Electrical stimulation

Scientific outcomes, related factors and patient needs

through cochlear implants

for tinnitus

UMC Utrecht Brain Center

Kelly K. S. Assouly

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COLOFON

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Electrical stimulation through cochlear implants for tinnitus

↳ Scientific outcomes, related factors and patient needs

Elektrische stimulatie via cochleaire implantaten voor tinnitus

↳ Wetenschappelijke resultaten, gerelateerde factoren en behoeften van de patiënt

(met een samenvatting in het Nederlands)

PROEFSCHRIFT

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General introduction

Preface

To date, there is no cure for tinnitus. Cochlear implantation may be an effective treatment for patients with moderate to severe tinnitus and hearing loss who do not respond to conventional treatments. So far, there is no high level of evidence on the effect of electrical stimulation through cochlear implants on tinnitus as a primary complaint. This thesis aims to bring high level evidence on the effect of electrical stimulation of the auditory nerve through cochlear implants for people suffering from moderate to severe tinnitus. In this thesis, we also discuss the influence of cochlear implant related factors on tinnitus outcomes and the impact of tinnitus on cochlear implant recipients with severe to profound hearing loss. To understand the relevance of the research questions answered in this thesis, this first chapter gives a short overview of tinnitus definition, prevalence, impact and the methods used to assess it, presents the current limitations to find a cure for tinnitus and finally discusses the gaps before establishing cochlear implant as a potential treatment for tinnitus.

Tinnitus definition and prevalence

Tinnitus is the conscious perception of a sound in absence of an external auditory input. As suggested by its Latin etymology tinnire meaning "to ring", it is often experienced as a ringing or buzzing sound in the ear or the head. Tinnitus is defined as chronic when experienced for more than 3 months[1]. It has a prevalence of 15% in the general population, meaning that 1 in 7 adults have chronic tinnitus[2,3]. This represents 26 million adults experiencing tinnitus in the European Union of which 4 million adults are experiencing severe tinnitus[2]. The prevalence increases with age, with up to 23% for adults over the age of 65 years, and with hearing loss, with up to 67% for adults with severe hearing loss[2–4]. The incidence of tinnitus is also expected to increase over time due to the aging population and the increasing noise exposure in modern life[5].

Although tinnitus prevalence has been increasing over time due to the increasing exposure to noise, tinnitus was already spoken of in ancient Egypt. Despites some controversies, the oldest record of tinnitus was found in the *Ebers Papyrus* and characterized as a "bewitched ear"[6]. Later, Hippocrates mentioned tinnitus in the *Corpus Hippocraticum* and already associated it with hearing loss and headache[7]. Over time and across civilisations, tinnitus has been acknowledged and considered as an imbalance of the Ying and the Yang in classical China, as ears inhabited by small animals in East India or as a wind

trapped in the ear in the Renaissance[8]. From the outset, different ways of treating tinnitus have been tried such as fumigation to chase away the small animals in East India or drilling a hole into the ear to release the wind in the Renaissance. Since then, tinnitus has been a research topic and to date no cure for tinnitus is available.

Tinnitus impact

Tinnitus can vary in sound, loudness, location and also impact people differently. Tinnitus becomes a tinnitus disorder when associated with emotional and/or cognitive dysfunction, and/or autonomic arousal, leading to behavioural changes and functional disability[1]. Although a high number of people report no impact on their daily lives, tinnitus can be disabling and bothersome for those individuals affected by it. Tinnitus disorder can affect hearing distress, communication, quality of life[9] and can cause anxiety, depression[10], sleep disorders[11], concentration problems as well as interference with social life and work[12]. Up to 3% of the general population suffers from severe and bothersome tinnitus.

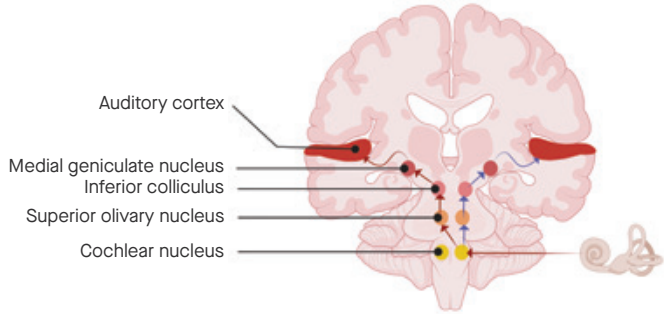
Limitations in tinnitus measurement

Subjective tinnitus is a symptom which is not measurable or quantifiable by objective physical recordings. Characterizing tinnitus sound can be achieved by using tinnitus pitch and loudness matching tests, where the patient is asked to compare the tinnitus with different sounds in order to find the sound that is the most similar to the perceived sound. The main focus when diagnosing tinnitus is to assess the associated impact. Tinnitus impact can be assessed using Patient Reported Outcomes Measures (PROMs) capturing patient's subjective experience. Tinnitus PROMs consists of visual analogue scale, rating tinnitus burden, distress, severity, annoyance, intrusiveness or loudness, and clinically validated questionnaires which evaluate the multifactorial domains associated with tinnitus impact[13]. To stratify the impact of tinnitus, its associated degree of severity is defined from PROMs scores, ranging from no to catastrophic handicap. So far, objectifying the presence of subjective tinnitus or its associated impact is not clinically available and still under investigation in research studies. This constitutes a limitation in diagnosing tinnitus origins, developing appropriate treatment and monitoring treatment-related changes.

Tinnitus : a symptom with different underlying causes

Tinnitus is not a disease but rather a symptom that can result from a heterogeneity of underlying causes, potentially requiring different treatments. The specific pathophysiology of tinnitus is often difficult to identify. The most important risk factor is hearing loss, followed by age and stress. The underlying mechanism of tinnitus is still unclear and a matter of research. The cause of tinnitus is not solely due to damage to the cochlea, as the perception of tinnitus can persist even when input from the ear is suppressed by cutting of the auditory nerve[14]. Still subject to debate, tinnitus could originate from neural correlates generated either at the cochlear level or at the level of the auditory nerve, being a peripheral tinnitus, or beyond the auditory nerve and have a more central origin, namely a central tinnitus (Figure 1). One hypothesis is that tinnitus may be the consequence of changes in neural activity in the auditory pathway and the auditory cortex, caused by reduced or deprivation of auditory input, for instance due to hearing loss[15,16].

Figure 1. Schematic representation of the auditory pathway.



The central auditory pathway consists of the cochlear nucleus, the superior olivary complex, the inferior colliculus, the medial geniculate body and the auditory cortex. The action potentials generated in the auditory nerve is relayed to the central auditory pathway as an ascending auditory signal.

No cure for tinnitus

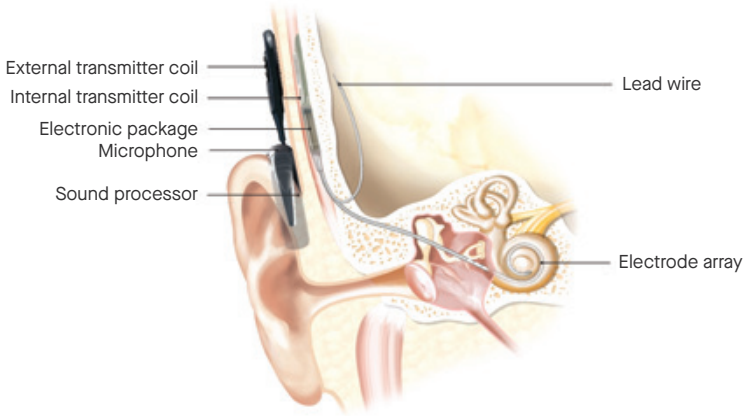
Therapeutic options for patients seeking help for tinnitus are limited. No evidence based curative treatment has been found, therefore reduction of tinnitus associated distress is currently the highest achievable goal[17,18]. To date, the only evidence-based effective therapy for the reduction of tinnitus burden is the cognitive behavioural therapy (CBT)[19,20]. CBT is a psychological-based therapy aiming at identifying and modifying maladaptive behaviours and negative thoughts resulting in tinnitus distress. This therapy is offered as a standard clinical care in many countries for people with bothersome tinnitus. Although this therapy reduces tinnitus associated distress, it does not reduce the perception of tinnitus and is not sufficient for some tinnitus patients. Sound therapy involves applying sounds through sound generators or hearing aids to mask or minimize the perception of tinnitus without interfering with the patient's hearing abilities. Sound therapy (masking) is not recommended for tinnitus whereas using hearing aids is for those with additional hearing loss according to NICE guidelines[21]. There is still no reliable evidence for the efficacy of sound therapy on tinnitus[22,23]. Currently, neuromodulation, medication or alternative medicine such as acupuncture or dietary supplements are not recommended due to a lack of efficacy and reported adverse effects[21,24–28].

Tinnitus has a substantial economic burden on society which involves not only the health care related cost but also meaningly the production losses. In the Netherlands, total mean estimated societal cost of tinnitus is €6.8 billion[29]. The production losses are estimated to be €3702 per patient while the annual health care costs are on average €1544 per patient ; these costs being significantly higher for the patients suffering from severe tinnitus[29]. Moreover, patients seeking help for tinnitus often try different therapeutic approaches without finding therapies leading to recovery. The absence of cure for tinnitus confers a significant financial cost both for patients and healthcare systems and has a significant economic impact more broadly on society.

Cochlear implant for tinnitus : lack of evidence

A cochlear implant is a surgically implantable device that restores hearing in case of severe to profound hearing loss by providing electrical stimulation to the auditory nerve. The device consists of an external part, which is worn on the head or behind the ear, and an internal part, which is implanted during cochlear implantation under general anaesthesia (Figure 2). Since the 1990s, cochlear implantation is an available treatment for people with severe to profound bilateral hearing loss who do not benefit from hearing aids. Contrary to the hearing aid which amplifies sound in the ear canal, the cochlear implant bypasses the damaged sensory structures in the cochlea and directly provides sound information to the auditory nerve and thereafter the central auditory system by electrically stimulating the spiral ganglion cells. After the introduction of the cochlear implant, the use has been expanded from only profound deafened adults to children and adults who have some residual hearing.

Figure 2. Schematic representation of the cochlear implant.



The external part consists of a microphone that converts external sound into an electrical signal, a sound processor that decomposes the signal into frequency bands and converts it, using a sound processing strategy, into electrical stimulation patterns and a radio frequent transmitter coil that conveys both an electrical stimulation signal and electrical energy to the internal part. The internal part consists of a subcutaneous radio frequent receiver coil that picks up the signal sent by the external coil, an electronic package that decodes the signal and a lead wire that runs through the mastoid bone to the cochlea. An electrode array is connected to the internal part and placed in the cochlea to provide electrical stimulation to the auditory nerve.

Since auditory deprivation is thought to be one of the causes of tinnitus, increasing the auditory input by electrical stimulation to the auditory nerve might be a possible treatment option. In patients with severe to profound hearing loss, electrical stimulation with a cochlear implant showed positive effects on tinnitus distress as a secondary benefit in addition to restoration of hearing function. It is still unclear what the effect of electrical stimulation with a cochlear implant will be for patients receiving a cochlear implant for their tinnitus as a primary complaint and not for hearing loss. So far, there is no high level of evidence on the effect of intracochlear electrical stimulation as a treatment for tinnitus. Indeed, no randomized controlled trial has been conducted to evaluate the effect of cochlear implantation on tinnitus as a primary complaint. The first part of this thesis aims to bring high level evidence on the effect of electrical stimulation of the auditory nerve through cochlear implants for people suffering from moderate to severe tinnitus.

Cochlear implant for hearing loss : heterogeneity in tinnitus outcomes

There is a high tinnitus prevalence among cochlear implant candidates i.e. patients with severe to profound hearing loss[30–32]. Although tinnitus was not their primary complaint, cochlear implant recipients often reported change in tinnitus after cochlear implantation. While some studies showed that tinnitus loudness, distress or annoyance can be reduced or suppressed after cochlear implantation, others report that tinnitus can also be worsened in up to 10% of recipients[30]. Induction of tinnitus has been reported in up to 4% of patients receiving a cochlear implant for bilateral severe to profound hearing loss without pre-operative tinnitus[30]. As the effect of cochlear implantation on tinnitus impact seems to vary widely between studies, it is of clinical importance to understand the factors underlying this variability. At this stage, clinicians have little certainty when counselling their patients prior to implantation regarding tinnitus post-implantation. Identifying key factors which can characterize tinnitus changes after implantation will help clinicians to counsel cochlear implant candidates on the risk of developing or improving tinnitus after implantation and thus help to manage patient expectations. The second part of this thesis aims to investigate the influence of cochlear implant related factors on tinnitus outcomes.

Surprisingly, little is known about the real-life impact that tinnitus has on those with a cochlear implant for their hearing loss. Given the complexity of tinnitus, it is of interest to understand patients' needs related to their tinnitus experience and the relationship between tinnitus and cochlear implant. The third part of the thesis aims to better understand the impact of tinnitus on cochlear implant recipients.

Aim of the thesis

Considering the principles of Evidence Based Medicine (EBM), one should integrate best available evidence, clinical expertise and patient values to improve quality of care and make clinical decision. Besides a lack of knowledge on the experience and views of cochlear implant recipients on tinnitus, there is a gap in high level evidence on the effectiveness of cochlear implant for primary tinnitus (Figure 3). Taken together, this thesis aims to contribute to a higher level of evidence and a better understanding of the effect of electrical stimulation of the auditory nerve as a treatment option for tinnitus.

Figure 3. Schematic representation of evidence-based medicine (EBM).

EBM is integrating the experience of the clinician, the values of the patient, and the best available scientific information to guide decision-making about clinical management.

