion of CI users with tinnitus (73%) reported experiencing such difficulties (Table 4). The high prevalence of sleep difficulties in CI users with tinnitus is in agreement with the high prevalence and importance found in the general tinnitus population (McKenna et al.

2014; Tyler & Baker 1983). These proportions and associations were also consistent with those found in our previous study analyzing data collected from adult CI users in the UK Biobank population using the same self-report questions (Pierzycki et al. 2016). This robust replicability of previous population-based findings not only suggests the generalizability of the findings from the present clinical sample (Cronlein et al. 2016), but further supports the prevalence and associations between previously identified aspects of tinnitus-related burden in adult CI users.

Clinical Impact of Tinnitus-Related Burden

A novel finding of the present study was the presence of clinically abnormal insomnia symptoms in about a third of CI users, and that these symptoms were far more likely to occur in CI users with tinnitus. The severity of insomnia symptoms was assessed using the ISI, a clinical measure used for detecting and assessing the impact of insomnia (Bastien et al. 2001; Gagnon et al. 2013), and this severity was also found to be associated with tinnitus-related handicap. These findings are in agreement with the presence and association of clinical insomnia with the severity of tinnitus found in the general population (Asnis et al. 2018; Cronlein et al. 2016; Miguel et al. 2014; Schecklmann et al. 2015), and reinforce the importance and clinical relevance of screening for insomnia symptoms when assessing the impact of tinnitus in CI recipients.

Exploratory post-hoc comparisons of the specific symptoms described in the ISI suggested the increased severity of insomnia in CI users with tinnitus compared to those without might be driven by difficulties falling asleep (Supplemental Digital Content Table S3). This finding was also in agreement with the increased severity of tinnitus-related problems at night time reported by CI users in our clinic (Fig.1). Their problems were connected with switching their CI off at night time and thus suggest that the perception of tinnitus sound was the most likely contributor to their perceived sleep difficulties rather than tinnitus- or insomnia-related anxiety (Cronlein et al. 2016). These observations were also

supported by the finding that on average the self-reported feelings of being worried about sleep problems were similar in CI users with and without tinnitus (see ISI item 7, Supplemental Digital Content Table S3). However, further research is needed to explore the impact of specific symptoms on the severity of insomnia and their impact on everyday life in CI recipients with tinnitus.

Previous studies have suggested an association between insomnia and anxiety or depression symptoms in people with tinnitus (Asnis et al. 2018; Cronlein et al. 2016). These psychological symptoms are major risk factors for developing insomnia (LeBlanc et al. 2009). In the current study, clinically abnormal anxiety and depression symptoms were measured using HADS, a widely used measure for clinical assessment of these symptoms in people with tinnitus (Andersson et al. 2009; Hoare et al. 2012), and were found to occur significantly more likely in CI users with tinnitus than in those without. This finding is in agreement with that from a previous study investigating the associations between anxiety and depression symptoms and tinnitus handicap (Andersson et al. 2009). These authors have found higher proportions of moderate-severe tinnitus handicap (35%) in CI users with tinnitus than those found in the present study (21%, Table 3) which may have been connected with the higher prevalence of tinnitus post-implantation in their sample (74%). However, the mild levels of tinnitus handicap in CI users with tinnitus found in that study (average THI score 29.8) were similar to those found in the present (21.14) and other studies (Kloostra et al. 2015; Ramakers et al. 2015). Andersson and colleagues (2009) found significant associations between THI score and HADS anxiety (Pearson product-moment correlation of .57) and depression scores (.54), and between HADS anxiety and depression scores (.58). The Pearson correlation analysis on the present data has also suggested significant, albeit slightly weaker correlations between THI and HADS anxiety (.42) and depression scores (.41), and similar correlation between HADS anxiety and depression scores (.59). However, the results of the present study suggested there was no significant effect of clinical anxiety on the perceived tinnitus-related handicap in CI users with tinnitus which may have been connected

with the fact that multivariable regression model estimated the marginal effects of all symptoms on tinnitus.

