Title: A systematic review and meta-analysis of extended high-frequency hearing thresholds in tinnitus with a normal audiogram

Running title: EHF hearing thresholds in tinnitus with a normal audiogram

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ABSTRACT

Objectives: Current evidence supports the growing application of extended high-frequency (EHF: 9-20 kHz) audiometry in hearing research, which likely results from the high vulnerability of this frequency region to damage induced by known auditory risk factors. The present systematic review and meta-analysis were performed to investigate whether adults with a normal audiogram and tinnitus show increased EHF hearing thresholds relative to control peers.

Design: A comprehensive search was undertaken on electronic databases consisting of PubMed, ScienceDirect, Wiley, and Google Scholar using combined keywords: “tinnitus”, “extended high frequency”, “normal audiogram”, and “hidden hearing loss”.

Results: From 261 papers found by searching databases, 9 studies met the inclusion criteria for the meta-analysis. A significant difference was observed between tinnitus and control groups in the effect size analysis of hearing thresholds at 10, 12.5, 14, 16, and 18 kHz ($p \leq 0.001$), and the I-square heterogeneity analysis was below 50% in all studies ($p \geq 0.131$). Visual inspection by the Funnel plot and Egger’s regression test ($p \geq 0.211$) also exhibited no publication bias in the meta-analyses.

Conclusions: Our findings are in support of the idea that in most cases, tinnitus is associated with some degree of cochlear mechanical dysfunction, which may not be detected by conventional audiometry alone. This finding underscores the significance of EHF audiometry in clinical practice, which may help both early identification of individuals susceptible to developing tinnitus and reduce the number of new cases through preventive counseling programs.

Keywords: Tinnitus; Extended high frequencies; Normal audiogram; Cochlear dysfunction; Hidden hearing loss

INTRODUCTION

Tinnitus is defined as the conscious awareness of sound for which there is no identifiable corresponding external acoustic source (De Ridder et al. 2021; Shargorodsky et al. 2010). Tinnitus has a prevalence of 10-15% in the adult population and its incidence rate (Martinez et al. 2015) and prevalence show an age-related increase up to approximately 70 years (Jafari et al. 2019). Whereas hearing loss, especially at higher audiometric frequencies, is a known risk factor for tinnitus (Jafari et al. 2020), approximately 7.4-42.8% of adults with tinnitus demonstrate hearing thresholds within normal limits in conventional pure-tone audiometry (PTA) (Barnea et al. 1990; Henry et al. 2008; Jastreboff et al. 2003; Martines et al. 2015; Sanchez et al. 2005; Savastano 2008). It also has been found that more than 70% of cases with tinnitus and a normal audiogram (TNA) show elevated hearing thresholds at one or more extended high frequency (EHF) relative to both audiometric norms, e.g., >15 dB HL (Vielsmeier et al. 2015) or >25 dB HL (Kim et al. 2011), and non-tinnitus control peers (Song et al. 2021). EHFs are characterized as hearing thresholds at frequencies above 8 kHz, which are not considered in standard audiometry (i.e., 0.25-8 kHz) (Hunter et al. 2020). Existing evidence supports the contribution of this frequency region to auditory processing and speech perception (Hunter et al. 2020; Motlagh Zadeh et al. 2019). For instance, it has been found that EHFs facilitate sound localization (Heffner et al. 2008). A link between increased EHF hearing thresholds and difficulties with speech perception in noise (Badri et al. 2011; Cameron et al. 2007; Guest et al. 2018; King et al. 1992; Shaw et al. 1996; Yeend et al. 2019), as well as self-reports of listening difficulties (Gatehouse et al. 2004) also have been reported. In addition, EHF hearing loss is highly age-dependent and becomes clinically significant in the fourth age decade (Lee et al. 2012; Polinga et al. 2014).

Mechanisms associated with SNHL have been linked to the presence of tinnitus; however, fewer mechanistic hypotheses support the presence of tinnitus in individuals with normal hearing. Findings of animal studies suggest that synapses between hair cells and cochlear nerve terminals in the high-frequency region of the cochlea, which are, on average, most susceptible to degeneration with the normal aging process, noise exposure, or other auditory risks, are among the most vulnerable parts of the inner ear (Kujawa et al. 2009; Liberman et al. 2016). Although this neural degeneration, which has been referred to as "cochlear synaptopathy" (CS), may not affect hearing thresholds in the standard audiometric frequency range (≤8 kHz), it has been suggested that it might contribute to difficulties understanding speech in adverse listening conditions as well as the generation of tinnitus and/or hyperacusis (Hickox et al. 2014; Knipper et al. 2013; Liberman et al. 2016; Schaette et al. 2011). Likewise, several studies support the role of CS in attenuating inhibitory processes and increased central gain related to tinnitus in normal hearing (Eggermont et al. 2015), but the evidence and the relevance of this type of hearing damage are not supported by some contradictory findings (Guest, Munro and Plack 2017; Marmel et al. 2020; Shim et al. 2017). In addition, the relation of CS to the EHF hearing loss is not well-understood. It is unknown whether or not CS and EHF hearing loss contribute to separate explanations of TNA or are linked in some way that my explain TNA. Indeed, it has been suggested that EHF might be a biomarker of CS (Guest et al. 2018; Liberman et al. 2016). Hunter et al. (2020) also suggested that hidden hearing loss (HHL) might be used to refer to perceptual deficits in cases with normal audiograms. In EHF hearing loss, HHL points to reduced hearing thresholds in EHFs despite normal hearing sensitivity in the standard frequency range (i.e., ≤8 kHz).

EHFs are highly susceptible to auditory detriments. Current evidence shows the growing application of EHF audiometry in different clinical populations such as early detection of hearing loss in cases with ototoxicity or noise exposure, and screening or monitoring of individuals vulnerable to tinnitus with normal audiograms (Hunter et al. 2020). During the past decade, several studies have used EHF audiometry on individuals with TNA to investigate the likelihood of increased SNHL in EHFs relative to the control group. This paper reports a systematic review and meta-analysis of these studies to characterize whether the pooled data are in support of greater EHF hearing loss in adults with TNA compared to control peers. This finding may further emphasize the importance of including EHF audiometry in daily clinical practice, as well as to support intervention programs such as EHF stimulation from hearing aids and sound-enrichment devices. In addition, it may have a preventive value through early diagnosis of EHF hearing loss and counseling to protect the auditory system against known auditory detriments.

MATERIALS AND METHODS

Systematic Review: Search Strategy

The present systematic review was conducted based on the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) (Moher et al. 2009). A comprehensive search was performed on electronic databases including PubMed, ScienceDirect, Wiley, and Google Scholar in Apr 2020, updated in Jun and Sep 2021 (Figure 1), using combined keywords: “tinnitus AND extended high frequency”, “tinnitus AND extended high frequency AND normal audiogram”, “tinnitus AND hidden hearing loss”, and “tinnitus AND hidden hearing loss AND normal audiogram”.

Inclusion Criteria: The criteria for inclusion in the systematic review were defined in terms of participants, intervention(s), comparators, outcomes, and study designs (PICOS) (Morgan et al. 2018) as follows: (P) studies in the English language on adults with subjective tinnitus and a clinically normal audiogram (i.e., hearing thresholds ≤25 dB HL at octave-band frequencies from

0.25 to 8 kHz) (Mujdeci et al. 2019; Omidvar et al. 2016; Song et al. 2021); (I) no intervention; (C) the age-matched adults with a clinically normal audiogram, without tinnitus; (O) hearing thresholds at EHFs; (S) e.g., cross-sectional, cohort, or case-control studies.