Outline of this thesis

This thesis consists of three parts. In the first part, we focused on the effect of electrical stimulation of the auditory nerve through a cochlear implant on tinnitus impact, exploring different patient groups and study designs. In the second part, we investigated the influence of cochlear implant related factors on tinnitus outcomes. Finally, in the third part, we addressed the impact of tinnitus on cochlear implant recipients.

PART I : EFFECT OF ELECTRICAL STIMULATION THROUGH A COCHLEAR IMPLANT ON TINNITUS

In the first part, the following questions were addressed :

What is the effect of electrical stimulation through a cochlear implant on tinnitus as a primary complaint ?

In **Chapter 2**, we systematically reviewed the literature on the effect of electrical stimulation through a cochlear implant on tinnitus as a primary complaint. As a follow up project, **Chapter 3** describes the research protocol of an individual patient data meta-analysis in which we aimed to determine the effect of electrical stimulation with a cochlear implant on tinnitus impact for individual adult patients with tinnitus. In addition, by means of a meta-analysis, we aimed to develop prediction models for individual patient data from clinical trials to find predictive factors for the effect of electrical stimulation on tinnitus impact.

What is the effect of electrical stimulation through a cochlear implant on adult patients with moderate to severe tinnitus and moderate to severe bilateral hearing loss ?

In **Chapter 4**, we described the research protocol of a randomised controlled trial assessing the effect of cochlear implantation for tinnitus as a primary complaint. For this purpose, 50 patients primarily seeking help for tinnitus with moderate to severe tinnitus burden, moderate to severe hearing loss and perceived failure for other tinnitus therapies will be randomised to cochlear implantation or no intervention. Tinnitus burden, the primary outcome of the study, speech perception, comorbidities such as depression and anxiety, and quality of life will be evaluated at follow-up visits at 3 and 6 months after implantation. The randomised controlled trial started in January 2021 and is currently conducted at the University Medical Center Utrecht.

What are the changes in tinnitus prevalence and distress after cochlear implantation for adult patients with bilateral severe to profound hearing loss?

In **Chapter 5**, we estimated the prevalence and severity of tinnitus before and after implantation in patients with bilateral severe to profound hearing loss receiving one or two implants for the purpose of their hearing loss. In this study, a pooled dataset of 300 adult cochlear implant recipients with bilateral severe to profound hearing loss was analysed on pre- and post-implantation tinnitus outcomes.

PART II : INFLUENCE OF COCHLEAR IMPLANT RELATED FACTORS ON TINNITUS OUTCOMES

In the second part of the thesis, we tried to answer the two following questions :

What is the influence of the electrode array design on post-implantation tinnitus outcomes?

In **Chapter 6**, we assessed the relationship between the tinnitus characteristics and impact on daily life and the electrode array types and positions in 25 single-sided deaf patients at three months post-activation.

What is the effect of extra- and intracochlear electrical stimulation on tinnitus?

In **Chapter 7**, we performed a systematic review that gives an overview of the effect of intra- and extracochlear electrical stimulation on tinnitus.

PART III : IMPACT OF TINNITUS ON COCHLEAR IMPLANT RECIPIENTS

The third part of the thesis addresses the impact of tinnitus on cochlear implant recipients based on two questions :

What is the influence of tinnitus annoyance on hearing-related quality of life in cochlear implant recipients?

In **Chapter 8**, we assessed the relationship between hearing-related quality of life measured by the Speech, Spatial and Qualities of Hearing scale (SSQ12) and tinnitus annoyance or perceived change in tinnitus annoyance after cochlear implantation. The study sample size consisted of 2322 implanted adults participating to a post-market cochlear implant survey.

What is the impact of tinnitus in adult cochlear implant recipients?

We conducted an observational study to understand the impact of tinnitus in cochlear implant recipients. This observational study is based on a mixed-method approach consisting of two parts : (1) an exploratory sequential design, involving collecting qualitative exploratory data and (2) using the findings to develop a survey for cochlear implant recipients experiencing tinnitus to quantitatively measure the themes emerging in the first part. **Chapter 9** describes the exploratory study involving a forum discussion and a qualitative analysis followed by the development of a survey, the dissemination of the survey to a selected population sample and the analysis of the survey replies. Four hundred and fourteen eligible cochlear implant recipients with tinnitus completed the developed survey.

As the final part of this thesis, **Chapter 10** provides a general discussion of the results of previous chapters. Finally, clinical implications of the work presented in this thesis and perspectives for future research were discussed.

References

1. De Ridder, D. et al. Tinnitus and tinnitus disorder : Theoretical and operational definitions (an international multidisciplinary proposal). in Progress in Brain Research vol. 260 1–25 (Elsevier B.V., 2021).
2. Biswas, R. et al. Tinnitus prevalence in Europe : a multi-country cross-sectional population study. Lancet Reg. Heal. - Eur. 12, 100250 (2022).
3. Jarach, C. M. et al. Global Prevalence and Incidence of Tinnitus : A Systematic Review and Meta-analysis. JAMA Neurol. (2022) doi :10.1001/jamaneurol.2022.2189.
4. Schubert, N. M. A., Rosmalen, J. G. M., van Dijk, P. & Pyott, S. J. A retrospective cross-sectional study on tinnitus prevalence and disease associations in the Dutch population-based cohort Lifelines. Hear. Res. 411, 108355 (2021).
5. Dillard, L. K. et al. Prevalence and global estimates of unsafe listening practices in adolescents and young adults : a systematic review and meta-analysis. BMJ Glob. Heal. 7, e010501 (2022).
6. Stephens, S. D. . Historical aspects of tinnitus. in Hazell, J.W.P, ed. Tinnitus. New York : Churchill Livingstone 1–9 (1987).
7. Dietrich, S. Earliest historic reference of 'tinnitus' is controversial. J. Laryngol. Otol. 118, 487–488 (2004).
8. Sound Bounce. Tinnitus Throughout the Years. https://www.sound-bounce.com/news/2018/05/09/tinnitus-throughout-the-years-tzgtm (2018).
9. Stegeman, I. et al. Tinnitus and its associations with general health and hearing loss. Prog. Brain Res. Press. (2021).
10. Langguth, B., Landgrebe, M., Kleinjung, T., Sand, G. P. & Hajak, G. Tinnitus and depression. World J. Biol. Psychiatry 12, 489–500 (2011).
11. Koning, H. M. Sleep disturbances associated with tinnitus : Reduce the maximal intensity of tinnitus. Int. Tinnitus J. (2019) doi:10.5935/0946-5448.20190012.
12. McCormack, A., Edmondson-Jones, M., Somerset, S. & Hall, D. A systematic review of the reporting of tinnitus prevalence and severity. Hearing Research (2016) doi:10.1016/j.heares.2016.05.009.
13. Hall, D. A. et al. Systematic review of outcome domains and instruments used in clinical trials of tinnitus treatments in adults. Trials 17, 270 (2016).
14. House, J. W. & Brackmann, D. E. Tinnitus : surgical treatment. Ciba Found. Symp. 85, 204–216 (1981).
15. Eggermont, J. J. & Roberts, L. E. The neuroscience of tinnitus. Trends in Neurosciences (2004) doi:10.1016/j.tins.2004.08.010.
16. Eggermont, J. J. & Kral, A. Somatic memory and gain increase as preconditions for tinnitus : Insights from congenital deafness. Hear. Res. 333, 37–48 (2016).
17. McFerran, D. J., Stockdale, D., Holme, R., Large, C. H. & Baguley, D. M. Why is there no cure for tinnitus? Front. Neurosci. 13, 1–13 (2019).

18. Hoare, D. J., Kowalkowski, V. L., Kang, S. & Hall, D. A. Systematic review and meta-analyses of randomized controlled trials examining tinnitus management. Laryngoscope 121, 1555–1564 (2011).

19. Cima, R. F. F. et al. Specialised treatment based on cognitive behaviour therapy versus usual care for tinnitus : A randomised controlled trial. Lancet 379, 1951–1959 (2012).

20. Fuller, T. et al. Cognitive behavioural therapy for tinnitus. Cochrane Database Syst. Rev. (2020) doi:10.1002/14651858.CD012614.pub2.

21. National Institute for Health and Care Excellence. Tinnitus : assessment and management. NICE Guideline 155. www.nice.org.uk/guidance/ng155 (2020).

22. Hobson, J., Chisholm, E. & El Refaie, A. Sound therapy (masking) in the management of tinnitus in adults. Cochrane Database Syst. Rev. (2012) doi:10.1002/14651858.cd006371.pub3.

23. Sereda, M., Xia, J., El Refaie, A., Hall, D. A. & Hoare, D. J. Sound therapy (using amplification devices and/or sound generators) for tinnitus. Cochrane Database of Systematic Reviews (2018) doi:10.1002/14651858.CD013094.pub2.

24. Person, O. C., Puga, M. E., da Silva, E. M. & Torloni, M. R. Zinc supplementation for tinnitus. Cochrane Database Syst. Rev. 11, CD009832 (2016).

25. Wegner, I., Hall, D. A., Smit, A. L., McFerran, D. & Stegeman, I. Betahistine for tinnitus. Cochrane Database Syst. Rev. (2018) doi:10.1002/14651858.CD013093.pub2.

26. Baldo, P., Doree, C., Lazzarini, R., Molin, P. & McFerran, D. J. Antidepressants for patients with tinnitus. Cochrane Database Syst. Rev. 2012, CD003853 (2012).

27. Sereda, M. et al. Ginkgo biloba for tinnitus. Cochrane Database Syst. Rev. 2019, CD013514 (2019).

28. Stegeman, I., Velde, H. M., Robe, P. A. J. T., Stokroos, R. J. & Smit, A. L. Tinnitus treatment by vagus nerve stimulation : A systematic review. PLoS One 16, 1–12 (2021).

29. Maes, I. H. L., Cima, R. F. F., Vlaeyen, J. W., Anteunis, L. J. C. & Joore, M. A. Tinnitus : a cost study. Ear Hear. 34, 508–514 (2013).

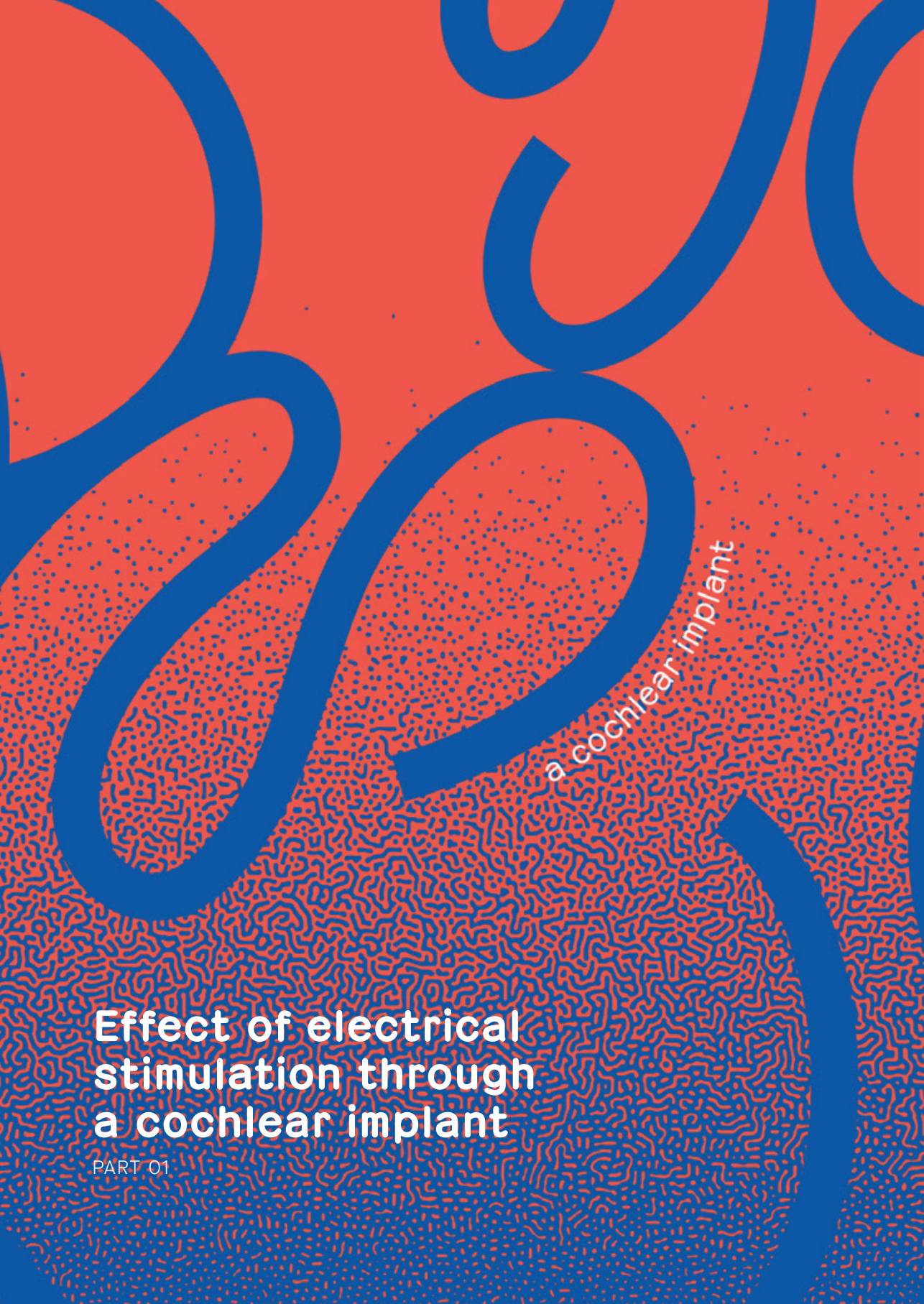
30. Quaranta, N., Wagstaff, S. & Baguley, D. M. Tinnitus and cochlear implantation. International Journal of Audiology vol. 43 245–251 (2004).