The current model of associations between clinical symptoms and tinnitus-related handicap suggests that clinical anxiety may not be a significant contributor to the tinnitus handicap after controlling for clinical insomnia, and thus the increased anxiety in CI users with tinnitus may be driven by the elevated insomnia symptoms. Significant interactions between clinical insomnia and anxiety support this observation. However, the effect of clinical insomnia on tinnitus handicap varied based on the clinical depression levels suggesting that the impact of tinnitus and related insomnia should be monitored together with psychological disorders that CI recipients might experience (Bruggemann et al. 2017).

The exploratory analysis of ISI questionnaire responses showed that on average CI users with tinnitus experience greater interference of their sleep problems with their daily functioning. The combination of greater difficulties with falling asleep and greater interference with daily activities suggests that these patients may be more susceptible to developing an insomnia disorder (American Psychiatric Association 2013). Reported insomnia symptoms also appeared to be significant enough to contribute to the greater dissatisfaction with their sleep patterns and the perception that their sleep problems were having an impact on their quality of life that was noticeable to others. Taken together, the present findings are consistent with the observations that difficulties with sleep are the major tinnitus-related complaint reported by both tinnitus patients and their significant others (Hall et al. 2018a), and have the potential to negatively impact quality of life, physical health and daily activities (Bolge et al. 2009).

Implications for Future Studies

Information about the presence of anxiety, depression and insomnia symptoms prior to implantation was not available in the present study, and it is not clear whether these symptoms changed as a result of undergoing cochlear implantation or affected the perceived

tinnitus outcomes. Further prospective studies are needed to investigate the mechanisms and factors behind the causes of abnormal clinical symptoms, and such studies should investigate insomnia, anxiety and depression symptoms to adequately characterize and assess the clinical importance of any residual tinnitus-related symptoms after cochlear implantation.

Despite the potential impact of tinnitus on sleep due to CIs being typically switched off at night time (Chadha et al. 2009), and known contribution of insomnia symptoms to poorer quality of life (Bolge et al. 2009), the number of studies reporting effects of cochlear implantation on tinnitus-related difficulties with sleep is limited (Bruggemann et al. 2017; Di Nardo et al. 2007). Recent efforts to standardize the reporting of results from clinical trials of tinnitus interventions have identified sleep quality as one of a set of core outcomes that should be measured when evaluating the effects of sound-based interventions for tinnitus (Hall et al. 2019; Hall et al. 2018b). The present findings support the inclusion of sleep-related measures in evaluations of the effectiveness of cochlear implantation for the alleviation of tinnitus and in studies seeking to predict tinnitus outcomes following cochlear implantation.

Implications for Clinical Management

It is not known whether and how many CI users access healthcare services to manage their sleep difficulties and insomnia, but the present results suggest that CI users with tinnitus might benefit from the management of insomnia symptoms. Previous studies have suggested that evidence of the presence of psychological disorders, including those of anxiety and depression, among cochlear implantation candidates and CI recipients with tinnitus is sufficient to justify monitoring psychological symptoms in these patient groups and including the management of those symptoms in the routine care pathway (Andersson et al. 2009; Bruggemann et al. 2017; Kloostra et al. 2015; Olze et al. 2011). Clinically abnormal insomnia identified by the current study highlights the importance of also screening for insomnia

symptoms, both to assess their clinical impact and to inform the ongoing management of CI users with tinnitus (Asnis et al. 2018; Miguel et al. 2014).