Exclusion Criteria: Reviews, books, case reports, case series, letters, editorials, and notes/commentaries were excluded.

Duplicates were eliminated using Endnote software (Thomson Reuters, Philadelphia, Pennsylvania, USA, version X7). The final papers were included through a three-stage process: title screening, abstract screening, and full-text screening. In each section, the papers that did not meet the inclusion criteria were excluded. In the cases of uncertainty, first the abstracts and then the full texts were screened. All three stages were independently carried out by two reviewers. Overall, there was a complete agreement between the reviewers on included papers (i.e., publications reporting EHF hearing thresholds in individuals with TNA, including a control group).

Quality Assessment

The Crowe Critical Appraisal Tool (CCAT) was used for quality measurement (Crowe et al. 2012). The CCAT is one of the few instruments that has undergone both reliability and validity evaluations and is applied to appraise different research designs (Crowe et al. 2011; Crowe et al. 2012). In each paper, eight aspects including preliminaries, introduction, design, sampling, data collection, ethical issues, results/findings, and discussion were evaluated using a 6-point scale (from 0 to 5 for each category) with a total potential score of 40 (Jafari et al. 2021).

Meta-Analysis

The meta-analysis was carried out using Comprehensive Meta-Analysis (CMA) Version 3.0 (Biostat, Englewood, New Jersey, USA). The analysis of effect size using standard mean differences was performed to determine whether EHF hearing thresholds are significantly increased in adults with TNA compared to the control group. The I-square (I^2) test was used to assess the influence of heterogeneity among studies on the meta-analysis output (Omidvar et al. 2019). I^2 statistics of 0, 25, 50, and 75% corresponded to no, low, medium, and high heterogeneity, respectively. According to the Cochrane review guidelines, a random-effect model should be used when $I^2 \geq 50\%$ (high heterogeneity). Otherwise, a fixed-effect model is used (Higgins et al. 2003). "In practice, I^2 values for each of the meta-analyses were $\leq 50\%$, prompting the use of fixed-effects models only." Forest plots also were used to present the pooled estimates of effect size by standard mean difference and 95% CIs. A *p*-value of less than 0.05 was considered as the threshold for statistical significance. Publication bias was visually assessed by funnel plots as well as Egger's regression test.

RESULTS

Systematic Review

The database search yielded 261 papers, including 202 duplicate records that were removed (Figure 1). After screening titles, 31 more records were eliminated, i.e., non-English papers (n=6), reviews (n=7), case reports/case series (n=5), editorials/notes/commentaries (n=2), books (n=3), and publications out-of-scope of the study (n=8). Out-of-scope papers refer to publications that did not meet the inclusion criteria. This initial screening resulted in a set of 28 papers. Subsequently, 15 more papers were eliminated during the screening of abstracts (i.e., reviews= 1, case reports/case series= 14). Among 13 studies extracted for the full-text review, four papers were removed (i.e., three studies with no control group (Abu-Eta et al. 2020; Al-Swiahb et al. 2016; Vielsmeier et al. 2015) and one study with a lack of necessary statistics (Campbell et al. 2019)), leaving nine studies appropriate for meta-analysis (Table 1). The average age of participants in the studies was between 28.0 and 41.2 years. From each paper (Elmoazen et al. 2018; Guest, Munro and Plack 2017; Mujdeci and Dere 2019; Omidvar et al. 2016; Sanches et al. 2010; Shim et al. 2017; Song et al. 2021; Yildirim et al. 2010), EHF hearing thresholds (i.e., 10, 12.5, 14, 16, and 18 kHz), sample size, and standard deviations (SDs) were collected for meta-analysis. *P*-values were only used for one paper because the SDs were not reported (Fabijańska et al. 2012). The reference lists for the selected publications were also hand-searched for any additional related publications. No further related article, however, was found. The bias resulting from only searching databases in the English language (language bias) is acknowledged.

The strength of the Evidence: The included studies were assessed for methodological quality using CCAT (Crowe and Sheppard 2011; Crowe et al. 2012). Table 2 shows the studies' scores as a total score and a percentage. The quality of the studies was rated between 50.0 to 80.0% (mean: 66.66 %). Among the nine studies included, the study design was case-control (n=4) (Elmoazen et al. 2018; Guest, Munro and Plack 2017; Mujdeci and Dere 2019; Song et al. 2021) or cross-sectional (n=5) (Fabijańska et al. 2012; Omidvar et al. 2016; Sanches et al. 2010; Shim et al. 2009; Yildirim et al. 2010). The studies were deficient from several aspects such as sampling (e.g., low sample size and/or imperfect inclusion/exclusion criteria), not reporting tinnitus duration, and poor or not reporting ethical considerations (i.e., ethical approval).

Meta-Analysis

Figure 2 illustrates the weighted mean of hearing thresholds in conventional audiometry and EHFs for the tinnitus and control groups in the included studies. Figures 3 to 7 illustrate the results of meta-analyses in five EHFs. In each Figure, section A represents the details of statistical analysis consisting of standard difference in mean, standard error, variance, lower and upper CI limits, and Z- and *p*-values in each included study as well as in total. Section A also exhibits a

Forest plot. In the Forest plot, each horizontal line shows a separate study included in the meta-analysis. The result of each study consists of two components: 1) a black box reflecting both a point estimate of the study result and the study sample size, and 2) a horizontal line representing the 95% CIs of the study result. A diamond in each Forest plot indicates the overall point estimate from the meta-analysis. The center of the diamond points to the pooled point estimate, and its horizontal tips display the 95% CI (Jafari et al. 2021). Due to an $I^2 \leq 50\%$ in all EHFs, a fixed-effect model was applied in all meta-analyses. The pooled estimate of hearing thresholds in all EHFs was significantly increased in the tinnitus group compared with the control group. Section B in Figures 3 to 7 exhibits the analysis of publication bias. Using visual inspection by the Funnel plot as well as Egger's regression test, no publication bias was observed in the meta-analyses. For instance, in Figure 3A at 10 kHz, a significant difference is observed between tinnitus (mean= 29.54 dB HL) and control (mean= 22.62 dB HL) groups (Z= 7.461, *p*= 0.000, CI: 0.476-0.816), and the I^2 test demonstrates no heterogeneity within studies (I^2= 0.000%, *p*= 0.816). Figure 3B also displays the Funnel plot delineated by a standard difference in means in the horizontal axis and a standard error in the vertical axis. As the plot shows, all studies are inside the Funnel plot and the result of Egger's regression test (t= 1.308, *p*(1-tailed)= 0.115) indicates no publication bias in the meta-analysis.

DISCUSSION

In this study, we aimed to investigate whether EHF hearing thresholds are significantly increased in adults with TNA compared to control peers. After a systematic review of related papers, nine studies were included for meta-analysis. According to our findings: 1) EHF hearing thresholds are significantly elevated in adults with TNA relative to the control group; 2) this finding is supported by a heterogeneity score of less than 50% in all EHFs, which shows the consistency of findings in the included studies (Higgins et al. 2003); and 3) the findings may have a predictive value to aid early identification of those more susceptible to developing tinnitus, as well as a counseling value to protect vulnerable ears against risk factors for hearing loss and tinnitus, (e.g., noise exposure and ototoxicity), which can accelerate the onset and progress of tinnitus.