31. Pierzycki, R. H. et al. Tinnitus and Sleep Difficulties after Cochlear Implantation. Ear Hear. (2016) doi:10.1097/AUD.0000000000000341.

32. Baguley, D. M. & Atlas, M. D. Cochlear implants and tinnitus. in Tinnitus : Pathophysiology and Treatment (eds. Langguth, B., Hajak, G., Kleinjung, T., Cacace, A. & Møller, A. R. B. T.-P. in B. R.) vol. 166 347–355 (Elsevier, 2007).

PART 01

Effect of electrical stimulation through



Effect of electrical stimulation through a cochlear implant

PART 01

2

Cochlear implantation for patients with tinnitus : *a systematic review*

Progress in Brain Research 2021; 260:27-50

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Robert J. Stokroos
Inge Stegeman
Adriana L. Smit

Abstract

Background

Cochlear implantation (CI) is used in patients with severe-to-profound hearing loss when hearing aids provide limited or no benefit for speech perception. Studies on this topic reported tinnitus reduction as a common side effect of the electrical activation after cochlear implantation. So far, it is unclear what the effect is when patients do receive their implant primarily because of tinnitus complaints.

Objectives

To assess the effectiveness of the electrical stimulation with a cochlear implant in patients with tinnitus as a primary complaint, by systematically reviewing the literature.

Methods

Two independent authors identified studies, extracted data and assessed risk of bias of included studies. Original studies reporting outcomes of electrical stimulation by cochlear implantation for primarily tinnitus (defined as severe or incapacitating distress levels) were included, if they reported a follow-up of at least three months. The pre- and post-implantation tinnitus distress scores on single and/or multi-item questionnaires of the included studies were extracted.

Results

In total, 4091 unique articles were retrieved. After screening titles, abstracts and full texts, we included seven prospective cohort studies (105 subjects in total, range : 10–26). All studies had considerable risks of bias. All tinnitus patients in the included studies had asymmetrical hearing loss or single-sided deafness. A statistically significant tinnitus distress improvement based on tinnitus questionnaire scores was found in every study.

Conclusion

Our systematic review reveals that electrical stimulation by cochlear implants in patients with a primary complaint of tinnitus has a positive impact on tinnitus distress. Nevertheless, only small sample sizes were found and studies showed considerable risks of bias.

Introduction

Tinnitus is the perception of a sound without an external auditory input, often experienced as a ringing or buzzing sound in the ear or the head. It has a prevalence of 10–15% in the general population, increasing to 30% for adults over the age of 50 years[1]. Tinnitus can become severe and disabling, affecting communication, quality of life[2] and can cause anxiety, depression[3] or sleep disorders[4]. So far, no evidence based curative treatment has been found, therefore symptom reduction is currently the highest achievable goal[5,6].

Tinnitus is considered to be the consequence of changes in neural activity in the auditory pathway and the auditory cortex, caused by reduced or lack of auditory input, for instance due to hearing loss[7]. More than 60% of patients with severe to profound hearing loss have tinnitus[8,9]. To improve speech perception for those affected with severe to profound hearing loss, cochlear implantation (CI) is an effective treatment when hearing aids are no longer beneficial[10,11]. This treatment might alter the tinnitus related changes in neural activity in the auditory pathway and thereby diminish tinnitus complaints[12,13].

So far, several systematic reviews reported the positive, but not conclusive, effect of intracochlear electrical stimulation after cochlear implantation on tinnitus, in patients with a primary indication of bilateral hearing loss[7] or single-sided deafness[14] to restore hearing outcome. Nonetheless, some studies described tinnitus worsening in a few patients after cochlear implantation[8,9,15–17]. Though, evidence for the effect of intracochlear stimulation on tinnitus in patients with a primary indication for CI of tinnitus, instead of hearing loss, is still lacking. Therefore, we aim to systematically review the literature on the effect of electrical stimulation after cochlear implantation for patients with tinnitus as a primary complaint.

Methods

PROTOCOL AND REGISTRATION

We used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) for this systematic review[18]. The protocol of this systematic review has been registered in PROSPERO with registration number 146773.

SEARCH STRATEGY

We conducted a systematic search in PubMed, Embase, the Cochrane Library, CINAHL, and Web of Science. We used search terms and their synonyms of domain (tinnitus) and determinant (cochlear implantation) in title/abstract, medical subject headings (MeSH) terms, and Emtree fields. Search syntaxes can be found in Table 1. In addition to electronic database searches, reference lists were scanned to identify additional studies. ClinicalTrials.gov and the Netherlands Trial Register (trialregister.nl) were searched for ongoing trials and protocols. The last search was conducted on February 26th, 2020.

STUDY SELECTION

After removing the duplicates, two authors (K.A., J.v.H) independently performed the title/abstract and full text screening of the retrieved articles according to our inclusion and exclusion criteria (Figure 1). Studies describing patients with tinnitus as a primary complaint were included, only if they reported measures of tinnitus distress with a minimum of 3-months follow-up after cochlear implantation. A follow-up of 3 months or more after cochlear implantation was considered to be essential to investigate the long-term effect of the intervention. Tinnitus was considered as a primary complaint when it was characterized by tinnitus questionnaire scores as severe or incapacitating before implantation (e.g., Tinnitus Functional Index (TFI) > 32, Tinnitus Handicap Inventory (THI) > 58, Tinnitus Questionnaire (TQ) > 42, Visual Analogue Scale (VAS) on tinnitus loudness or annoyance > 6).

Table 1. Search strategy.

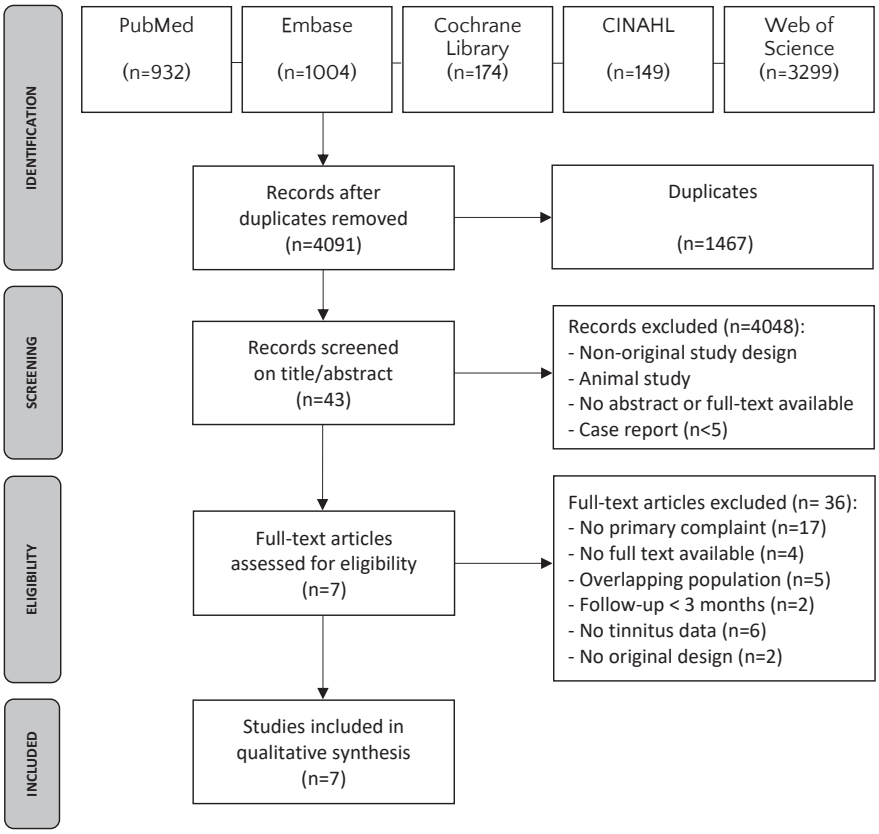
Database	Search	Syntax	Result
PubMed	1	((((((tinnitus [Title/Abstract]) OR tinnit*[Title/Abstract]) OR ringing[Title/Abstract]) OR booming[Title/Abstract]) OR buzzing[Title/Abstract]) OR tinnitus[MeSH Terms])	932
	2	((((((((((cochlear[Title/Abstract]) AND implant*[Title/Abstract])) OR ((cochlear[Title/Abstract]) AND prosthes*[Title/Abstract])) OR (((cochlear[Title/Abstract]) AND prosthetic*[Title/Abstract]) AND device*[Title/Abstract])) OR ((auditory[Title/Abstract]) AND implant*[Title/Abstract])) OR ((cochlear[Title/Abstract]) AND system[Title/Abstract])) OR CI[Title/Abstract]) OR cochlear implantation[MeSH Terms]) OR cochlear implants[MeSH Terms])	
	3	1 AND 2	
Cochrane	Modelled search strategy designed for Cochrane		174
CINAHL	Modelled search strategy designed for CINAHL		149
Embase	Modelled search strategy designed for Embase		1004
Web of Science	Modelled search strategy designed for Web of Science		4636

Last date of search February 26th, 2020.

We excluded studies with a non-original study design, animal studies, case reports (n < 5), or studies with non-available abstract or full text after the title/abstract screening. Exclusion criteria for the full text screening were studies with a duration of follow-up shorter than 3 months, other interventions than cochlear implantation, no tinnitus distress scores reported after implantation, or studies presenting overlapping populations. In case of overlapping study populations, the most complete publication was included. We contacted corresponding authors to retrieve full text articles if these were not available in our databases or for clarification and further data.

Conflicts on the study selection were resolved by discussion. The screening tool used was Rayyan[19].

Figure 1. PRISMA flowchart of the literature search and study selection.



Last date of search February 26th, 2020.

DATA COLLECTION AND ANALYSIS

Quality assessment of the studies

Four authors (K.A., J.v.H., I.S., A.S.) determined the criteria for the critical appraisal of the included studies. Two authors (K.A., J.v.H.) independently assessed the risk of bias (RoB). For randomized controlled trials (RCTs), we used the revised Cochrane risk-of-bias tool (RoB 2) to assess risk of bias in five domains : randomization process, deviations from intended interventions, missing outcome data, measurement of outcomes, and selection of the reported results[20]. For non-randomized studies, we used the ROBINS-I tool (Risk Of Bias In Non-randomized Studies—of Interventions) to evaluate risk of bias in seven

domains : confounding, selection of participants, classification of interventions, deviation from intended intervention, missing data, measurement of outcomes, and selection of reported results[21]. The criteria were defined and adapted to our research question about cochlear implantation for tinnitus. Items were scored as low risk of bias, moderate risk of bias/some concerns, serious risk of bias, critical risk of bias, or unclear. Studies were judged as having an overall low, moderate, serious, or critical risk of bias based on the guidelines of the ROBINS-I tool[21]. Consensus was obtained after discussion between the two reviewers.

Data extraction and synthesis

All study characteristics and outcomes were extracted by two authors independently (K.A., J.v.H.). The primary outcome was the difference between pre- and post-implantation scores on multi-item tinnitus distress questionnaires. The secondary outcome was the difference between pre- and post-scores on single-item tinnitus distress questionnaires (measuring loudness, severity, burden, annoyance, irritability, awareness, and/or intrusiveness). Total tinnitus suppression (defined as a tinnitus distress score after implantation equal to zero) and adverse effects were also reported as secondary outcomes. The difference in pre- and post-implantation scores of the single- and multi-item tinnitus questionnaires were calculated when not provided. We reported scores of tinnitus questionnaires with the corresponding 95% confidence interval (95% CI), or the standard deviation (SD), and/or the p-value. A p-value lower than 0.05 indicates a statistically significant result. We considered an increase in self-reported tinnitus distress or negative effects related to the cochlear implant placement or activation (e.g., infection, pain or discomfort, facial nerve palsy, dizziness) as relevant adverse effects.

Outcomes measures

Used multi-item tinnitus distress questionnaires are the TFI, the THI, the TQ, the Tinnitus Reaction Questionnaire (TRQ), and the Subjective Tinnitus Severity Scale (STSS).

The TFI questionnaire contains 25 questions about eight domains : intrusiveness, sense of control, cognitive interference, sleep disturbance, auditory difficulties attributed to tinnitus, relaxation, quality of life, and emotional distress[22,23]. Possible answers are rated on a scale of 0 to 10, or 0 to 100%. An overall TFI score of 0 to 100 can be calculated, where a total score higher than 53 indicates severe tinnitus burden. A clinically relevant reduction is characterized by a decrease of 13 points or more on the TFI scores[22].

The THI is a 25 items questionnaire characterizing the effect of tinnitus on patient's emotions and daily life. Possible answers are 'no' (0 points), 'sometimes' (2 points) and 'yes' (4 points). The sum of all responses is the total THI score and results in 5 grades : slight or no handicap (0–16 points, grade 1), mild handicap (18–36 points, grade 2), moderate handicap (38–56 points, grade 3), severe handicap (58–76 points, grade 4), or catastrophic handicap (78–100 points, grade 5)[24]. A clinically relevant reduction is characterized by a decrease of 7 points or more on the THI scores[25].

The TQ evaluates the distress caused by the perceived tinnitus[26,27]. distress, intrusiveness, auditory perceptual difficulties, sleep disturbances, and associated somatic complaints. The answers 'true' (0 point), 'partly true' (1 point) or 'not true' (2 points) lead to a total score with a maximum of 84 points. The higher the score is, the more distressing the tinnitus is. A clinically relevant tinnitus reduction is characterized by a decrease of 12 points or more of the TQ scores[28].

The TRQ measures psychological distress associated with tinnitus with 26 questions about four domains : general distress, interference with daily activities, severity of tinnitus, and avoidance. Five answers are possible : not at all (scored 0), a little of the time (scored 1), some of the time (scored 2), a good deal of the time (scored 3), and almost all the time (scored 4)[29,30]. Total scores range from 0 to 104. Scores more than 60 indicate significant psychological distress.