There is robust evidence available suggesting that specific types of cognitive behavioral therapy (CBT) can be effective in treating tinnitus and insomnia (Cima et al. 2012; Geiger-Brown et al. 2015; Martinez-Devesa et al. 2010; for a review see McKenna & Daniel 2006), as well as anxiety and depression disorders (Carpenter et al. 2018; Twomey et al. 2015). Current trials suggest that CBT is an effective intervention for the management of tinnitus-related insomnia (Andersson et al. 2005; Beukes et al. 2017; Jasper et al. 2014; Marks et al. 2019; Weise et al. 2016). However, it is not clear whether CI users would be willing to undergo new therapies to treat their tinnitus-related sleep problems in addition to the therapies they may already receive to manage any adverse effects associated with their profound hearing loss. However, it is possible that a specific form of CBT could be devised for use in patients who find their tinnitus and related symptoms particularly bothersome (Andersson et al. 2009), particularly where such a therapy could alleviate more than one factor contributing to tinnitus-related handicap; e.g. clinically abnormal depression and insomnia symptoms.

The potential benefits of electrical stimulation with a CI on sleep throughout the night have been explored previously (Velluti et al. 2010). However, the present results suggest that it is difficulties falling asleep that are the main contributor to clinical insomnia in CI users with tinnitus. Therefore, a potentially simple management option might be to advise these patients to use their CI when trying to fall asleep to promote tinnitus suppression. However, two related practical aspects may require further consideration. First, nearly all of our participants (95%) reported that they do not use their CIs at night time, mainly because they were advised to take their CI off before going to sleep or were not aware that CI use might help with their sleep. The small proportion of those who used their CIs at night reported doing so occasionally and primarily in order to be able to hear during night (e.g. their children and partners, or alarms), but only in some instances to alleviate their tinnitus and

address difficulties with sleep. While these observations suggest that there may be potential benefits from night-time CI use in some patients, further research is needed to develop specific guidance for patients and clinicians on how to best support such use while avoiding discomfort or damage to the device, and to evaluate the effect of night-time use on tinnitus-related insomnia and quality of life. Second, previous studies have shown that residual inhibition of tinnitus is also possible in individual CI users (Arts et al. 2015; Chang & Zeng 2012; Osaki et al. 2005), and perhaps it could support the management of tinnitus at the point they are trying to fall asleep. However, systematic studies of residual inhibition following CI stimulation are needed to identify the patient groups in whom it would be possible to elicit reliably, the factors responsible for supporting sustained inhibition and ultimately whether it would be effective in managing the patient's tinnitus and related difficulties with sleep.