Chronic tinnitus is frequently accompanied by hearing loss as measured using standard clinical audiometry (≤8 kHz) (Han et al. 2009). The findings of some studies suggest a relationship between tinnitus pitch and audiogram edge frequency (i.e., the frequency at which the maximum slope occurs) (Henry et al. 1999; Jain et al. 2021; König et al. 2006; Sereda et al. 2015), which they may not be associated in cases with normal audiograms (Barnea et al. 1990; Jastreboff and Jastreboff 2003; Sanchez et al. 2005). Our meta-analysis findings, however, are in support of a link between hearing loss and tinnitus and indicate that, in TNA, hearing loss may begin from EHFs, which is not detectable by limiting pure-tone audiometry to frequencies below 8 kHz. In the Song et al. (2021) study (Song et al. 2021), the edge frequency was significantly lower in cases with tinnitus compared with the control group (10.40 kHz vs. 12.30 kHz). An interpretation of this finding is that, compared with controls, those with TNA initially exhibit EHF hearing loss at a lower frequency and that this then extends to high frequencies within the standard audiometric range (i.e., ≤8 kHz) due to the co-impact of age and other risk factors. In addition, findings of recent studies using fine frequency resolution (e.g., 1/24 octave step) audiometry, which is also known as high definition audiometry (Zhao et al. 2002; Zhao et al. 2014) or precision PTA (P-PTA) (Xiong et al. 2019), point to the existence of HHL in standard audiometry, as standard audiometry only samples octave or inter-octaves frequencies (Lefeuvre et al. 2019; Xiong et al. 2019). For instance, in the Xiong et al. (2019) study (Xiong et al. 2019), 49% of individuals with

TNA showed sharply notched hearing loss in non-audiometric frequencies, and most of the notches were at their tinnitus frequencies. This HHL detected by P-PTA may be driven by damage to hair cells or cochlear synaptopathy, which should be further investigated in the future.

In terms of tinnitus-related mechanisms, tinnitus represents a symptom of diverse pathologies, in which the contribution of both the peripheral and central auditory nervous system is expected, and multiple mechanisms also may be implicated in a single individual (Hazell et al. 1990; Jastreboff 1990). According to the "discordant dysfunction hypothesis" (Jastreboff 1990), the dysfunction of outer hair cells (OHC) prior to inner hair cells (IHC) may lead to unbalanced activity transmitted by type I and type II auditory nerve fibers and stimulate tinnitus-related neuronal activity in the dorsal cochlear nucleus (Jastreboff and Jastreboff 2003). It also has been proposed that OHCs control the sensitivity of IHCs by setting an operating point on the IHCs' transfer characteristic to a value (e.g., resting-state neural activity) that the brain normally interprets as absence of sound (LePage 1995). Hence, the loss of motility in OHCs might impact this ability and cause a 'phantom' sound from this normally inaudible neural activity, which is perceived as tinnitus (D. M. Baguley 2002). Patuzzi (2002) also suggested that OHC dysfunction may contribute to the excessive release of glutamate neurotransmitters from IHCs and the onset of tinnitus (Patuzzi 2002). The "predictive coding model" is a new framework comprising peripheral and/or central subcortical sources of spontaneous sensory activity and their hierarchical processing in a predictive coding structure, in which perception is largely modulated by precision and higher predictions (Kiang et al. 1974). Given this model, spontaneous activity in the subcortical auditory pathway can be considered as the potential source of tinnitus or "tinnitus precursor". If there is a sufficient rise in precision, which is defined as the degree of neural representation, such as synaptic gain, then the spontaneous activity is perceived as tinnitus. Thus, tinnitus is an inference about the cause of spontaneous activity in the subcortical auditory system with an excess of precision, and this model may explain both bottom-up (i.e., reduced auditory inputs) and top-down (i.e., failures to attenuate sensory precision) factors involved in tinnitus (Hullfish et al. 2019). Overall, the findings of this meta-analysis are consistent with the idea that, in most cases, the tinnitus onset is linked to some degree of threshold elevation, which may not be detected by standard audiometry alone (Cima et al. 2019). However, it should be noted that, whereas cochlear abnormalities may contribute to the initial source of tinnitus (Terao et al. 2011), subsequent neural plasticity such as changes in the level of spontaneous neural activity, modifications in the temporal pattern of neural activity, and the reorganization of tonotopic maps are more likely to be involved in developing chronic bothersome tinnitus (Adjamian et al. 2009; D. Baguley et al. 2013; Jafari et al. 2020).

In two studies (Bramhall et al. 2018; Schaette and McAlpine 2011), it was found that individuals with TNA show a significant decrease in the wave I amplitude (generated by primary auditory nerve fibers) in the auditory brainstem response (ABR) test. It has been proposed that the reduced amplitude of ABR wave I is linked to deafferentation of auditory nerve fibers following temporary threshold shift in mice (Kujawa and Liberman 2009), or behavioral evidence of tinnitus and permanent hearing loss in rats (Bauer et al. 2007). According to this model, reduced wave I amplitude might be an indicator of damage in the synapses between hair cells and auditory nerve fibers without loss of hair cells (i.e., CS). This physiological change may be considered as evidence of HHL and contribute to tinnitus perception (Omidvar et al. 2018; Schaette and McAlpine 2011). There are, however, discrepancies among human studies, in which recent findings do not support the reduction of wave I amplitude in TNA (Guest, Munro, Prendergast, et al. 2017; Shim et al. 2017), irrespective of matched (Guest, Munro, Prendergast, et al. 2017) or unmatched (Guest, Munro and Plack 2017) EHF hearing thresholds between tinnitus and control groups. These studies support the idea that the ABR is an indirect measure of CS and animal findings may not reflect the same involved mechanisms in humans.

In the Vielsmeier et al. (2015) (Vielsmeier et al. 2015) study on adults with left, right, or bilateral TNA, those with left tinnitus showed higher EHF hearing loss in the left ear, and those with right or bilateral tinnitus had higher EHF hearing loss in the right ear. The correspondence of tinnitus side with the degree of EHF hearing loss supports the role of cochlear damage in tinnitus generation and underscores the application of EHF audiometry in tinnitus diagnosis and follow-up. In cases with bilateral tinnitus, increased EHF hearing loss in the right ear also may suggest the involvement of different mechanisms in unilateral and bilateral tinnitus, which should be replicated and further examined in future studies. A study by Kim et al. (2011) (Kim et al. 2011) also showed reduced otoacoustic emission (OAE) amplitude in tinnitus cases with EHF hearing loss compared to those with normal hearing in both standard and EHF hearing thresholds, which is another evidence for cochlear damage in TNA.

Among included studies, the mean tinnitus pitch obtained by the frequency matching test was reported in three papers consisting of 7.63 ± 3.2 kHz in the Song et al. (2021) study, 3.9 ± 2.66 kHz in the Mujdeci et al. (2019) study, and 3.13 ± 2.04 kHz in the Elmoazen et al. (2018) study (Table 1). Tinnitus pitch also was reported above 8 kHz in 68.5% of participants in the Fabijańska et al. (2012) study. The relationship between tinnitus pitch and maximum hearing loss in behavioral audiometry is of interest to researchers in the area of elaborating hypotheses underlying tinnitus perception. For instance, whereas the tonotopic reorganization model suggests that auditory cortical neurons with characteristic frequencies within the deprived hearing region adopt the tuning properties of their less-affected frequency neighbors (Eggermont et al. 2004), the neural synchrony model posits that tinnitus is associated with increased neuronal synchrony in the hearing loss region (Noreña 2011), which enhances the likelihood of the tinnitus pitch falling within the hearing loss region (Norena et al. 2002; Schecklmann et al. 2012; Sereda et al. 2011). In the Song et al. (2021) study on TNA, no relationship, however, was found between the tinnitus pitch and the maximum EHF hearing loss. Overall, the results of these four studies (Elmoazen et al. 2018; Fabijańska et al. 2012; Mujdeci and Dere 2019; Song et al. 2021) show a wide range for tinnitus pitch in TNA, including both standard and EHF hearing regions, which is not necessarily in support of a specific hypothesis linked to tinnitus perception. To make a stronger conclusion, further studies on TNA using psychoacoustic tinnitus assessments are necessary.