The STSS questionnaire evaluates tinnitus severity. It consists of 16 questions organized in three subscales : intrusion, dominance, and distress[31,32]. Two answers are possible for each question : 0 for a negative answer and 1 for a positive answer. The total score ranges between 0 and 16.

The single-item questionnaires only assess one characteristic of tinnitus : e.g., loudness, severity, burden, annoyance, irritability, awareness, or intrusiveness. These tinnitus characteristics can be measured by a Visual Analogue Scale (VAS) or a Tinnitus Rating Scale (TRS). These scales follow the same rationale : the tinnitus characteristic is scored from 0 (not at all) to 10 (extremely).

Meta-analysis

Methodological heterogeneity (variability in study design) was assessed by four authors (K.A., J.v.H, I.S, A.S). Statistical heterogeneity was assessed with the I^2 test using Review Manager software[33]. We judged an $I^2 > 75\%$ as indicative for statistical heterogeneity[34,35]. Meta-analysis was performed in case of methodological homogeneity and if statistical heterogeneity (I^2) was ≤ 75%.

Results

SEARCH STRATEGY AND STUDY SELECTION

The complete selection process is summarized in the PRISMA flowchart in Figure 1. The search resulted in a total of 4091 articles after removal of the duplicates. After screening of title and abstract, 43 articles remained for the full-text screening.

Of these 43 articles, 36 were excluded after full-text screening. In 17 studies the primary indication for cochlear implantation was not tinnitus, but severe to profound hearing loss[15,16,36–50]. Full text was not available for four studies[51–54]. Two studies didn't report follow-up data equal to or more than 3 months[43,55]. In a more recent publication[56], outcomes of the same study population were reported in a publication already excluded because of its short follow-up[43]. In the most recent publication only post-implantation follow-up data was available[56]. However, the first author responded to our request for the original data with pre-implantation scores. Therefore, we were able to use the most recent publication with longest follow-up and added pre-implantation scores to the reported results[56]. In six studies no tinnitus outcomes were reported[57–62]. Two studies did not have an original design (conference papers)[63,64]. An overlapping population was found twice in seven studies[13,65–68 and 69,70], so the both most complete articles were included for further analysis[67,70].

Finally, seven studies were selected for further analysis and data extraction[56,67,70–74]. All patients in the selected studies had single-sided deafness or asymmetrical hearing loss.

QUALITY OF THE INCLUDED STUDIES

The critical appraisal can be found in Table 2. No randomized controlled trials were found, so we used only the ROBINS-I tool for assessment of the risks of bias. Logically, randomization and blinding were never achieved in the included studies. Overall risk of bias was judged as moderate in two studies[56,71] and as serious in five studies[67,70,72–74].

Confounding

Three studies did not mention specific hearing loss thresholds for inclusion criteria or an analysis to control for confounding, therefore we classified them as unclear risk of bias for this domain[67,70,72].

Selection of participants

Five studies had a low risk of selection bias[56,70–73], the other two had a serious risk of bias for the selection of participants[67,74]. Mertens et al. mentioned the recruitment of a subset of SSD subjects from an original study population of 21 subjects, reported in a previous study[13]. Besides, they did not report how they selected the other 11 asymmetrical hearing-impaired participants recruited for the trial. Additionally, the study of Poncet-Wallet et al. mentioned an enrolment of 30 patients in their protocol but only reported 26 subjects included in the study[74,75].

Classification of interventions

Five out of seven studies had a low risk of bias in classification of the interventions[56,70,72–74]. They reported and performed standard cochlear implantation, activation, and rehabilitation. Two studies were unclear about what exactly was done in the process of cochlear implantation and rehabilitation[67,71].

Deviation from intended intervention

Two out of seven studies had a low risk of bias for deviation from intended intervention, as they clearly defined standard cochlear implantation, activation and rehabilitation in the protocol before the intervention[43,56,74,75]. Three out of seven studies had an unclear risk of bias, because they did not report the intervention in a protocol[67,71,72]. Two studies presented deviations from the standard intervention, such as additional acoustic stimulation procedures[70] or additional fitting programs depending on the tinnitus outcomes[73].

Missing data

All studies correctly reported participant dropouts and withdrawals. Data were missing in one article because of a long follow-up period of at least 3 years[67].

Measurement of outcomes

We categorised all studies as medium risk of bias in the measurement of outcomes. Blinding of participants and surgeons is not an option in case of cochlear implantation. Blinding of outcome assessor was not mentioned in the included studies.

Selection of reported result

For one study, a protocol was published to evaluate the reported results and had no selection bias[43,56]. For another study, a protocol was available on Clinicaltrials.gov[74,75]. For none of the other studies a protocol was published with pre-defined primary and secondary outcomes, and none of the studies were submitted to a trial database. We classified two studies as serious risk of bias, because data were reported for a subset of tinnitus measures according to the intended outcome measures as stated in their methods section[72,73]. We judged the other three studies to have an unclear risk of bias because of the absence of a published protocol[67,70,71].

DATA EXTRACTION AND STUDY CHARACTERISTICS

Trial design and study sample

Study characteristics are reported in Table 3. We contacted four authors for additional data[56,67,70,72], of which two responded to our request and provided raw data of the study[56,70].

All studies had a prospective cohort design. The sample sizes were relatively small (n = 7–26). Follow-up duration differed between studies and ranged from 3 to 36 months. The study with the longest follow-up period showed a high number of lost to follow up[67]. All seven studies had patients with single-sided deafness included. In two studies also patients with asymmetrical hearing loss were included[67,73].

A considerable methodological and statistical heterogeneity ($I^2 > 75\%$) was found among the included studies due to different study designs, inclusion criteria, follow-up periods, and use of different tinnitus questionnaires. So, no meta-analysis could be performed.

Intervention

All studies performed a cochlear implantation, activation and rehabilitation phase. Five studies presented deviations from the standard activation and rehabilitation, such as specific electrode selection and activation[76], a white noise stimulation during the first month post-operative[74], a cross-over study with a tinnitus program and a standard CI program[56], additional acoustic stimulation procedures[70], or additional fitting programs depending on individual tinnitus outcomes[73]. Different implant types from four manufacturers were used in the studies (Advanced Bionics, Cochlear, MED-EL, Oticon).

Outcomes measures

The outcome measures are summarized in Table 4. All studies used multi-item tinnitus distress questionnaires in combination with a single-item questionnaire : the VAS loudness[56,67,70,72–74], the VAS annoyance[74] or the TRS severity[71]. Three studies measured the tinnitus distress separately with a VAS loudness score when the cochlear implant was on (CI On) and when it was turned off (CI Off)[67,70,72].

EFFECT OF INTERVENTIONS

Multi-item tinnitus questionnaire scores

Tinnitus distress was assessed using the THI in five studies[56,70,71,73,74] and the TQ in three studies[56,67,72]. Tinnitus severity, and psychological distress associated with tinnitus were measured in one study using the STSS, and the TRQ, respectively[74]. All studies reported a statistically significant reduction post-implantation compared to pre-implantation.

Table 2. Quality assessment of the included studies based on the ROBINS-I tool.

Study (author, year)	Study design	Sample size	Bias due to confounding	Bias in selection of participants	Bias in classification of interventions	Deviation from intended intervention	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of reported results	Overall bias
Ahmed *et al.*, 2017	PCS	13	●	●	?	?	●	◐	?	Moderate
Arts *et al.*, 2016	PCS	10	●	●	●	●	●	◐	●	Moderate
Kleine Punte *et al.*, 2013	PCS	7	?	●	●	?	●	◐	○	Serious
Mertens *et al.*, 2016	PCS	23	?	○	?	?	○	◐	?	Serious
Poncet-Wallet *et al.*, 2019	PCS	26	●	○	●	●	●	◐	●	Serious
Ramos *et al.*, 2018	PCS	16	?	●	●	○	●	◐	?	Serious
Ramos *et al.*, 2012	PCS	10	●	●	●	○	●	◐	○	Serious

CSS : cross-sectional study ; PCS : prospective cohort study ; RCS : retrospective cohort study.
● = low risk, ◐ = moderate risk, ○ = critical risk, ? = unclear.

Confounding : ● = no confounding / confounding expected with an analysis method to control it, ○ = confounding not appropriately measured / controlled by inclusion criteria on tinnitus severity and hearing loss cut off.

Selection of participants (based on participant characteristics observed after the start of the intervention) : ● = no bias in selection of participants, ○ = bias in selection of participants.

Classification of interventions : ● = intervention status well defined before application (CI), ○ = intervention status defined retrospectively.

Deviation from intended intervention : ● = standard cochlear implantation, activation and rehabilitation defined clearly in the protocol, ○ = deviations to the intervention protocol.

Missing data : ● = < 10% missing data, ○ = ≥ 10% missing data.

Measurement of outcomes : ● = similar measurement of outcomes between intervention groups AND blinding of the outcome assessors for intervention received by study participants, ◐ = similar measurement of outcomes between intervention groups AND no blinding of the outcome assessors for intervention received by study participants, ○ = difference of measurement between groups AND no blinding of the outcome assessors for intervention received by study participants.

Selection of reported results : ● = primary and secondary outcomes reported according to the protocol, ◐ = primary and secondary outcomes reported for all groups (no subset), ○ = missing outcomes / data reported for a subset of measures.

Table 3. Study characteristics of the included studies.

					Study population				Questionnaire(s)	
Study (author, year)	Study design	No. of patients	Gender, M:F	Age (years), mean (SD)	Tinnitus criteria	Hearing loss (n)	Implant type (company)	Follow-up (months)	Multi-item	Single-item
Ahmed *et al.*, 2017	PCS	13	8:5	40 (10)	THI >58	SSD	CONCERTO (MEDEL), CI24RE (Cochlear), HiRes90K (AB)	3	THI	TRS-S
Arts *et al.*, 2016	PCS	10	5:5	48.2 (12.5)	VAS >7; THI >38; TQ >42	SSD	CONCERTO (MEDEL)*	3	THI, TQ	VAS-L
Kleine Punte *et al.*, 2013	PCS	7	5:2	NR	VAS ≥6	SSD	Sonata TI100 (MEDEL)	6	TQ	VAS-L
Mertens *et al.*, 2016	PCS	23	11:12	51.8 (13.4)	VAS >6	SSD (12); AHL (11)	Sonata TI100 (MEDEL)*	36	TQ	VAS-L
Poncet-Wallet *et al.*, 2019	PCS	26	17:9	54.2 (10)	THI >58; VAS >8	SSD	Digisonic SP (Oticon)*	13	THI, TRQ, STSS	VAS-L, VAS-A
Ramos Macías *et al.*, 2018	PCS	16	8:8	52.8 (10.9)	THI >58	SSD	CP810, CI24RE, CI422 (Cochlear)*	12	THI	VAS-L
Ramos Macías *et al.*, 2012	PCS	10	4:6	42.7	THI >58	SSD (5); AHL (5)	CI24RE, CI24REH L, CI512 (Cochlear)	12	THI	VAS-L

AHL : asymmetrical hearing loss ; NR : not reported ; SD : standard deviation ; SSD : single-sided deafness ; STSS : subjective tinnitus severity scale ; THI : tinnitus handicap inventory ; TQ : tinnitus questionnaire ; TRQ : tinnitus reaction questionnaire ; TRS-S : tinnitus rating scale-severity ; VAS-A : visual analogue scale-annoyance ; VAS-L : visual analogue scale-loudness.
*The company funded this study. Follow-up : maximum months of follow-up after cochlear implantation.

Table 4. Extracted and processed data of tinnitus distress outcome of cochlear implantees from the included studies.