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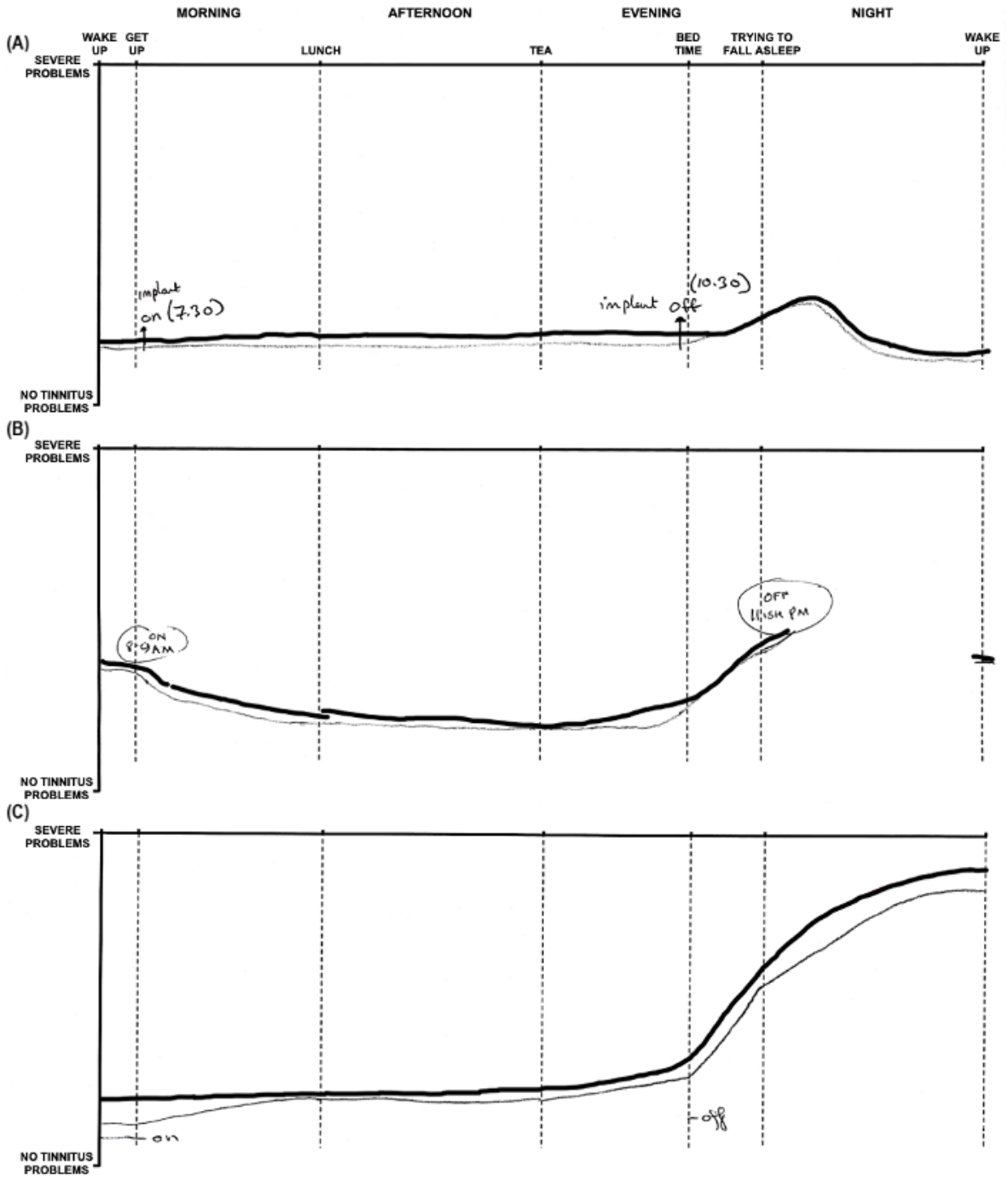
FIGURE CAPTIONS

Figure 1. Severity of tinnitus-related problems during the day reported by three adult cochlear implant users from the Nottingham clinic (A-C). Thick lines show "tinnitus problems at their worst". Tinnitus problems become more severe at night time, coinciding with switching cochlear implants off.

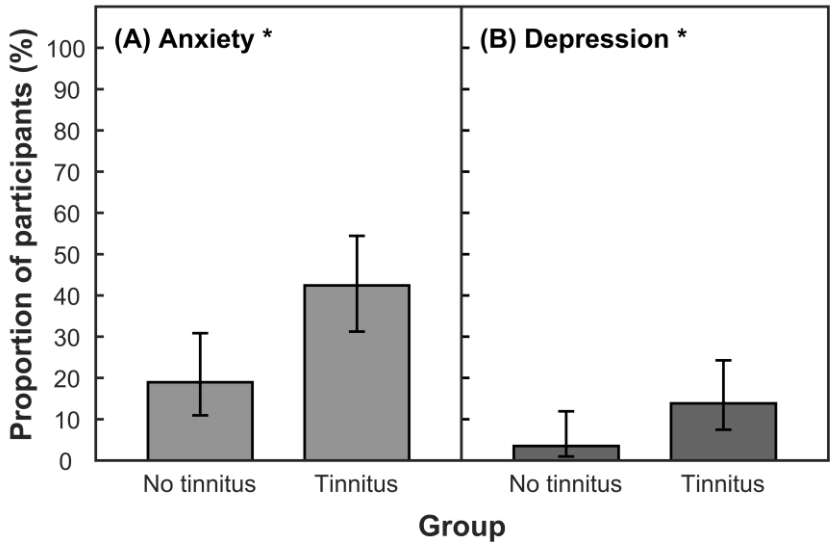
Figure 2. Proportion of clinically abnormal anxiety (A) and depression (B) symptoms on the Hospital Anxiety and Depression Scale in participants with and without tinnitus. Error bars show 95% confidence intervals for the proportions. Asterisks indicate a significant difference between the groups on the logistic regression (Table 5).