The studies included in this meta-analysis were not exactly the same in terms of EHFs chosen for hearing assessment, which is likely driven by the lack of a standard protocol for EHF audiometry in clinical research. Some of the studies also did not provide further information on tinnitus duration, tinnitus-related psychometric evaluations (i.e., tinnitus pitch and loudness matching), and tinnitus psychological impacts (i.e., using questionnaires such as tinnitus handicap inventory or tinnitus severity index), which could allow us to perform more in-depth meta-analyses. Future studies are suggested to investigate the occurrence frequency of EHF hearing loss in individuals with a normal audiogram, with and without tinnitus. In addition, longitudinal cohort studies can help to both provide age-appropriate norms for EHF hearing thresholds (i.e., 9, 10, 11.2, 12.5, 14, 16, 18, and 20 kHz) and understand the contribution of age-related EHF hearing loss to higher susceptibility to develop tinnitus.

Conclusions

The current systematic review and meta-analysis indicate a significant increase in EHF hearing thresholds in adults with TNA relative to control peers. Given the consistency of findings in the included studies, it can be concluded that in those with a normal audiogram, EHF hearing loss could be an audiological marker of higher susceptibility to develop tinnitus. This result may also have predictive value in clinical practice that may help to both aid early identification of individuals who are more vulnerable to experience tinnitus and decrease the number of new cases through preventive counseling programs. Future studies are proposed to 1) determine the prevalence and severity of hearing loss in both EHFs and P-PTA in individuals with TNA compared to control peers, 2) provide further information about patients' hearing history and tinnitus characteristics (e.g., tinnitus psychoacoustic measures, tinnitus duration, and tinnitus-related handicap), 3) report measures of cochlear function and auditory nerve fibers, i.e., otoacoustic emissions (OAE) and auditory brainstem response (ABR), 4) investigate the link between EHF/P-PTA hearing thresholds and other measures (i.e., tinnitus characteristics and OAE/ABR results), and 5) examine the impact of therapeutic interventions on alleviating tinnitus.

Conflict of interest: The authors disclose no competing interests.

Acknowledgments: We thank Dr. Jos J. Eggermont for his comments on an earlier version of the paper.

Funding: The present paper was supported by Canadian Institutes of Health Research (CIHR) Grant# 390930, Natural Sciences and Engineering Research Council of Canada (NSERC) Discovery Grant #40352, and Alberta Innovates (CAIP Chair) Grant #43568. This study was part of a postdoctoral fellowship to ZJ in the Canadian Center for Behavioral Neuroscience (CCBN) at the University of Lethbridge. DB is supported by the UK National Institute for Health Research (NIHR) but his views herein are his own and do not represent those of NIHR nor the UK Department of Health and Social Care.

Author contributions: Z.J., conceptualization, design, writing the original draft, review, and editing; D.B., and B.E.K., review and editing; M.H.M., funding acquisition, review, and editing.

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Figures

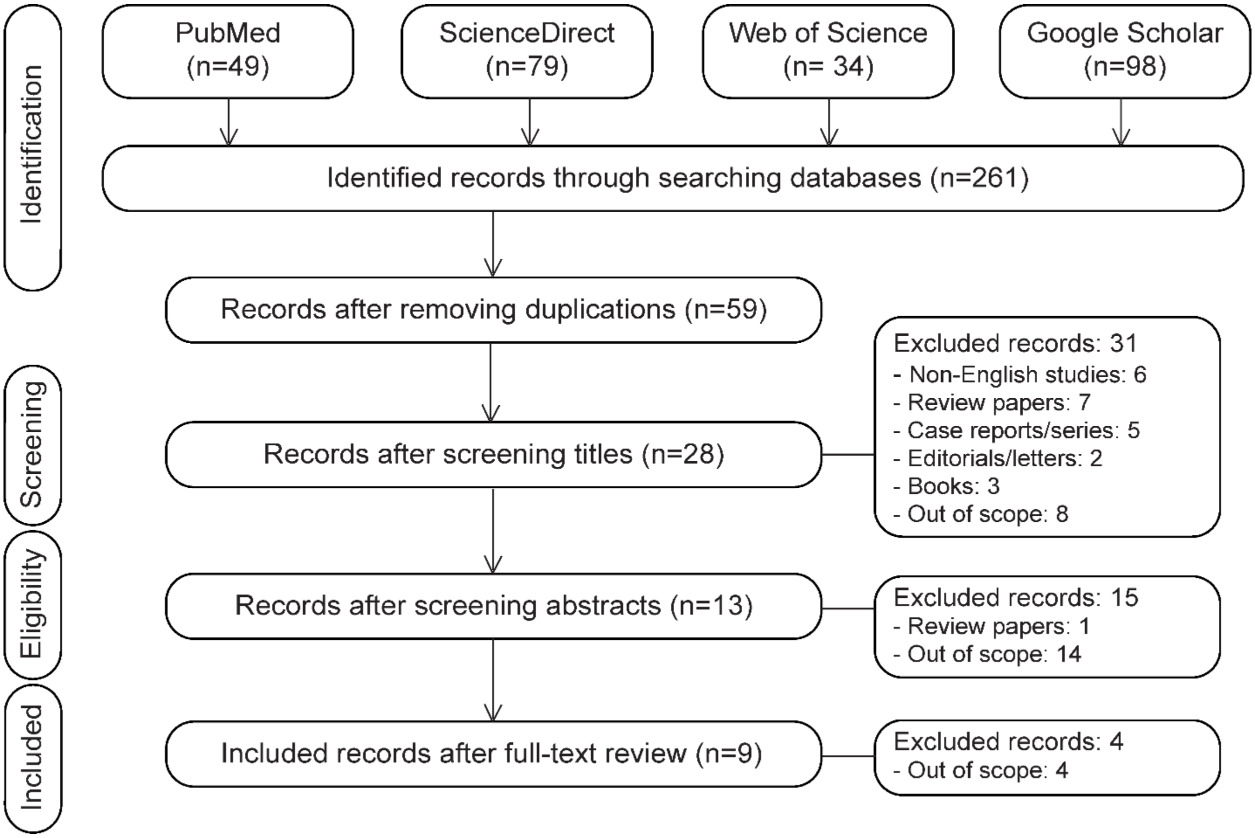


Fig 1. PRISMA flow diagram demonstrating the summary of literature search and screening process. The excluded records, consisting of out-of-scope publications, were those that did not meet the inclusion criteria based on PICOS. PICOS, capital letters represent participants, intervention(s), comparators, outcomes, and study designs, respectively; PRISMA, preferred reporting items for systematic reviews and meta-analyses.