		Tinnitus questionnaire						
Study (author, year)	No. of patients	Multi-item	Single-item	Pre-implantation score	Post-implantation score*, (SD or 95% CI)	Difference score (post - pre)	p-value	Total suppression, (n)
Ahmed *et al.*, 2017	13	THI		79.6 (7.0)	1M: 24.7 (18.9)	54.9	<0.05	54% (6)
					3M: 12 (13.5)	67.6	<0.05	
			TRS	4.53 (0.5)	1M: 1.76 (0.7)	2.77	<0.05	55% (7)
					3M: 1.46 (0.5)	3.07	<0.05	
Arts *et al.*, 2016	10	THI		45.0 (40-53)$	1M: 38.0 (21.5-44.5)	7.0	NR	NR
					3M: 31.0 (22.0-46.5)	14.0	NR	
		TQ		40.0 (33.0-51.0)$	1M: 27.0 (23.5-38.5)	13.0	NR	NR
					3M: 23.5 (13.8-43.3)	16.5	NR	
			VAS-L	7.1 (6.4-7.7)$	1M: 3.2 (2.0-5.8)	3.9	NR	NR
					3M: 3.5 (1.6-6.6)	3.6	NR	
Kleine Punte *et al.*, 2013	7	TQ		60.0 (15.7)	1M: 49.0 (14.3)	11.0	0.018	NR
					6M: 39.4 (12.4)	20.6	0.041	
			VAS-L	8.2 (1.2)	1M: 4.4 (1.3)	3.8	0.027	NR
					6M: 3.5 (1.7)	4.7	0.042	
Mertens *et al.*, 2016	23	TQ		55 (27-78)	1M: 41.5 (4-64)	13.5	<0.05	NR
					3M: 31 (5-59)	24.0	<0.05	
			VAS-L	8 (7-10)	1M: 4 (0-7)	4	<0.01	NR
					3M: 3 (0-7)	5	<0.01	
Ramos Macías *et al.*, 2018	16	THI		75 (10)$	Act.: 55 (28)$	20	<0.05	NR
					1M: 38 (27)$	37	<0.001	
					6M: 40 (29)$	35	<0.001	
					12M: 35 (31)$	40	<0.001	
			VAS-L	8.2 (1.2)$	Act.: 3.1 (3.5)$	5.1	<0.05	NR
					1M: 2.7 (3.16)$	5.5	<0.05	
					6M: 2.4 (3.1)$	5.8	<0.001	
					12M: 2.2 (2.1)$	6.0	<0.001	

Ramos Macías *et al.*, 2012	10	THI		72.1 (9.2)	1M: 27.4 (20.0)	44.7	<0.05	20% (2)
					3M: 14.3 (17.9)	57.8	<0.05	
			VAS-L	7.9 (2.0)	3M: 2.7 (1.6)	5.2	<0.05	
Poncet-Wallet *et al.*, 2019	26	THI		72 (9)	Act.: 62 (18)	10	0.34	NR
					2M: 45[$]	27	<0.05	
					4M: 40[$]	32	<0.05	
					7M: 34[$]	38	<0.05	
					13M: 26 (20)	46	<0.05	
		TRQ		51.6 (18.0)	Act.: 55.0[$]	-3.4	>0.05	NR
					2M: 34.0[$]	17.6	>0.05	
					4M: 36.0[$]	15.6	<0.05	
					7M: 30.0[$]	21.6	<0.05	
					13M: 19.5 (19)	32.1	<0.05	
		STSS		12.5 (2.0)	Act.: 13.0[$]	-0.5	>0.05	NR
					2M: 11.0[$]	1.5	>0.05	
					4M: 10.5[$]	2.0	>0.05	
					7M: 9.0[$]	3.5	<0.05	
					13M: 7.6 (4)	4.9	<0.05	
			VAS-A	8.1 (1.0)	Act.: 7.9[$]	0.2	NR	NR
					2M: 6.0[$]	2.1	<0.05	
					4M: 5.5[$]	2.6	<0.05	
					7M: 4.5[$]	3.6	<0.05	
					13M: 3.6[$]	4.5	<0.05	
			VAS-L	8.0 (1.0)	Act.: 7.4[$]	0.6	NR	NR
					2M: 6.0[$]	2.0	<0.05	
					4M: 5.6[$]	2.4	<0.05	
					7M: 4.0[$]	4.0	<0.05	
					13M: 4.0[$]	4.0	<0.05	

Scores mentioned are the mean followed by the standard deviation (SD), or the median followed by 95% confidence intervals (Arts et al., 2016) or the median followed by the range (Mertens et al., 2016), depending on the results reported in the publications. Difference in scores are calculated values.

Act. : (at) activation ; M : month(s) of follow-up ; NR : not reported ; STSS : subjective tinnitus severity scale ; THI : tinnitus handicap inventory ; TQ : tinnitus questionnaire ; TRQ : tinnitus reaction questionnaire ; TRS-S : tinnitus rating scale-severity ; VAS-A : visual analogue scale-annoyance ; VAS-L : visual analogue scale-loudness.

*Post-implantation score corresponds to the condition CI On. [$]Data not available in publication : extracted from graphs or obtained after email requests.

The decrease between pre-implantation and post-implantation THI scores at 3 months post-implantation ranged between 14.0 points (pre-implantation : 45.0 (95% CI 40.0-53.0) ; 3M : 31.0 (95% CI 22.0-46.5))[56] and 67.6 points (pre-implantation : 79.6 (SD 7.0) ; 3M : 12.0 (SD 13.5) ; $p < 0.05$)[71]. Only Ramos et al. presented longer follow-up periods[70]. The difference in THI scores found by Ramos et al. was 35 points at 6 months and 40 points at 12 months (pre-implantation : 75 (SD 10) ; 6M : 40 (SD 29) ; 12M : 35 (SD 31) ; $p < 0.001$).

The decrease on the TQ scores at 3 months post-implantation was 16.5 points (pre-implantation : 40.0 (95% CI 33.0-51.0) ; 3M : 23.5 (95% CI 13.7-43.2)[56] and 24 points (pre-implantation : 55 (range 27-78) ; 3M : 31 (range 5-59))[67]. The only available data between pre-implantation and 6 months post-implantation demonstrated a decrease of 20.6 points (pre-implantation : 60.0 (SD 15.7) ; 6M : 39.4 (SD 12.4) ; $p = 0.041$)[72].

The TRQ showed a decrease of 32.1 points between pre- and the longest follow-up of 13 months post-implantation (pre-implantation : 51.6 (SD 18.0) ; 13M : 19.5 (SD 19.0) ; $p < 0.05$)[74]. The TRQ decrease was already statistically significant at 2, 4 and 7 months post-implantation.

The decrease on the STSS scores pre- and 13 months post-implantation was 4.9 points (pre-implantation : 12.5 (SD 2.0) ; 13M : 7.6 (SD 4.0) ; $p < 0.05$)[74]. Tinnitus severity scores were statistically significant after 7 months of follow-up.

Single-item tinnitus questionnaires

The decrease in VAS loudness pre- and 3 months post-implantation was 3.6 points (pre-implantation : 7.1 (95% CI 6.4-7.7) ; 3M : 3.5 (95% CI 1.55-6.63))[56], 5 points (pre-implantation : 8 (range 7-10) ; 3M : 3 (range 0-7))[67], and 5.2 points (pre-implantation : 7.9 (SD 2.0) ; 3M : 2.7 (SD 1.6) ; $p < 0.05$)[73]. The difference in VAS loudness scores between pre- and 6 months post-implantation were 5.8 points (pre-implantation : 8.2 (SD 1) ; 6M : 2.4 (SD 3.0) ; 12M : 2.2 (SD 2.0) ; $p < 0.001$)[70] and 4.7 points (pre-implantation : 8.2 (SD 1.2) ; 6M : 3.5 (SD 1.7) ; $p = 0.042$)[72]. Differences between pre- and post-implantation were statistically significant in all studies ($p < 0.05$).

The study of Ahmed et al. reported a significant difference in TRS scores of 3.07 points (pre-implantation : 4.53 (0.5) ; 3M : 1.46 (0.5) ; $p < 0.05$) for a duration of 3 months follow-up[71].

CI On vs CI Off

The differences between the two conditions CI On (active) and CI Off (inactive) have the same range among the three studies reporting this outcome : 4.3 points (CI On : 2.4 (SD 3.1) ; CI Off : 6.7 (SD 6.7) ; $p < 0.001$)[70], 4.5 points (CI On : 3.5 (SD 1.7) ; CI Off : 8.0 (SD 1.2) ; $p < 0.05$)[72] and 4.9 points (CI On : 3 (range 0-7) ; CI Off : 7.9 (range 7.1-8.8))[67]. All these differences were reported to be significant ($p < 0.05$).

Table 5. Results for CI On and CI Off.

Study (author, year)	No. of patients	Questionnaire	Score CI On	Score CI Off	Difference (Off - On)	p-value
Kleine Punte *et al.*, 2013	7	VAS-L	6M: 3.5 (1.7)	6M: 8.2 (1.2)	4.7	0.042
Mertens *et al.*, 2016	23	VAS-L	3M: 3.0 (0.0-7.0)[$]	3M: 7.9 (0.7-10.0)[$]	4.9	<0.01
Ramos Macías *et al.*, 2018	16	VAS-L	6M: 2.4 (3.1)[$]	6M: 6.7 (2.6)[$]	4.3	<0.05
			12M: 2.2 (2.1)[$]	12M: 6.5 (2.7)[$]	4.3	<0.05

Difference in scores between CI Off and On are calculated values. Scores mentioned are the mean score followed by the standard deviation (SD) or the median followed by the range, depending on the results reported in the publications.

M : months of follow-up ; VAS-L : visual analogue scale-loudness.

[$]Data not available in publication : extracted from graphs or obtained after email requests.

Total suppression

In two studies total tinnitus suppression was reported. Ahmed et al. reported a total suppression for 7 out of 13 (54%) participants post-implantation[71]. In the study of Ramos et al., 2 out of 10 (20%) experienced total tinnitus suppression post-implantation[73]. Total suppression in these two studies was observed in an active CI condition. Mertens et al. reported a total tinnitus relief in 2 out of 23 (9%) participants, even when the CI was turned off[67].

Adverse effects

One subject experienced a worsening of his tinnitus loudness after implantation in the study of Poncet-Wallet et al., and therefore ended his participation after the 4 months visit[74]. No other adverse effects were reported in the included studies, such as the occurrence of negative effects related to the cochlear implant placement or activation (e.g. infection, pain or discomfort, facial nerve palsy, dizziness).

Discussion

In this study, we described the results of a systematic review on the effect of intracochlear electrical stimulation by cochlear implantation for patients with tinnitus as a primary complaint. A total of 105 patients out of 7 studies were included in the review. All patients had single-sided deafness or asymmetrical hearing loss. All seven studies showed a statistically significant reduction in tinnitus distress and loudness assessed by multi- and single-item questionnaires[56,67,70–73]. Moreover, cases of total suppression were reported in three studies[67,71,73]. An increase in tinnitus loudness was reported in one subject[74]. Except for this case, tinnitus reduction was reported for all patients who received the intervention.

We found a clinically relevant tinnitus reduction in all included studies for every reported follow-up moment from 3 months and beyond. We observed a large difference in reported pre- and post-operative THI scores between studies. This can be due to interindividual variability and the difference in THI score cut-off used for inclusion. In fact, on the basis of the THI score, the study of Arts et al. recruited patients with moderate to severe tinnitus burden (THI > 38[56] ; note that all included patients in this study had severe tinnitus based on the VAS loudness (> 7) and the TQ (> 42)) whereas all the others studies recruited patients with only severe tinnitus burden with a THI score > 58).

There was a statistically significant difference in tinnitus scores between the CI On and CI Off situation. This outcome can isolate the contribution of the electrical stimulation from the effect of the cochlear implantation. In Mertens et al., the tinnitus scores pre-implantation and post-implantation with a CI Off-mode were similar[67]. Hence, the positive effect on the tinnitus after cochlear implantation seems to be caused by the electrical stimulation of the auditory nerve and not by the cochlear trauma due to the intervention[77]. The mechanism of tinnitus suppression after cochlear implantation is not yet fully understood. A masking effect could have modulated the tinnitus perception. Moreover, neuroplasticity of the auditory pathway could be triggered by the electrical stimulation and contribute to the tinnitus improvement[78,79]. More research needs to be conducted to investigate the physiology of electrical stimulation as a factor of tinnitus reduction in CI recipients.

Until now, two systematic reviews focused on cochlear implantation for severe-to-profound hearing loss and its effect on tinnitus[7,14]. Ramakers et al. reviewed the effect of cochlear implantation on tinnitus in patients with bilateral hearing loss[7]. Another recent review presented an overview of the effect of cochlear implantation on tinnitus in single-sided deaf patients[14]. In this review, in the

majority of the included studies patients did not receive their implant primarily for tinnitus reduction. This could explain why tinnitus burden in the included studies of this review was generally low. Three studies of this review (with single-sided deaf patients)[56,71,73] were also included in our review. Both previous reviews reported improvement of tinnitus after cochlear implantation. Cases of tinnitus worsening after cochlear implantation were also mentioned (2.5%[14] and 0-25%[7]). Both systematic reviews reported a high degree of heterogeneity among the included studies. Therefore, the authors were not able to perform a meta-analysis. Only one out of 105 included patients in our review suffered from increased tinnitus distress after cochlear implantation. This can be explained by the fact that we focused on patients with severe or incapacitating tinnitus as primary complaint.

There are considerable risks of bias in the included studies in our review. The effect estimates are based on only seven studies investigating the effect of cochlear implantation on primary tinnitus distress. These studies were not randomized, had relatively small sample sizes, and showed considerable risks of bias. In all the studies, patients also had single-sided deafness or asymmetrical hearing loss besides tinnitus complaints. This is a restricted population which cannot be extended to all hearing-impaired profiles. In fact, the study of Mertens et al. reported scores of tinnitus in SSD and asymmetrical hearing-impaired patients receiving a cochlear implant, which could not be extracted separately[67]. The use of different tinnitus questionnaires and different follow-up periods in each study presented challenges to strive for a common conclusion. For instance, the study of Poncet-Wallet et al. used different follow-up moments of 4, 7 and 13 months instead of the more standard evaluations at 3, 6 and 12 months post-implantation[74]. Most of the studies performed a deviation to the standard intervention, like specific electrode selection and activation, additional acoustic stimulation procedures, or fitting programs depending on the tinnitus outcomes. Three studies used specific tinnitus fittings (i.e. a personalized tinnitus program[56], white noise stimulation[74], or specific location of electrode stimulation[72]) during the first months after activation of the CI, after which they performed standard stimulation. This could result in bias, possibly influencing the outcomes. In addition, only a few studies reported outcomes of the active (CI On) and inactive (CI Off) conditions of the CI[67,70,72].

Our study population included only patients with single-sided deafness or asymmetrical hearing loss, even though we had no inclusion criteria for type of hearing loss. As a consequence, the outcomes of this systematic review cannot

be extended to a more general tinnitus population with other types of hearing loss. This finding can be explained by the fact that bilateral hearing-impaired patients experience hearing-related problems in daily functioning as primary concern, potentially necessitating cochlear implantation to restore hearing primarily. As single-sided deaf patients still have one (near-) normal hearing ear, tinnitus complaints could more often be the major concern to seek help in this group of patients[14,80]. The SSD population is therefore more exposed to studies investigating cochlear implantation for tinnitus.

All studies only focused on tinnitus distress outcomes. The most commonly used multi-item tinnitus questionnaire was the THI[24]. The Tinnitus Functional Index (TFI) is a new internationally validated questionnaire for treatment-related changes and is considered nowadays as a reference standard in tinnitus evaluation[23,81]. To make outcomes of future studies comparable this outcome measure needs to be considered to be used in future studies.