Figure 3. Proportion of self-reported sleep difficulties using the UK Biobank question (A) and clinically abnormal insomnia symptoms on the Insomnia Severity Index scores (B) in participants with and without tinnitus. Error bars show 95% confidence intervals for the proportions. Asterisks indicate a significant difference between the groups on the logistic regression (Table 5).

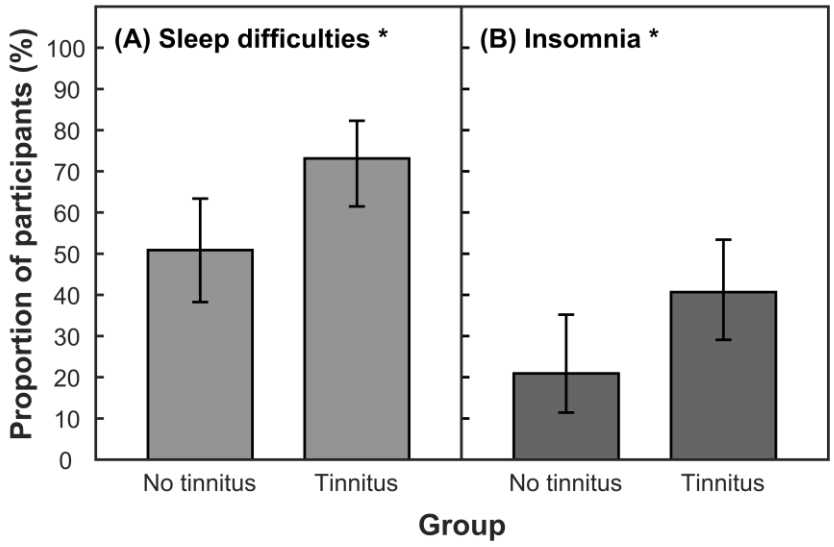
Figure 4. Schematic associations between tinnitus-related handicap and clinical anxiety, depression and insomnia reported by cochlear implant users with tinnitus. Values in bold denote significant associations in the multivariable regression model (HADS, Hospital Anxiety and Depression Scale; ISI, Insomnia Severity Index, THI, Tinnitus Handicap Inventory).


MORNING
AFTERNOON
EVENING
NIGHT
(A)
WAKE UP
GET UP
LUNCH
TEA
BED TIME
TRYING TO FALL ASLEEP
WAKE UP
SEVERE PROBLEMS
NO TINNITUS PROBLEMS
implant on (7.30)
implant off (10.30)
(B)
SEVERE PROBLEMS
NO TINNITUS PROBLEMS
on 8.9AM
OFF 11ish PM
(C)
SEVERE PROBLEMS
NO TINNITUS PROBLEMS
on
off