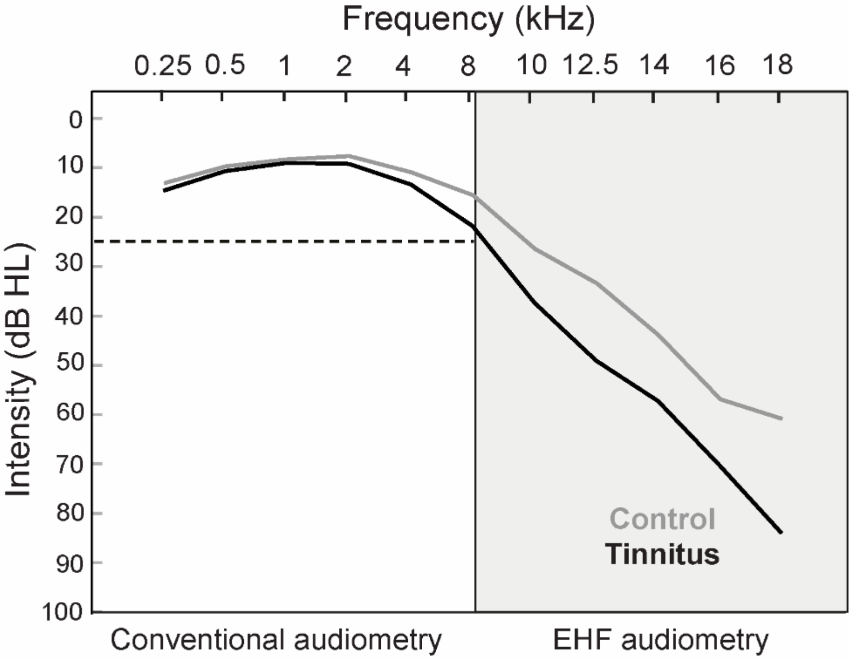
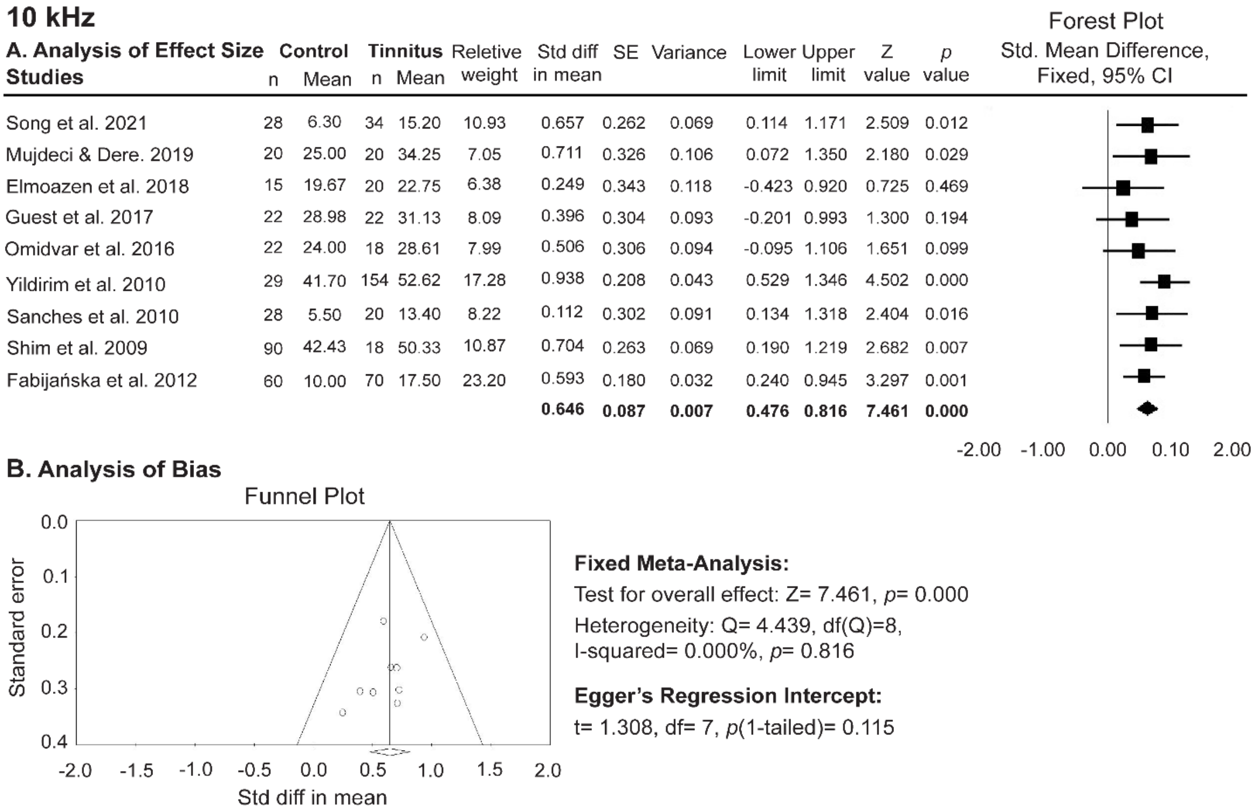


Fig 2. The weighted mean of hearing thresholds in conventional audiometry (≤ 8kHz) and extended high-frequency audiometry (≥ 8kHz) in the studies included in the meta-analysis. The area above the dash-line represents hearing thresholds within normal limits in adults. EHF: extended high-frequency.



10 kHz

A. Analysis of Effect Size

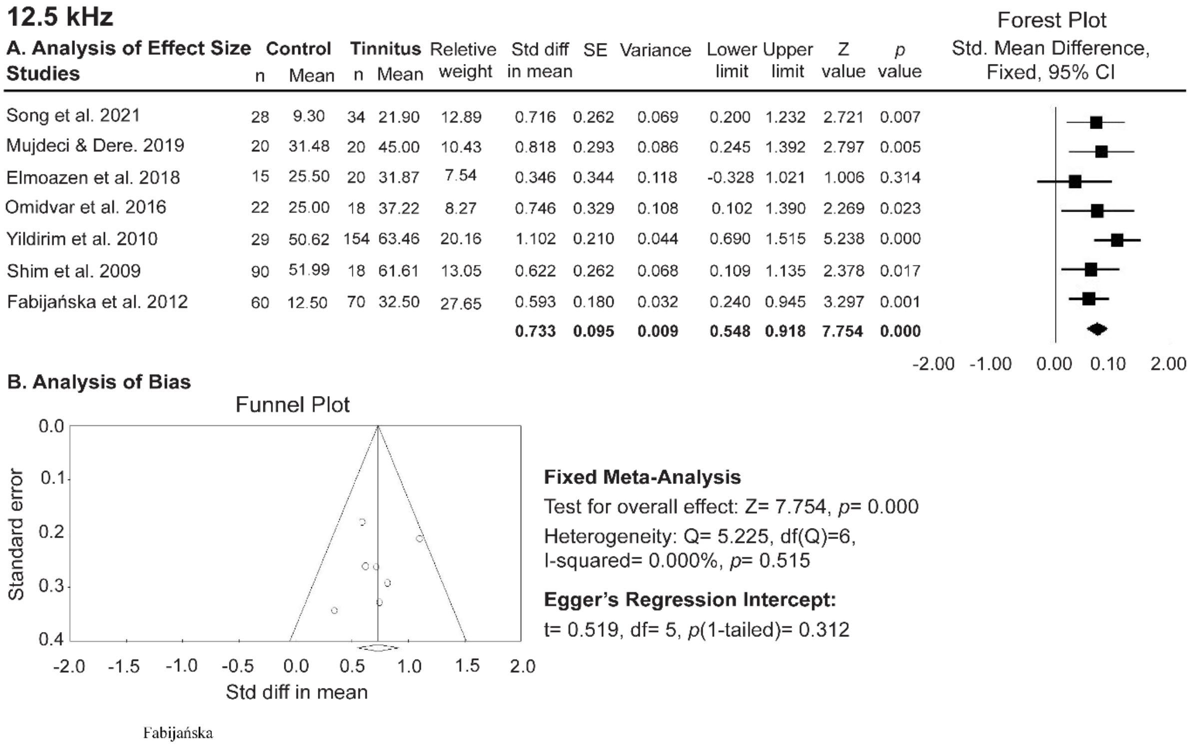
Studies	Control n	Control Mean	Tinnitus n	Tinnitus Mean	Reletive weight	Std diff in mean	SE	Variance	Lower limit	Upper limit	Z value	*p* value
Song et al. 2021	28	6.30	34	15.20	10.93	0.657	0.262	0.069	0.114	1.171	2.509	0.012
Mujdeci & Dere. 2019	20	25.00	20	34.25	7.05	0.711	0.326	0.106	0.072	1.350	2.180	0.029
Elmoazen et al. 2018	15	19.67	20	22.75	6.38	0.249	0.343	0.118	-0.423	0.920	0.725	0.469
Guest et al. 2017	22	28.98	22	31.13	8.09	0.396	0.304	0.093	-0.201	0.993	1.300	0.194
Omidvar et al. 2016	22	24.00	18	28.61	7.99	0.506	0.306	0.094	-0.095	1.106	1.651	0.099
Yildirim et al. 2010	29	41.70	154	52.62	17.28	0.938	0.208	0.043	0.529	1.346	4.502	0.000
Sanches et al. 2010	28	5.50	20	13.40	8.22	0.112	0.302	0.091	0.134	1.318	2.404	0.016
Shim et al. 2009	90	42.43	18	50.33	10.87	0.704	0.263	0.069	0.190	1.219	2.682	0.007
Fabijańska et al. 2012	60	10.00	70	17.50	23.20	0.593	0.180	0.032	0.240	0.945	3.297	0.001
						0.646	**0.087**	**0.007**	**0.476**	**0.816**	**7.461**	**0.000**