Evidence-based medicine suggests that the highest level of evidence needs to be achieved to make clinical decisions[82]. In the context of this systematic review, the research question "what is the effect of cochlear implantation for patient with incapacitating tinnitus?" can be qualified as a treatment question. The highest level of evidence for this type of question should allow for comparison between an intervention group and a control group. An adequate power calculation based on a specific population and sample size, could boost the level of evidence.

Conclusion

In summary, this systematic review provides an overview of the current literature about the effect of cochlear implantation on tinnitus as a primary complaint. It shows that cochlear implantation is an effective treatment option for patients with severe tinnitus and accompanying asymmetrical hearing loss or single-sided deafness to reduce tinnitus distress. Though, till date, studies on this topic have generally considerable risks of bias and suboptimal research methods. Therefore, studies with a higher level of evidence are essential to assess the effect of cochlear implantation on tinnitus.

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References

1. Møller, A. R., Langguth, B., De Ridder, D. & Kleinjung, T. Textbook of tinnitus. Textb. Tinnitus 1–785 (2011) doi:10.1007/978-1-60761-145-5.
2. Erlandsson, S. I. & Hallberg, L. R.-M. Prediction of Quality of Life in Patients with Tinnitus. Br. J. Audiol. 34, 11–19 (2000).
3. Langguth, B., Landgrebe, M., Kleinjung, T., Sand, G. P. & Hajak, G. Tinnitus and depression. World J. Biol. Psychiatry 12, 489–500 (2011).
4. Alster, J., Shemesh, Z., Ornan, M. & Attias, J. Sleep disturbance associated with chronic tinnitus. Biol. Psychiatry 34, 84–90 (1993).
5. Dobie, R. A. A Review of Randomized Clinical Trials in Tinnitus. Laryngoscope 109, 1202–1211 (1999).
6. Hoare, D. J., Kowalkowski, V. L., Kang, S. & Hall, D. A. Systematic review and meta-analyses of randomized controlled trials examining tinnitus management. Laryngoscope 121, 1555–1564 (2011).
7. Ramakers, G. G. J., Van Zon, A., Stegeman, I. & Grolman, W. The effect of cochlear implantation on tinnitus in patients with bilateral hearing loss : A systematic review. Laryngoscope 125, 2584–2592 (2015).
8. Baguley, D. M. & Atlas, M. D. Cochlear implants and tinnitus. in Tinnitus : Pathophysiology and Treatment (eds. Langguth, B., Hajak, G., Kleinjung, T., Cacace, A. & Møller, A. R. B. T.-P. in B. R.) vol. 166 347–355 (Elsevier, 2007).
9. Kim, D. K. et al. Tinnitus in patients with profound hearing loss and the effect of cochlear implantation. Eur. Arch. Oto-Rhino-Laryngology 270, 1803–1808 (2013).
10. Blamey, P. & Beynon, A. Factors Affecting Auditory Performance of Postlinguistically Deaf Adults Using Cochlear Implants : An Update with 2251 Patients. 3002, 36–47 (2013).
11. Hamzavi, J., Franz, P., Baumgartner, W. D. & Gstöettner, W. Hearing Performance in Noise of Cochlear Implant Patients versus Severely-Profoundly Hearing-Impaired Patients with Hearing Aids : Rendimiento auditivo en ambiente ruidoso en pacientes con implante coclear versus hipoacúsicos profundos con auxiliar auditivo. Audiology 40, 26–31 (2001).
12. Dixon, Ã. P. R. et al. Predicting Reduced Tinnitus Burden After Cochlear Implantation in Adults. (2019) doi:10.1097/MAO.0000000000002481.
13. Van De Heyning, P. et al. Incapacitating unilateral tinnitus in single-sided deafness treated by cochlear implantation. Ann. Otol. Rhinol. Laryngol. 117, 645–652 (2008).
14. Peter, N., Liyanage, N., Pfiffner, F., Huber, A. & Kleinjung, T. The Influence of Cochlear Implantation on Tinnitus in Patients with Single-Sided Deafness : A Systematic Review. Otolaryngol. - Head Neck Surg. (2019) doi:10.1177/0194599819846084.
15. Amoodi, H. A. et al. The effects of unilateral cochlear implantation on the tinnitus handicap inventory and the influence on quality of life. Laryngoscope 121, 1536–1540 (2011).

16. Daneshi, A., Mahmoudian, S., Farhadi, M., Hasanzadeh, S. & Ghalebaghi, B. Auditory electrical tinnitus suppression in patients with and without implants. Int. Tinnitus J. 11, 85–91 (2005).

17. Olze, H. et al. The Impact of Cochlear Implantation on Tinnitus, Stress and Quality of Life in Postlingually Deafened Patients. Audiol. Neurotol. 17, 2–11 (2012).

18. Moher, D. et al. Preferred reporting items for systematic reviews and meta-analyses : The PRISMA statement. PLoS Med. 6, (2009).

19. Ouzzani, M., Hammady, H., Fedorowicz, Z. & Elmagarmid, A. Rayyan-a web and mobile app for systematic reviews. Syst. Rev. 5, 1–10 (2016).

20. Sterne, J. et al. RoB 2 : A revised tool for assessing risk of bias in randomised trials. BMJ 366, 1–8 (2019).

21. Sterne, J. et al. ROBINS-I : A tool for assessing risk of bias in non-randomised studies of interventions. BMJ 355, 4–10 (2016).

22. Meikle, M. B. et al. The tinnitus functional index : Development of a new clinical measure for chronic, intrusive tinnitus. Ear Hear. (2012) doi:10.1097/AUD.0b013e31822f67c0.

23. Rabau, S., Wouters, K. & Van de Heyning, P. Validation and translation of the Dutch tinnitus functional index. B-ENT 10, 251–258 (2014).

24. Newman, C. W., Sandridge, S. A. & Jacobson, G. P. Psychometric adequacy of the Tinnitus Handicap Inventory (THI) for evaluating treatment outcome. J. Am. Acad. Audiol. 9, 153–60 (1998).

25. Zeman, F. & Koller, M. Tinnitus Handicap Inventory for Evaluating Treatment Effects : Which -- Head and Neck Surgery Tinnitus Handicap Inventory for Evaluating Treatment Effects : Which Changes Are Clinically. (2011) doi:10.1177/0194599811403882.

26. Goebel, G. & Hiller, W. [The tinnitus questionnaire. A standard instrument for grading the degree of tinnitus. Results of a multicenter study with the tinnitus questionnaire]. HNO 42, 166–172 (1994).

27. Meeus, O., Blaivie, C. & Van de Heyning, P. Validation of the Dutch and the French version of the Tinnitus Questionnaire. B-ENT 3 Suppl 7, 11–17 (2007).

28. Hall, D. A., Mehta, R. L. & Argstatter, H. Interpreting the Tinnitus Questionnaire (German version) : what individual differences are clinically important? Int. J. Audiol. 57, 553–557 (2018).

29. Meric, C., Pham, E. & Chery-Croze, S. Validation of French translation of the 'Tinnitus Reaction Questionnaire', Wilson et al. 1991. Encephale. 23, 442–446 (1997).

30. Wilson, P. H., Henry, J., Bowen, M. & Haralambous, G. Tinnitus reaction questionnaire : psychometric properties of a measure of distress associated with tinnitus. J. Speech Hear. Res. 34, 197–201 (1991).

31. Halford, J. B. & Anderson, S. D. Tinnitus severity measured by a subjective scale, audiometry and clinical judgement. J. Laryngol. Otol. 105, 89–93 (1991).

32. Méric, C., Pham, E. & Chéry-Croze, S. Translation and validation of the subjective scale of Tinnitus severity. J Fr ORL 45, 409–12 (1996).

33. Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen : The Nordic Cochrane Centre, The Cochrane Collaboration. (2014).

34. Higgins, J. et al. Cochrane Handbook for Systematic Reviews of Interventions. (Chichester (UK) : John Wiley & Sons, 2019).

35. Higgins, J. & Thompson, S. G. Quantifying heterogeneity in a meta-analysis. Stat. Med. 21, 1539–1558 (2002).

36. Wang, Q. et al. Interaction of tinnitus suppression and hearing ability after cochlear implantation. Acta Otolaryngol. 137, 1077–1082 (2017).

37. Aschendorff, Pabst, Klenzner & Laszig. Tinnitus in Cochlear Implant Users : The Freiburg Experience. Int. Tinnitus J. 4, 162–164 (1998).

38. Di Nardo, W. et al. Tinnitus modifications after cochlear implantation. Eur. Arch. Otorhinolaryngol. 264, 1145–1149 (2007).

39. Fukuda & Albernaz. The AllHear Cochlear Implant and Tinnitus. Int. Tinnitus J. 4, 159–161 (1998).

40. Holder, J. T., O'Connell, B., Hedley-Williams, A. & Wanna, G. Cochlear implantation for single-sided deafness and tinnitus suppression. Am. J. Otolaryngol. 38, 226–229 (2017).

41. Kitoh, R. et al. The effects of cochlear implantation in Japanese single-sided deafness patients : five case reports. Acta Otolaryngol. 136, 460–464 (2016).

42. McKerrow, W. S., Schreiner, C. E., Snyder, R. L., Merzenich, M. M. & Toner, J. G. Tinnitus suppression by cochlear implants. Ann. Otol. Rhinol. Laryngol. 100, 552–558 (1991).

43. Arts, R. A. G. J., George, E. L. J., Griessner, A., Zierhofer, C. & Stokroos, R. J. Tinnitus suppression by intracochlear electrical stimulation in single-sided deafness : A prospective clinical trial - Part i. Audiol. Neurotol. 20, 294–313 (2015).

44. Liu, Y. et al. Suppression of Tinnitus in Chinese Patients Receiving Regular Cochlear Implant Programming. Ann. Otol. Rhinol. Laryngol. 125, 303–310 (2016).

45. Olze, H., Szczepek, A. J., Reich, U., Gräbel, S. & Uecker, F. Tinnitus suppression using electrical stimulation. Curr. Dir. Biomed. Eng. 4, 5–8 (2018).

46. Quaranta, N., Fernandez-Vega, S., D'elia, C., Filipo, R. & Quaranta, A. The effect of unilateral multichannel cochlear implant on bilaterally perceived tinnitus. Acta Otolaryngol. 128, 159–163 (2008).

47. Ruckenstein, M. J., Hedgepeth, C., Rafter, K. O., Montes, M. L. & Bigelow, D. C. Tinnitus suppression in patients with cochlear implants. Otol. Neurotol. Off. Publ. Am. Otol. Soc. Am. Neurotol. Soc. [and] Eur. Acad. Otol. Neurotol. 22, 200–204 (2001).

48. Seo, Y. J., Kim, H. J., Moon, I. S. & Choi, J. Y. Changes in Tinnitus After Middle Ear Implant Surgery : Comparisons With the Cochlear Implant. Ear Hear. 36, 705–709 (2015).

49. Skarzynski, H. et al. The hearing benefit of cochlear implantation for individuals with unilateral hearing loss, but no tinnitus. Acta Otolaryngol. 137, 723–729 (2017).

50. Tavora-Vieira, D., Marino, R., Krishnaswamy, J., Kuthbutheen, J. & Rajan, G. P. Cochlear implantation for unilateral deafness with and without tinnitus : a case series. Laryngoscope 123, 1251–1255 (2013).Cochrane Collaboration. (2014).

51. Battmer, R. D., Heermann, R. & Laszig, R. Suppression of tinnitus by electric stimulation in cochlear implant patients. HNO 37, 148–152 (1989).

52. Despreaux, G., Tison, P., Van Den Abbeele, T., Moine, A. & Frachet, B. [Tinnitus and implants]. Ann. Otolaryngol. Chir. Cervicofac. 107, 462–465 (1990).

53. Harada, C. Electrical tinnitus suppression--a comparative study of clinical trials and animal experiments. Hokkaido J. Med. Sci. 67, 785–800 (1992).

54. Wang, Q. et al. [Effect of cochlear implantation on bilateral perceived tinnitus of postlingually deafened patients]. Zhonghua Er Bi Yan Hou Tou Jing Wai Ke Za Zhi 50, 268–273 (2015).

55. Demajumdar, R., Stoddart, R., Donaldson, I. & Proops, D. W. Tinnitus, cochlear implants and how they affect patients. J. Laryngol. Otol. Suppl. 24, 24–26 (1999).

56. Arts, R. A. G. J. et al. Tinnitus Suppression by Intracochlear Electrical Stimulation in Single Sided Deafness – A Prospective Clinical Trial : Follow-Up. PLoS One 11, e0153131 (2016).

57. Arts, R. A. G. J. et al. The effect of tinnitus specific intracochlear stimulation on speech perception in patients with unilateral or asymmetric hearing loss accompanied with tinnitus and the effect of formal auditory training. Int. J. Audiol. 57, 426–439 (2018).

58. Mertens, G., Kleine Punte, A., De Ridder, D. & Van de Heyning, P. Tinnitus in a single-sided deaf ear reduces speech reception in the nontinnitus ear. Otol. Neurotol. 34, 662–666 (2013).

59. Mertens, G., Hofkens, A., Kleine Punte, A., De Bodt, M. & Van de Heyning, P. Hearing performance in single-sided deaf cochlear implant users after upgrade to a single-unit speech processor. Otol. Neurotol. 36, 51–60 (2015).

60. Thedinger, B., House, W. F. & Edgerton, B. J. Cochlear Implant for Tinnitus : Case Reports. Ann. Otol. Rhinol. Laryngol. 94, 10–13 (1985).