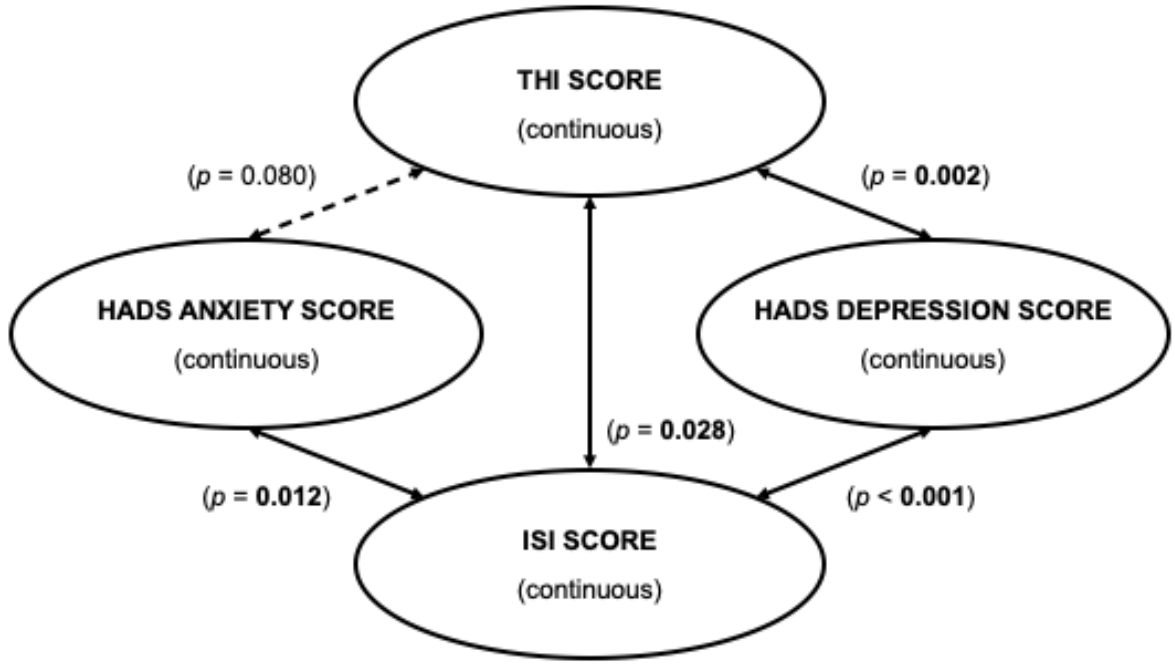
1


(A) Anxiety *
(B) Depression *
Proportion of participants (%)
100
90
80
70
60
50
40
30
20
10
0
No tinnitus
Tinnitus
No tinnitus
Tinnitus
Group

1


(A) Sleep difficulties *
(B) Insomnia *
Proportion of participants (%)
100
90
80
70
60
50
40
30
20
10
0
No tinnitus
Tinnitus
No tinnitus
Tinnitus
Group

2


THI SCORE
(continuous)
(p = 0.080)
(p = 0.002)
HADS ANXIETY SCORE
(continuous)
HADS DEPRESSION SCORE
(continuous)
(p = 0.028)
(p = 0.012)
(p < 0.001)
ISI SCORE
(continuous)

3

TABLE 1. UK Biobank questions used in the present study.

ID	Question and response options
H11	Do you get or have you had noises (such as ringing or buzzing) in your head or in one or both ears that lasts for more than five minutes at a time? a) Yes, now most or all of the time b) Yes, now a lot of the time c) Yes, now some of the time d) Yes, but not now, but have in the past e) No, never f) Do not know g) Prefer not to answer
H11A	How much do these noises worry, annoy or upset you when they are at their worst? a) Severely b) Moderately c) Slightly d) Not at all e) Do not know f) Prefer not to answer
SL2	Do you have trouble falling asleep at night or do you wake up in the middle of the night? a) Never/rarely b) Sometimes c) Usually d) Prefer not to answer

TABLE 2. Definitions of outcomes.

Outcome	Category	Questions	Response
Tinnitus presence (UK Biobank)	No	H11	Ticked (d) or (e)
	Yes		Ticked (a), (b) or (c)
Tinnitus persistence (UK Biobank)	Infrequent	H11	Ticked (c)
	Frequent		Ticked (a) or (b)
Tinnitus emotional distress (UK Biobank)	Slight	H11A	Ticked (c) or (d)
	Upsetting		Ticked (a) or (b)
Sleep difficulties (UK Biobank)	Rare		Ticked (a)
	Usual		Ticked (b) or (c)
Clinical anxiety (HADS)	Normal	Anxiety subscale	Score 0-7
	Abnormal		Score 8-21
Clinical depression (HADS)	Normal	Depression subscale	Score 0-7
	Abnormal		Score 8-21
Clinical insomnia (ISI)	Normal	1-7	Score 0-7
	Abnormal		Score 8-28

HADS, Hospital Anxiety and Depression Scale; ISI, Insomnia Severity Index

TABLE 3. Demographics of the sample.