B. Analysis of Bias

Fixed Meta-Analysis:
Test for overall effect: Z= 7.461, *p*= 0.000
Heterogeneity: Q= 4.439, df(Q)=8,
I-squared= 0.000%, *p*= 0.816

Egger's Regression Intercept:
t= 1.308, df= 7, *p*(1-tailed)= 0.115

Figure 3. The meta-analysis results on 9 studies at 10 kHz. A) Analysis of effect size: a significant difference was observed between the tinnitus and control groups (Z= 7.461, *p*= 0.000), and no heterogeneity was observed within the studies (I^2= 0.000%, *p*= 0.816). B) Analysis of bias: no publication bias was found in the meta-analysis (t= 1.308, *p*= 0.115). CI: confidence interval.



12.5 kHz

A. Analysis of Effect Size

Studies	Control n	Control Mean	Tinnitus n	Tinnitus Mean	Reletive weight	Std diff in mean	SE	Variance	Lower limit	Upper limit	Z value	p value
Song et al. 2021	28	9.30	34	21.90	12.89	0.716	0.262	0.069	0.200	1.232	2.721	0.007
Mujdeci & Dere. 2019	20	31.48	20	45.00	10.43	0.818	0.293	0.086	0.245	1.392	2.797	0.005
Elmoazen et al. 2018	15	25.50	20	31.87	7.54	0.346	0.344	0.118	-0.328	1.021	1.006	0.314
Omidvar et al. 2016	22	25.00	18	37.22	8.27	0.746	0.329	0.108	0.102	1.390	2.269	0.023
Yildirim et al. 2010	29	50.62	154	63.46	20.16	1.102	0.210	0.044	0.690	1.515	5.238	0.000
Shim et al. 2009	90	51.99	18	61.61	13.05	0.622	0.262	0.068	0.109	1.135	2.378	0.017
Fabijańska et al. 2012	60	12.50	70	32.50	27.65	0.593	0.180	0.032	0.240	0.945	3.297	0.001
						0.733	**0.095**	**0.009**	**0.548**	**0.918**	**7.754**	**0.000**

Fixed Meta-Analysis

Test for overall effect: Z= 7.754, *p*= 0.000

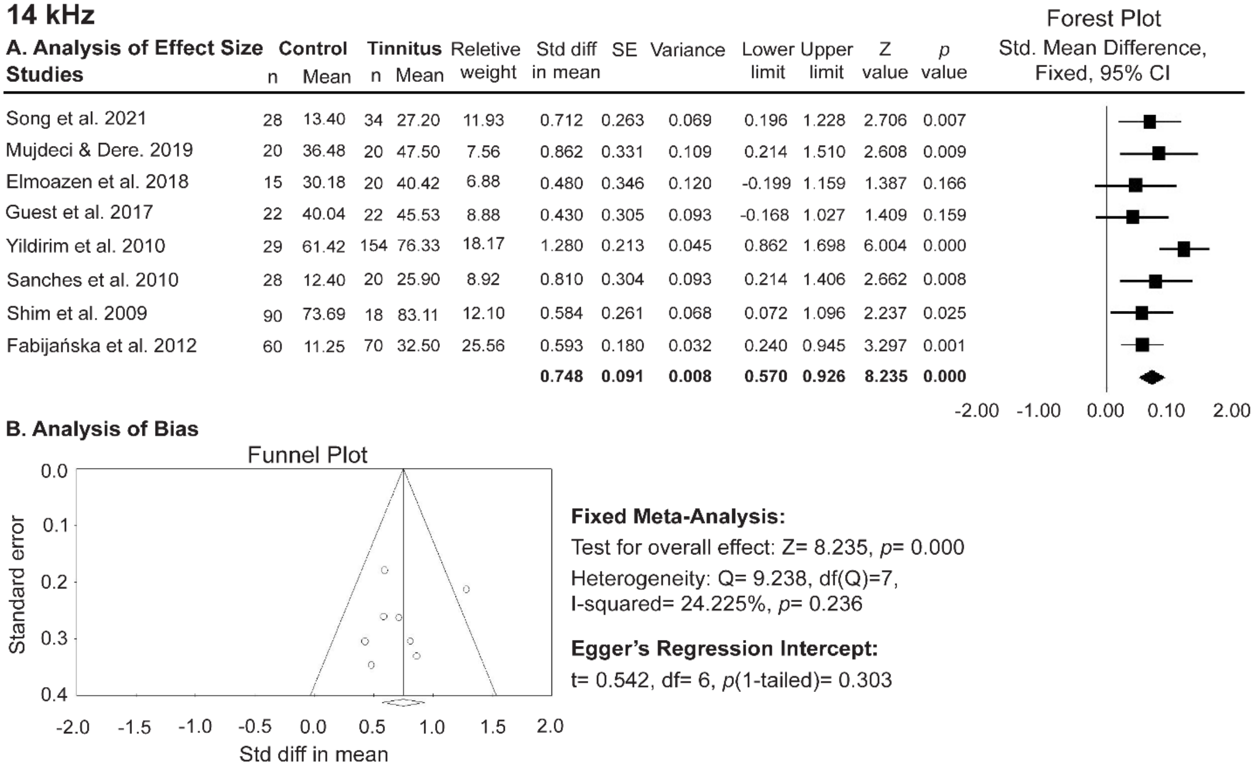
Heterogeneity: Q= 5.225, df(Q)=6,
I-squared= 0.000%, *p*= 0.515

Egger's Regression Intercept:

t= 0.519, df= 5, *p*(1-tailed)= 0.312

Fabijańska

Figure 4. The meta-analysis results on 7 studies at 12.5 kHz. A) Analysis of effect size: a significant difference was observed between the tinnitus and control groups (Z= 7.754, *p*= 0.000), and no heterogeneity was observed within the studies (I^2= 0.000%, *p*= 0.515). B) Analysis of bias: no publication bias was found in the meta-analysis (t= 0.519, *p*= 0.312). CI: confidence interval.