61. Vermeire, K. & Van De Heyning, P. Binaural hearing after cochlear implantation in subjects with unilateral sensorineural deafness and tinnitus. Audiol. Neurotol. 14, 163–171 (2009).

62. Vermeire, K. et al. Neural tonotopy in cochlear implants : an evaluation in unilateral cochlear implant patients with unilateral deafness and tinnitus. Hear. Res. 245, 98–106 (2008).

63. Boeheim, K., Pok, S. M. & Schloegel, M. B – Expanding criteria for cochlear implant candidacy ; Assessment and candidacy ; Surgical techniques. Int. J. Pediatr. Otorhinolaryngol. 75, 21 (2011).

64. Kleine Punte, A. B076 Cochlear implantation in single-sided deafness improves spatial hearing and tinnitus. Int. J. Pediatr. Otorhinolaryngol. 75, 24 (2011).

65. Kleine Punte, A. et al. Cochlear implantation as a durable tinnitus treatment in single-sided deafness. Cochlear Implants Int. 12 Suppl 1, (2011).

66. Song, J. J., Kleine Punte, A., De Ridder, D., Vanneste, S. & Van de Heyning, P. Neural substrates predicting improvement of tinnitus after cochlear implantation in patients with single-sided deafness. Hear. Res. 299, 1–9 (2013).

67. Mertens, G., De Bodt, M. & Van de Heyning, P. Cochlear implantation as a long-term treatment for ipsilateral incapacitating tinnitus in subjects with unilateral hearing loss up to 10 years. Hear. Res. 331, 1–6 (2016).

68. Mertens, G., Van Rompaey, V. & Van de Heyning, P. Electric-acoustic stimulation suppresses tinnitus in a subject with high-frequency single-sided deafness. Cochlear Implants Int. (2018) doi:10.1080/14670100.2018.1473940.

69. Ramos Macías, A. et al. Cochlear implants as a treatment option for unilateral hearing loss, severe tinnitus and hyperacusis. Audiol. Neurootol. 20 Suppl 1, 60–66 (2015).

70. Ramos Macías, A. et al. One-Year Results for Patients with Unilateral Hearing Loss and Accompanying Severe Tinnitus and Hyperacusis Treated with a Cochlear Implant. Audiol. Neurotol. 23, 8–19 (2018).

71. Ahmed, M. F. & Khater, A. Tinnitus suppression after cochlear implantation in patients with single-sided deafness. Egypt. J. Otolaryngol. 33, 61 (2017).

72. Kleine Punte, A., De Ridder, D. & Van De Heyning, P. On the necessity of full length electrical cochlear stimulation to suppress severe tinnitus in single-sided deafness. Hear. Res. 295, 24–29 (2013).

73. Ramos Macías, A. et al. Cochlear Implant in Patients With Sudden Unilateral Sensorineural Hearing Loss and Associated Tinnitus. Acta Otorrinolaringol. (English Ed. 63, 15–20 (2012).

74. Poncet-Wallet, C. et al. Prospective Multicentric Follow-up Study of Cochlear Implantation in Adults With Single-Sided Deafness : Tinnitus and Audiological Outcomes. 0, (2019).

75. Frachet, B. Protocol : Tinnitus Treatment With Cochlear Implant in Single Sided Deafness. Clin. [Online] (2018) doi:NCT02966366.

76. Punte, A. K., De Ridder, D. & Van de Heyning, P. On the necessity of full length electrical cochlear stimulation to suppress severe tinnitus in single-sided deafness. Hearing research vol. 295 24–29 (2013).

77. Mallen, J. R. et al. Quantifying tinnitus suppression in cochlear implantation using tinnitus interval-limited tracking. Laryngoscope 1–6 (2019) doi:10.1002/lary.28414.

78. Noreña, A. J. Revisiting the Cochlear and Central Mechanisms of Tinnitus and Therapeutic Approaches. Audiol. Neurotol. 20(suppl 1, 53–59 (2015).

79. Tyler, R. S. et al. Electrical Stimulation of the Cochlea to Reduce Tinnitus. Semin Hear 29, 326–332 (2008).

80. Tokita, J., Dunn, C. & Hansen, M. R. Cochlear implantation and single-sided deafness. Curr. Opin. Otolaryngol. Head Neck Surg. 22, 353–358 (2014).

81. Meikle, M. B. et al. Erratum : The tinnitus functional index : Development of a new clinical measure for chronic, intrusive tinnitus (Ear and Hearing (2012) 33 (153-176)). Ear Hear. 33, 443 (2012).

82. Burns, P. B., Rohrich, R. J. & Chung, K. C. The Levels of Evidence and their role in Evidence-Based Medicine. Plast Reconstr Surg. 128, 305–310 (2011).

3

Effect of electrical stimulation with a cochlear implant on tinnitus impact : *protocol of an individual patient data meta-analysis*

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Abstract

Introduction

Tinnitus is the perception of sound without an external stimulus, often experienced as a ringing, buzzing sound. While several studies have shown a reduction in tinnitus distress following cochlear implantation, others showed an increase or no change after implantation. At this stage, clinicians have little certainty when counselling their patients prior to implantation regarding tinnitus post-implantation. To help clinicians to counsel cochlear implant (CI) candidates on the risk of developing or improving tinnitus after implantation, we aim to assess the effect of electrical stimulation with a CI on tinnitus impact for individual adult patients with tinnitus. We will also apply prediction models to individual patient data (IPD) of clinical trials to find predictive factors of the effect of electrical stimulation on tinnitus impact.

Method and analysis

The IPD meta-analysis is a follow-up project of the systematic review on cochlear implantation in patients with tinnitus as a primary complaint. First, the systematic searches will be updated to date. Methodological quality of eligible studies will be assessed using the Risk of Bias In Non-randomised Studies of Intervention tool (ROBINS-I). Based on a data-sharing agreement, authors of the eligible studies will be invited to share their deidentified and complete IPD. The primary outcome is the effect of electrical stimulation with a CI on tinnitus impact 1 month or more post-implantation. IPD meta-analysis will be used to assess the primary outcome, while differentiating the tinnitus impact questionnaires. Second, linear regression analyses will be used to model the effect of electrical stimulation on tinnitus impact based on relevant predictors.

Ethics and dissemination

The Medical Research Involving Human Subject Act does not apply, and ethical approval is not required. The study results will be made accessible to the public in a peer-review open access journal.

PROSPERO registration number CRD42022319367, review ongoing.

Strengths and limitations of the study

- → This IPD-meta-analysis (IPD) is a further step towards evidence-based medicine for the clinical efficacy of electrical stimulation with a cochlear implant on tinnitus.
- → The IPD approach permits to combine different scales of tinnitus impact measurement and to allow in-depth exploration of patient factors.
- → The large number of participants in the IPD set allows us to evaluate up to 31 parameters in the model, if available.
- → Due to the retrospective nature, it is possible that some predictors cannot be included in our predictive models due to unavailability in the included studies.
- → Due to the heterogeneity in tinnitus impact assessment, a sensitivity analysis is needed to differentiate scores from different tinnitus multi-item and single-item questionnaires.

Introduction

Tinnitus is the perception of sound without an external stimulus, often experienced as a ringing, buzzing sound[1,2]. It is a common symptom with an approximate prevalence between 10 and 30% depending on the population[3]. Tinnitus can be disabling or incapacitating for people affected. Tinnitus impact can be defined by several functional effects such as tinnitus burden, distress, severity, annoyance, intrusiveness and loudness. Until now, there is no treatment for tinnitus but only therapy to reduce symptoms[4–8].

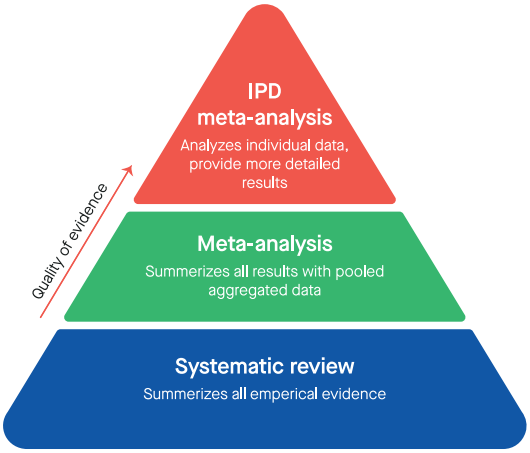
While the pathophysiology of tinnitus is still not fully understood, one hypothesis is that tinnitus origins from an auditory deprivation in combination with a stressing factor resulting in neural synchrony. Hearing loss is the most common risk factor associated with tinnitus[9,10]. Approximately 66-86% of patients with severe to profound hearing loss report tinnitus[11,12].

Providing electrical stimulation to the auditory pathway might be a possible treatment for tinnitus. In fact, electrical stimulation through a cochlear implant already showed positive effects on tinnitus distress in patients receiving a cochlear implant to restore hearing function[13,14]. Some studies reported cases of tinnitus worsening after cochlear implantation[11,14]. The variability of tinnitus outcomes following cochlear implantation might be associated with patient characteristics, hearing characteristics, tinnitus characteristics prior to surgery, trauma provoked by the implantation procedure or different electrical stimulation strategies[15–19]. Moreover, it is still unclear what the effect of electrical stimulation with a cochlear implant will be when patients do receive an implant primarily for tinnitus and not for hearing loss. Our systematic review could not conclude on the effect of electrical stimulation for tinnitus as a primary complaint due to small sizes and considerable risk of bias within included studies[20].

At this stage, clinicians have little certainty when counselling their patients prior to implantation regarding tinnitus post-implantation. To help clinicians to counsel CI candidates on the risk of developing or improving tinnitus impact after implantation and thus help to manage patient expectations, an individual patient data (IPD) meta-analysis will be conducted. In an IPD meta-analysis, rather than extracting summary (aggregate) data from study publications, the original research data are sought directly from the researchers responsible for each study. These data can then be re-analysed centrally and combined, if appropriate, in meta-analyses. Although IPD meta-analysis requires more resources, IPD meta-analysis allows more uniformly consistent analyses and better characterization

of subgroups and outcomes compared to meta-analysis based on aggregated data (AD-MA)[21] (Figure 1). An IPD meta-analysis can provide a more accurate estimate of treatment efficacy and help identify individual factors influencing treatment outcomes[22]. We aim to assess the effect of electrical stimulation with a cochlear implant on tinnitus impact using an IPD meta-analysis. Second, we will identify predictive factors of the effect of electrical stimulation on tinnitus impact in individual adult patients with tinnitus.

Figure 1. Level of evidence of systematic reviews, meta-analyses and IPD meta-analyses.



IPD, individual patient data.

Method

The protocol is reported according to the Preferred Reporting Items for Systematic Review and Meta-Analysis protocols (PRISMA-P) statement[23]. The IPD meta-analysis will be reported according to the PRISMA-IPD statement[24].

PATIENT AND PUBLIC INVOLVEMENT

Patients were not involved in development of the protocol.

IDENTIFICATION OF RELEVANT STUDIES : A SYSTEMATIC REVIEW

A systematic review will be performed to identify and select any relevant studies published on the effect of electrical stimulation after cochlear implantation for patients with tinnitus as a primary complaint, since the systematic review published in October 2020[20].

Study eligibility criteria

All studies describing adult patients with tinnitus as a primary complaint will be included, only if they reported measures of tinnitus impact with a minimum of one-month or longer follow-up after cochlear implantation. A follow-up of one month or more after cochlear implantation is considered to be essential to investigate the effect of the intervention. Only subjective or primary tinnitus as defined by De Ridder et al. will be included[2]. Tinnitus is considered as a primary complaint when it is characterized by tinnitus questionnaire scores as severe or incapacitating before implantation (e.g., Tinnitus Functional Index (TFI) > 32[25], Tinnitus Handicap Inventory (THI) > 58[26], Tinnitus Questionnaire (TQ) > 42[27], Visual Analogue Scale (VAS) on tinnitus loudness or annoyance > 6[28]) or when it is explicitly mentioned that a cochlear implant is used primarily for tinnitus reduction purpose. No language or publication date restrictions will be applied. Studies involving children (< 18 years) or involving other interventions than cochlear implantation as well as studies with no tinnitus impact scores reported after implantation will be excluded.

Search strategy

The search strategy of the 2020 systematic review on cochlear implantation for tinnitus as a primary complaint will be reviewed and adapted if needed. The systematic search of PubMed, the Cochrane Library, CINHAL, Embase and Web of Science will be updated to May 2022 to find any potentially relevant studies. In addition to electronic database searches, reference lists were scanned to identify additional relevant studies. Trial registers such as ClinicalTrials.gov and the Netherlands Trial Register (trialregister.nl) will be searched for ongoing trials. Available datasets will also be scanned to identify relevant data to reply to our research question. Finally, contributing authors will be contacted to share any additional (published or unpublished) studies they are aware of.

Study selection

One review author will review the reference list of the 2020 systematic review for additional trials, where relevant full texts will be retrieved.

Next, after removing duplicates, two review authors will independently perform the titles/abstracts and full text screening of the retrieved articles according to the predefined in- and exclusion criteria. The screening tool used will be Rayyan[29]. Any conflict will be resolved by a discussion between the two reviewers.

DATA EXTRACTION AND MANAGEMENT

Corresponding authors of eligible studies published will be contacted by email by one review author. They will be invited to collaborate and share their de-identified and complete dataset. They will be asked to provide unpublished data where available. A data sharing agreement will be used before data transfer. Corresponding authors replying to the request email will be mentioned in the Acknowledgement section of the study manuscript. Study data will be considered unavailable when none of the authors indicate that the requested data are not available or cannot be shared.

After retrieval, the IPD of individual studies will be compared with published data. In case discrepancies, collaborators will be contacted to ask to clarification. The amount of missing data within each study will be discussed with collaborators and will be reduced as much as possible.