Characteristic	No tinnitus		Tinnitus	
	N	%	N	%
All participants	60	47	67	53
Male sex	28	47	26	39
Unilateral CI users	57	95	65	97
CI make				
Cochlear Ltd.	42	72	46	70
Advanced Bionics	15	26	18	27
Med-El	1	2	2	3
Missing	*2*	—	*1*	—
Tinnitus onset				
Before CI surgery	—	—	54	84
After CI surgery, before activation	—	—	3	5
After CI surgery, after activation	—	—	7	11
Missing	—	—	*3*	—
Tinnitus handicap (THI score) *				
No (0-16)	—	—	37	59
Mild (18-36)	—	—	13	20
Moderate (38-56)	—	—	8	13
Severe (58-100)	—	—	5	8
Missing	—	—	*4*	—
	Mean	SD	Mean	SD
Age (years)	57.8	22.32	53.93	18.98
Duration of deafness (years)	15.03	16.71	13.04	14.71
Time since CI activation (years)	7.17	6.24	7.18	6.84
THI score	—	—	21.14	21.51

SD, standard deviation; THI, tinnitus handicap inventory.
Missing data were excluded when calculating percentages.
* Tinnitus handicap categories were calculated after Newman et al. (1998).

TABLE 4. Self-reported characteristics of tinnitus and sleep difficulties assessed with the UK Biobank questions, and clinical symptoms of anxiety and depression assessed with HADS, and insomnia assessed with ISI.

	No tinnitus		Tinnitus	
Characteristic	N	%	N	%
Tinnitus presence				
Past/Never	60	47	—	—
Current	—	—	67	53
Tinnitus persistence				
Infrequent	—	—	31	46
Frequent	—	—	36	54
Missing	—	—	*0*	—
Tinnitus emotional distress				
Slight	—	—	39	59
Upsetting	—	—	27	41
Missing	—	—	*1*	—
Sleep difficulties				
Rare	28	49	18	27
Usual	29	51	49	73
Missing	*3*	—	*0*	—
Clinical anxiety				
Normal	47	81	38	58
Abnormal	11	19	28	42
Missing	*2*	—	*1*	—
Clinical depression				
Normal	55	96	56	86
Abnormal	2	4	9	14
Missing	*3*	—	*2*	—
Clinical insomnia				
Normal	34	79	35	59
Abnormal	9	21	24	41
Missing	*17*	—	*8*	—

HADS, Hospital Anxiety and Depression Scale;
ISI, Insomnia Severity Index.
Missing data were excluded when calculating percentages.

TABLE 5. Results from linear and logistic regression modeling of group differences in mean scores from standard clinical diagnostic tools and proportions with clinically abnormal anxiety, depression and insomnia symptoms.

	No tinnitus			Tinnitus			Tinnitus vs No tinnitus			
Outcome score	Mean		SD	Mean		SD	*β*	95% Conf. Int.		p value
HADS anxiety	4.59		3.71	7.26		4.66	2.59	1.13 to	4.06	<0.001
HADS depression	2.61		2.76	3.83		3.22	1.40	0.34 to	2.46	0.011
ISI	4.44		5.53	7.64		6.14	3.25	0.91 to	5.60	0.008
Outcome category	%	95% Conf. Int.		%	95% Conf. Int.		OR	95% Conf. Int.		p value
Clinical anxiety (HADS)	18.97	10.93 to	30.85	42.42	31.24 to	54.44	3.50	1.49 to	8.22	0.004
Clinical depression (HADS)	3.51	0.97 to	11.92	13.85	7.46 to	24.27	6.18	1.17 to	32.82	0.032
Clinical insomnia (ISI)	20.93	11.42 to	35.21	40.68	29.09 to	53.41	2.60	1.04 to	6.45	0.040

Conf. Int., confidence interval; HADS, Hospital Anxiety and Depression Scale; ISI, Insomnia Severity Index; *β,* linear regression coefficient; OR, odds ratio; SD, standard deviation.