14 kHz

A. Analysis of Effect Size

Studies	**Control** n	**Control** Mean	**Tinnitus** n	**Tinnitus** Mean	Reletive weight	Std diff in mean	SE	Variance	Lower limit	Upper limit	Z value	*p* value
Song et al. 2021	28	13.40	34	27.20	11.93	0.712	0.263	0.069	0.196	1.228	2.706	0.007
Mujdeci & Dere. 2019	20	36.48	20	47.50	7.56	0.862	0.331	0.109	0.214	1.510	2.608	0.009
Elmoazen et al. 2018	15	30.18	20	40.42	6.88	0.480	0.346	0.120	-0.199	1.159	1.387	0.166
Guest et al. 2017	22	40.04	22	45.53	8.88	0.430	0.305	0.093	-0.168	1.027	1.409	0.159
Yildirim et al. 2010	29	61.42	154	76.33	18.17	1.280	0.213	0.045	0.862	1.698	6.004	0.000
Sanches et al. 2010	28	12.40	20	25.90	8.92	0.810	0.304	0.093	0.214	1.406	2.662	0.008
Shim et al. 2009	90	73.69	18	83.11	12.10	0.584	0.261	0.068	0.072	1.096	2.237	0.025
Fabijańska et al. 2012	60	11.25	70	32.50	25.56	0.593	0.180	0.032	0.240	0.945	3.297	0.001
						0.748	**0.091**	**0.008**	**0.570**	**0.926**	**8.235**	**0.000**

B. Analysis of Bias

Fixed Meta-Analysis:

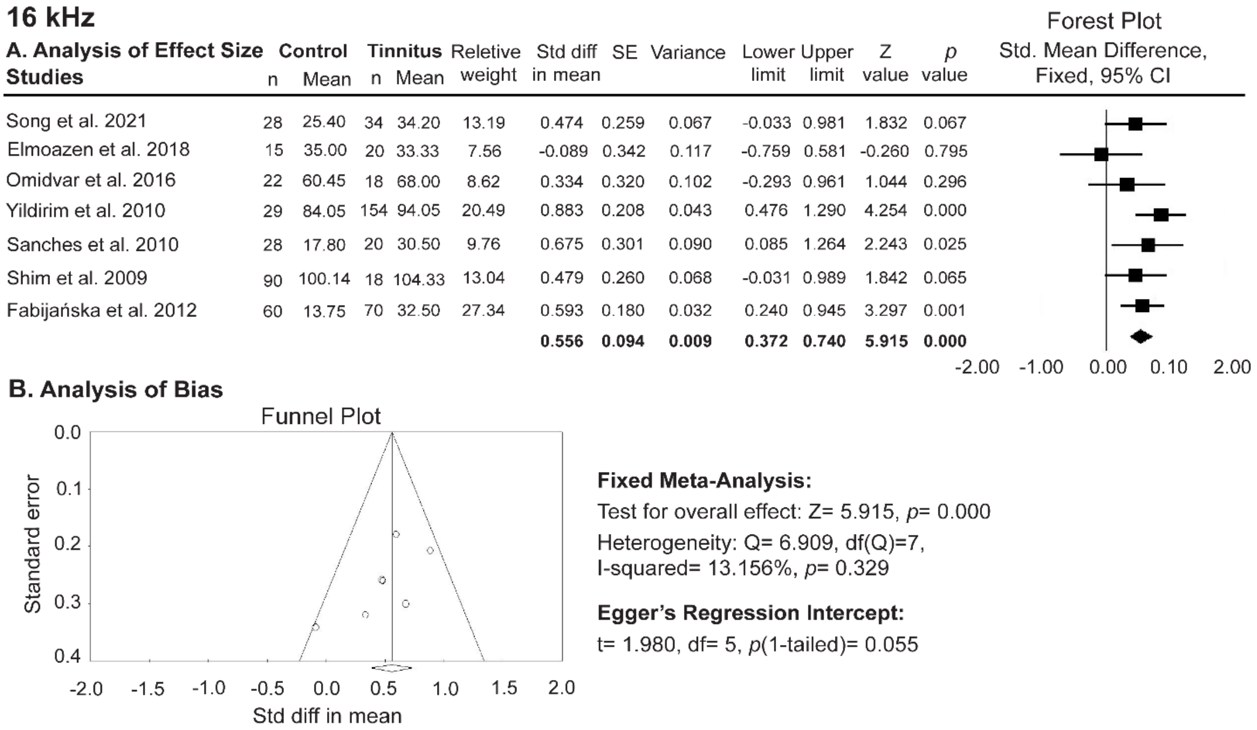
Test for overall effect: Z= 8.235, *p*= 0.000

Heterogeneity: Q= 9.238, df(Q)=7,
I-squared= 24.225%, *p*= 0.236

Egger's Regression Intercept:

t= 0.542, df= 6, *p*(1-tailed)= 0.303

Figure 5. The meta-analysis results on 8 studies at 14 kHz. A) Analysis of effect size: a significant difference was observed between the tinnitus and control groups (Z= 8.235, *p*= 0.000), and no heterogeneity was observed within the studies (I^2= 24.225%, *p*= 0.236). B) Analysis of bias: no publication bias was found in the meta-analysis (t= 0.542, *p*= 0.303). CI: confidence interval.



16 kHz

A. Analysis of Effect Size

Studies	Control n	Control Mean	Tinnitus n	Tinnitus Mean	Reletive weight	Std diff in mean	SE	Variance	Lower limit	Upper limit	Z value	*p* value
Song et al. 2021	28	25.40	34	34.20	13.19	0.474	0.259	0.067	-0.033	0.981	1.832	0.067
Elmoazen et al. 2018	15	35.00	20	33.33	7.56	-0.089	0.342	0.117	-0.759	0.581	-0.260	0.795
Omidvar et al. 2016	22	60.45	18	68.00	8.62	0.334	0.320	0.102	-0.293	0.961	1.044	0.296
Yildirim et al. 2010	29	84.05	154	94.05	20.49	0.883	0.208	0.043	0.476	1.290	4.254	0.000
Sanches et al. 2010	28	17.80	20	30.50	9.76	0.675	0.301	0.090	0.085	1.264	2.243	0.025
Shim et al. 2009	90	100.14	18	104.33	13.04	0.479	0.260	0.068	-0.031	0.989	1.842	0.065
Fabijańska et al. 2012	60	13.75	70	32.50	27.34	0.593	0.180	0.032	0.240	0.945	3.297	0.001
						0.556	**0.094**	**0.009**	**0.372**	**0.740**	**5.915**	**0.000**

B. Analysis of Bias

Fixed Meta-Analysis:

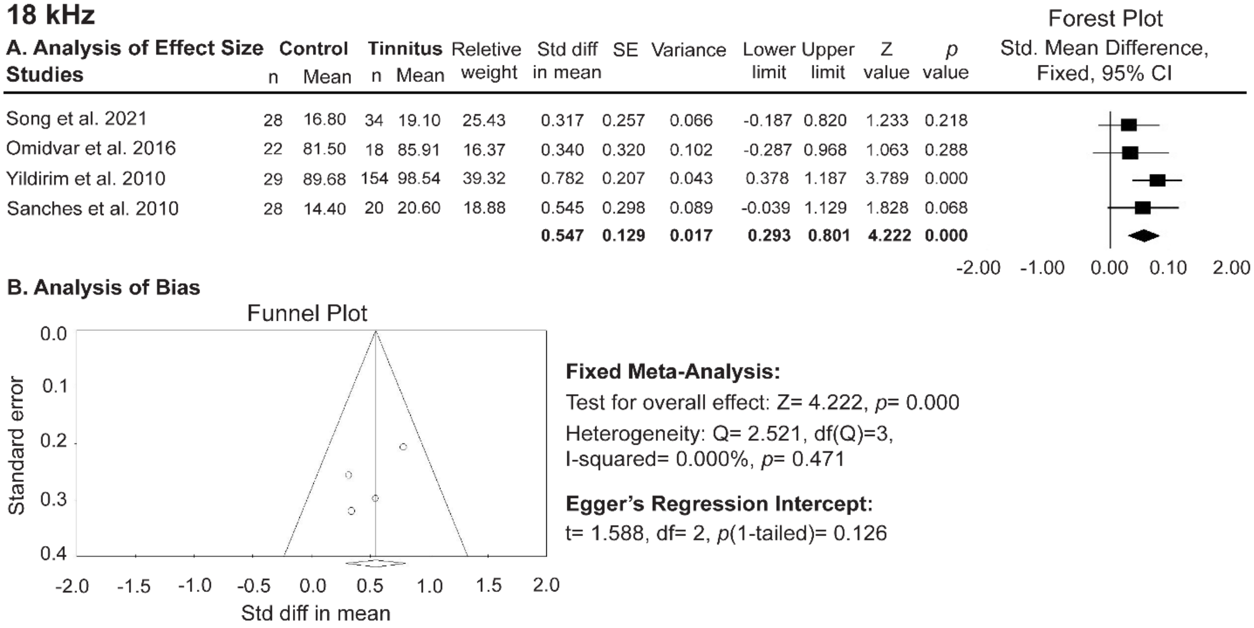
Test for overall effect: Z= 5.915, *p*= 0.000

Heterogeneity: Q= 6.909, df(Q)=7,
I-squared= 13.156%, *p*= 0.329

Egger's Regression Intercept:

t= 1.980, df= 5, *p*(1-tailed)= 0.055

Figure 6. The meta-analysis results on 7 studies at 16 kHz. A) Analysis of effect size: a significant difference was observed between the tinnitus and control groups (Z= 5.915, *p*= 0.000), and no heterogeneity was observed within the studies (I^2= 13.156%, *p*= 0.329). B) Analysis of bias: no publication bias was found in the meta-analysis (t= 1.980, *p*= 0.055). CI: confidence interval.



Studies	Control n	Control Mean	Tinnitus n	Tinnitus Mean	Reletive weight	Std diff in mean	SE	Variance	Lower limit	Upper limit	Z value	*p* value
Song et al. 2021	28	16.80	34	19.10	25.43	0.317	0.257	0.066	-0.187	0.820	1.233	0.218
Omidvar et al. 2016	22	81.50	18	85.91	16.37	0.340	0.320	0.102	-0.287	0.968	1.063	0.288
Yildirim et al. 2010	29	89.68	154	98.54	39.32	0.782	0.207	0.043	0.378	1.187	3.789	0.000
Sanches et al. 2010	28	14.40	20	20.60	18.88	0.545	0.298	0.089	-0.039	1.129	1.828	0.068
						0.547	**0.129**	**0.017**	**0.293**	**0.801**	**4.222**	**0.000**

Fixed Meta-Analysis:
Test for overall effect: Z= 4.222, *p*= 0.000
Heterogeneity: Q= 2.521, df(Q)=3,
I-squared= 0.000%, *p*= 0.471

Egger's Regression Intercept:
t= 1.588, df= 2, *p*(1-tailed)= 0.126

Figure 7. The meta-analysis results on 4 studies at 18 kHz. A) Analysis of effect size: a significant difference was observed between the tinnitus and control groups (Z= 4.222, *p*= 0.000), and no heterogeneity was observed within the studies (I^2= 0.000 %, *p*= 0.471). B) Analysis of bias: no publication bias was found in the meta-analysis (t= 1.588, *p*= 0.126). CI: confidence interval.

TABLE 1. Overview of studies included in the meta-analysis

Study	Country	Sample size	Age (year)	Tinnitus duration	Pitch (kHz)	Loudness (dB)	Ear	THI score	Study design	Findings
Song et al., 2021	China	T: 28/15f C: 34/33f	28.0 29.1 (18-35)	17.9mo	7.63 ± 3.2	-	13U 15B	37.4	Case-control	Increased HT at 8, 10, 12.5, 14, and 16kHz, and a lower edge frequency (10.4 vs. 12.3 kHz).
Mujdeci and Dere, 2019	Turkey	T: 20/12f C: 20/11f	32.0 31.85 (19-45)	-	3.9 ± 2.66	10.50	U	-	Case-control	Increased HT at 10, 12.5, 14, and 16 kHz.
Elmoazen et al., 2018	Egypt	T: 20/16f C: 15/12f	20-50	-	3.13 ± 2.04		B	-	Case-control	Increased, but not significant EHF hearing thresholds.
Guest et al., 2017	UK	T: 22/55%f C:22/55%f	26.6 26.5 18-40	4mo-15yr>	-	-	-	-	Case-control	Increased HT at 10 and 14 kHz.
Omidvar et al., 2016	Iran	T: 18/9f C: 22/13f	38.11 35.36	-	-	-	U/B	-	Cross-sectional	Increased HT at 10, 12.5, and 16 kHz.
Fabijańska et a1., 2012	Poland	T: 70/40f C:60/32f	28.7 28.6 (14-40)	6mo>	68.5% above 8 kHz	-	U	-	Cross-sectional	Increased HT at 12.5, 16, and 16 kHz.
Sanches et al., 2010	Brazil	T: 20/17f C: 28/18f	33.5 28.8 (21-56)	12mo>	-	-	7U 13B	-	Cross-sectional	Increased HT at 9, 10, 11.2, 12.5, 14, 16, and 18 kHz.
Yildirim et al., 2010	Turkey	T: 154/98f C: 29/13f	40.5 (17-68)	2mo-10yr	-	-	88U 66B	-	Cross-sectional	Increased HT at 9, 10, 11.2, 12.5, 14, 16, and 18 kHz.
Shim et al., 2009	South Korea	T:18/15f C:90/75f	41.2 - 31-54	3mo>	-	-	U	39.1	Case-control	Increased HT at 10 kHz.

B: bilateral, C: control, EHF: extended high-frequency, f: female, HT, hearing threshold, M to H, medium to high, mo: month, T: tinnitus, THI: tinnitus handicap inventory, U: unilateral, yr: year.

TABLE 2. Quality assessment of the included papers using Crowe Critical Appraisal Tool (CCAT)

Study	**Preliminaries**	**Introduction**	**Design**	**Sampling**	**Data collection**	**Ethics**	**Results**	**Discussion**	**Total/40**	**Total (%)**
Song et al., 2021	4	4	5	4	3	4	4	4	32/40	80.0
Mujdeci and Dere, 2019	3	3	4	3	4	4	3	2	26/40	65.0
Elmoazen et al., 2018	3	2	3	2	2	2	3	3	20/40	50.0
Guest et al., 2017	4	4	4	3	4	2	4	4	29/40	72.5
Omidvar et al., 2016	3	4	4	4	3	5	3	3	29/40	72.5
Fabijańska et a1., 2012	4	3	4	4	4	3	3	3	28/40	70.0
Sanches et al., 2010	4	4	3	3	4	5	4	4	31/40	77.5
Yildirim et al., 2010	3	3	3	2	3	1	3	3	21/40	52.5
Shim et al., 2009	3	3	4	3	3	1	4	3	24/40	60.0