INSOMNIA, ANXIETY AND DEPRESSION IN ADULT COCHLEAR IMPLANT USERS WITH TINNITUS. SUPPLEMENTAL DIGITAL CONTENT

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TABLE S1. Differences between the no tinnitus and tinnitus groups on HADS items reporting anxiety symptoms.

Item	t statistic	df	p value *	95% CI			Question
HADS1	–3.48	122.24	**<0.001**	–0.74	to	–0.20	I feel tense or wound up
HADS3	–2.84	119.62	**0.005**	–0.75	to	–0.13	I get a sort of frightened feeling as if something awful is about to happen
HADS5	–1.93	121.63	0.06	–0.63	to	0.01	Worrying thoughts go through my mind
HADS7	–3.71	121.50	**<0.001**	–0.70	to	–0.21	I can sit at ease and feel relaxed
HADS9	–1.55	122.77	0.12	–0.45	to	0.06	I get a sort of frightened feeling like 'butterflies' in the stomach
HADS11	–3.24	122.97	**0.002**	–0.76	to	–0.18	I feel restless as if I have to be on the move
HADS13	–2.27	122.93	0.025	–0.60	to	–0.04	I get sudden feelings of panic

Conf. Int., confidence interval; df, degrees of freedom; HADS, Hospital Anxiety and Depression Scale
* p values in bold were significant after correcting for multiple comparisons using the Holm-Bonferroni method at 0.05 level

TABLE S2. Differences between the no tinnitus and tinnitus groups on HADS items reporting depression symptoms.

Item	t statistic	df	p value *	95% Conf. Int.			Question
HADS2	–2.84	122.59	**0.005**	–0.53	to	–0.09	I still enjoy the things I used to enjoy
HADS4	–0.64	122.98	0.52	–0.20	to	0.10	I can laugh and see the funny side of things
HADS6	–1.91	120.39	0.06	–0.38	to	0.01	I feel cheerful
HADS8	–1.99	118.79	0.049	–0.56	to	0.00	I feel as if I am slowed down
HADS10	–0.73	122.58	0.46	–0.34	to	0.15	I have lost interest in my appearance
HADS12	–1.44	122.95	0.15	–0.39	to	0.06	I look forward with enjoyment to things
HADS14	–1.83	117.51	0.07	–0.38	to	0.01	I can enjoy a good book or radio or TV programme

Conf. Int., confidence interval; df, degrees of freedom; HADS, Hospital Anxiety and Depression Scale
* p values in bold were significant after correcting for multiple comparisons using the Holm-Bonferroni method at 0.05 level

TABLE S3. Differences between the no tinnitus and tinnitus groups on ISI items.

Item	t statistic	df	p value *	95% CI			Question
ISI1	–2.55	108.96	0.012	–0.87	to	–0.11	Difficulty falling asleep
ISI2	–1.00	99.46	0.32	–0.64	to	0.21	Difficulty staying asleep
ISI3	–1.68	101.54	0.10	–0.84	to	0.07	Problem waking up too early
ISI4	–2.03	113.30	0.045	–0.81	to	–0.01	How satisfied/dissatisfied are you with your current sleep pattern?
ISI5	–2.28	121.90	0.024	–0.80	to	–0.06	To what extent do you consider currently your sleep problem to interfere with your daily functioning (e.g. daytime fatigue, ability to function at work/daily chores, concentration, memory, mood, etc.)?
ISI6	–2.19	120.86	0.031	–0.67	to	–0.03	How noticeable to others do you think your sleep problem is in terms of impairing the quality of your life?
ISI7	–1.18	119.66	0.24	–0.52	to	0.13	How worried/distressed are you about your current sleep problem?

CI, confidence interval; df, degrees of freedom; ISI, Insomnia Severity Index

* p values in bold were significant after correcting for multiple comparisons using the Holm-Bonferroni method at 0.05 level