An aggregated database will be created containing a trial ID variable, patient demographics and characteristics, treatment conditions (surgery used, cochlear implant type, follow-up period) and outcome measure of interest. The aggregated database will have a multilevel structure, with individual trials as levels.

QUALITY ASSESSMENT ON INCLUDED STUDIES

Two reviewers will independently assess the methodological quality of eligible studies using the ROBINS-I. With this tool, the risk of bias will be evaluated in seven domains : confounding, selection of participants, classification of interventions, deviation from intended intervention, missing data, measurement of outcomes, and selection of reported results[30]. The criteria will be defined and adapted to our research question. Items will be scored as low risk of bias, moderate risk of bias, serious risk of bias, critical risk of bias, or unclear. Studies will be judged as having an overall low, moderate, serious, or critical risk of bias based on the guidelines of the ROBINS-I tool. Consensus will be obtained after discussion between the two reviewers. If the quality of eligible studies remains unclear, corresponding study authors will be contacted to obtain complementary information.

DATA SYNTHESIS

Descriptive analysis and evidence synthesis

Study and participant characteristics will be extracted from the data. If any, we will review the characteristics of eligible studies that did not contribute to the IPD to find any evidence of selection bias. Proportion will be used for categorical or binary variables and mean and standard deviation (SD) or median and interquartile (IQR) will be used for continuous variables.

The efficacy of electrical stimulation for each included study will be summarized at fixed time points by the IPD meta-analysis approach.

IPD META-ANALYSIS

Outcomes of interest

The primary outcome will be the effect of electrical stimulation on tinnitus impact (or synonyms) measured by multi-item tinnitus questionnaires or single-item VAS scores of acceptance, annoyance, awareness, intrusiveness, unpleasantness[31] or loudness[32].

Sample size considerations

Missing data will be studied and appropriate methods for handling them, such as multiple imputation, will be used[33]. Heterogeneity will be assessed with I^2.

STATISTICAL ANALYSIS

A two-stage approach will be used for the IPD meta-analysis[34–36]. In the first stage, each individual study will be analysed independently and a summary of the aggregated data will be provided. In the second stage, individual data will be combined to provide a pooled estimate of effect. Standard statistics and forest plots will result from the second phase. Odds ratios with 95% confidence intervals (95% CI) will be reported.

We will conduct one main and two sensitivity analyses. First, for the main analysis, individual meta-analysis will be performed for each type of multi- and single-item tinnitus questionnaire scores included. High convergent validities between different multi-item and single-item questionnaires are summarized in Table 1. Thereafter, as a first sensitivity analysis, multi-item and single-item tinnitus questionnaire scores measuring tinnitus impact will be pooled and analysed together if enough data are available. A regression analysis will be performed to correct scores from each type of tinnitus multi-item validated questionnaires. Finally, as a second sensitivity analysis, multi-item and single-

item tinnitus questionnaire scores will be standardized to a scale ranging between 0 and 100. The analysis will then be performed using the standardized tinnitus questionnaires scores per domain (e.g. loudness, distress, impact on daily life).

Table 1. Convergent validity between tinnitus questionnaires, reported by previous studies.

Study (authors, year)	N	Tinnitus questionnaires	Correlation coefficients	p-value
Baguley et al., 2000 [37]	78	TFI/TQ	0.881	<0.001
Zenner et al., 2005 [38]	273	TQ/VAS-L	0.54	<0.001
		TQ/VAS-A	0.66	<0.001
		TQ/VAS-C	0.58	<0.001
Huang et al., 2006 [39]	20	THI / VAS-L	0.64	0.002
Zeman et al., 2012 [40]	1318	THI / TQ	0.9	<0.05
Müller et al., 2016 [41]	260	TFI / THI	0.85	<0.01
Fackrell et al., 2016 [25]	294	TFI / THI	0.82	NI
		TFI / VAS-L	0.46	NI
		THI / VAS-L	0.41	NI
Hoff et al., 2017 [42]	100	TFI / THI	0.8	NI
		TFI / VAS-D	0.69	NI
Nascimento et al., 2019 [43]	148	THI / VAS-L	0.57	0.001
Jacquemin et al., 2019 [44]	100	TFI / TQ	0.82	NI
Boecking et al., 2021 [45]	210	TFI / TQ	0.78	NI
		TFI / THI	0.8	NI
		THI / TQ	0.83	NI

N : sample size ; NI : no information ; THI : Tinnitus Handicap Inventory ; TFI : Tinnitus Functional Index ; TQ : Tinnitus Questionnaire ; VAS-A : Visual analogue scale tinnitus annoyance ; VAS-C : Visual analogue scale tinnitus comfort ; VAS-D : Visual analogue scale tinnitus distress ; VAS-L : Visual analogue scale tinnitus loudness. The rows with similar colours correspond to a comparison between two similar tinnitus questionnaires.

SECONDARY ANALYSIS USING LINEAR REGRESSION MODEL

Outcome of interest

The secondary outcome is the prediction model of the effect of electrical stimulation on tinnitus impact (or synonyms) measured by multi-item tinnitus questionnaires or single-item VAS scores of acceptance, annoyance, awareness, intrusiveness, unpleasantness[31] or loudness[32].

Sample size considerations

Analysis of the secondary outcome will be carried out provided enough data are available ; else, only summary statistics will be reported.

Potential candidate predictors that are missing in more than 50% of the included studies will not be included in multivariable analyses. Variables with missing data will be studied and appropriate methods for handling them, such as multiple imputation, will be used[33].

Model development

As a secondary analysis, we will predict the effect of electrical stimulation on tinnitus impact using potential candidate predictors a priori selected by co-authors (Table 2). The selected predictors will be included in the linear regression analysis to assess their relative importance. Initially, all possible predictors will be examined individually in an univariable model to assess its relationships with the outcome of interest. All significant variables with a p-value lower than 0.05 will then be added to the multivariable model. The multivariable model will be fitted using backwards selection by eliminating candidate predictors one by one using the 5% significance level.

We will conduct one main and two sensitivity analyses. First, for the main analysis, individual meta-analysis will be performed for each type of multi- and single-item tinnitus questionnaire scores included. Thereafter, as a first sensitivity analysis, multi-item and single-item tinnitus questionnaire scores measuring tinnitus impact will be pooled and analysed together if enough data are available. A regression analysis will be performed to correct scores from each type of tinnitus multi-item validated questionnaires. Finally, as a second sensitivity analysis, multi-item and single-item tinnitus questionnaire scores will be standardized to a scale ranging between 0 and 100. The analysis will then be performed using the standardized tinnitus questionnaires scores per domain (e.g. loudness, distress, impact on daily life).

The Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) guidelines will be used for the modelling.

Candidate predictors

Candidate predictors will be based on the existing literature, clinical relevance and availability in the IPD set.

There is currently insufficient evidence and no consensus on potentially predictive factors of the effect of electrical stimulation with a cochlear implant on tinnitus impact. A few researchers have attempted to find predictive factors for the effect of cochlear implantation on tinnitus impact amongst individuals with bilateral severe-to-profound hearing loss. In these studies some pre-implantation tinnitus characteristics have been reported to predict a positive effect of cochlear implantation on tinnitus : unilateral localization of tinnitus[17] and higher pre-implantation tinnitus severity[16,46]. Hearing characteristics such poorer pre-implantation hearing thresholds[46], poor pre-implantation speech perception[17] and larger deterioration of residual hearing at 250 Hz (i.e. the difference in hearing threshold before and after surgery at this frequency)[17] were identified as potential predictive factors for tinnitus improvement after cochlear implantation. Comorbidities such as a less severe depression state was found to be associated with better post-implantation tinnitus outcomes[16]. In contrast, Kloostra et al. were not able to find predictors for a positive tinnitus outcome, using speech comprehension scores and pre-operative tinnitus distress, personality characteristics, anxiety and depression, hearing handicap questionnaires, although they did find predictors that negatively influence tinnitus outcome in terms of lower pre-implantation tinnitus handicap and hearing handicap[18]. None of the factors identified in the abovementioned studies were consistent among the various prediction models, which might be partly due to the small sample sizes of studies and high risk of bias of the presented models.

Based on these considerations and clinical reasoning, 31 potential candidate predictors can be found in Table 2 organized in six domains : demographics, tinnitus characteristics, hearing characteristics, imaging, comorbidities and treatment.

Table 2. Potential candidate predictors organized in domains.

Domains	Potential predictors
Demographics	1. Age at implantation 2. Gender 3. Social economic status 4. Highest education level
Tinnitus characteristics	5. Pre-implantation tinnitus impact multi- or single-item validated questionnaire 6. Tinnitus duration at the time of the implantation 7. Tinnitus localization 8. Tinnitus pitch-matched 9. Tinnitus loudness-matched 10. Tinnitus temporal pattern (constant or intermittent)
Hearing characteristics	11. Pre-implantation speech perception scores in quiet 12. Pre-implantation speech perception scores in noise 13. Pre-implantation hearing level in the future implanted ear (including means and per frequencies ranging from 125 Hz to 20 kHz) 14. Pre-implantation hearing level in the contralateral ear (including means and per frequencies ranging from 125 Hz to 20 kHz) 15. Pre-implantation subjective hearing disability measure (total score) assessed by a multi- or single-item validated questionnaire, holding outcomes on one or multiple domains covering body function, activity limitations and participation restrictions, environmental factors and personal factors[47,48]. 16. Pre-implantation electrophysiological outcomes (ABR or ECochG)
Imaging	17. Cochlear anatomy limiting cochlear implant performance based on imaging (e.g. cochlear ossification, cochlear dysplasia)
Comorbidities	18.Hyperacusis presence 19. Depression symptoms assessed by a multi- or single-item validated questionnaire 20.Anxiety symptoms assessed by a multi- or single-item validated questionnaire 21. Stress symptoms assessed by a multi- or single-item validated questionnaire 22. Personality assessed by a multi- or single-item validated questionnaire 23. Coping strategies assessed by a multi- or single-item validated questionnaire 24. Measure of general health assessed by a multi- or single-item validated questionnaire 25. Measure of quality of life assessed by a multi- or single-item validated questionnaire 26. Measure of sleep quality assessed by a rating 27. Cardiovascular disease presence diagnosed by a clinician 28. Metabolic disease presence diagnosed by a clinician 29.Neurological disease presence diagnosed by a clinician
Treatment	30.Hearing aid use in the future implanted ear 31. Hearing aid use in the contralateral ear

Subgroup analyses

Analyses will be conducted by subgroups of follow-up timelines and by subgroups of patients identified by previous tinnitus research on population data, if data permit.

FURTHER DEVELOPMENT OF STATISTICAL ANALYSIS PLAN

The main analysis is planned as described above. Modification or additional analyses may be performed as the data collection progresses. Updated statistical analysis plans will be available in PROSPERO if required.

SOFTWARE

All analyses will be performed using R Studio version 1.3.1073 (®R Studio). The IPD meta-analysis will be performed using RevMan[49].

ETHICS AND DISSEMINATION

There will be no identifiable patient data in any of datasets. If any identifiable patient is available, it will be anonymized. Therefore, the Medical Research Involving Humans Subject Act (WMO) does not apply to this study. The Medical Research Ethics Committee Utrecht, the Netherlands, reviewed the study protocol and concluded that an official approval was not required.

All corresponding authors of the included studies will provide written confirmation that all participants included in the original studies had given full written informed consent. The paper data files will be stored in a locked cabin in a locked room. The data will be stored within a secured folder of the data management department of the University Medical Center Utrecht. Data will be stored for at least 15 years at a central drive of the data management department of the University Medical Center Utrecht and will be made available for the use by third parties on request and approval of the research team.

The IPD meta-analysis will be published in a peer-review international journal.

REVIEW REGISTRATION AND ANTICIPATED END DATE OF STUDY

The protocol of the IPD meta-analysis has been registered in PROSPERO with the registration number CRD42022319367. The anticipated date of data collection is May 2022 and the anticipated end date of the study is May 2023.

Discussion

The IPD meta-analysis is complementary to the systematic review of 2020 in which seven studies were included investigating the effect of electrical stimulation with a cochlear implant for tinnitus as a primary complaint. This systematic review reported a high degree of heterogeneity among included studies and therefore a meta-analysis could not be performed. In IPD meta-analysis, data from several trials are standardized and analysed in a uniform way, which is useful to tackle heterogeneity between studies. Pooling individual patient data together increases power and enables to investigate interaction and subgroups effect. In this IPD meta-analysis, we aim to assess the effect of electrical stimulation with a cochlear implant on tinnitus impact and secondly predict the effect of cochlear implantation for individual adult patients with tinnitus.

Multiple tinnitus questionnaires are available to assess tinnitus impact and treatment responsiveness. Due to a lack of method standardization, interventional studies often differ in the questionnaires used. Therefore, literature on convergence between different tinnitus questionnaires has been reviewed by authors before drafting the protocol (Table 1). High convergence between validated multi-items questionnaires was shown in several studies[25,37,40,42,44,45,50]. Based on these findings, multi-item tinnitus questionnaires will be analysed together, if enough data are available. In a second stage, a sensitivity analysis will be performed to differentiate scores from each type of tinnitus multi-item validated questionnaires. Due to missing evidence on the convergence between multi-items and single-item tinnitus questionnaires, individual meta-analysis will be performed for each type of single-item tinnitus questionnaires.

This IPD meta-analysis is an efficient way to investigate whether the effect of electrical stimulation with a cochlear implant varies by patient characteristics. For this purpose, authors reviewed the current literature on predictive models of the effect of cochlear implantation on tinnitus and organized brainstorming sessions to discuss the clinical relevance of potential candidate predictors. This resulted in the selection of 31 candidate predictors classified in six domains (demographics, tinnitus characteristics, hearing characteristics, imaging, comorbidities and treatment) that could be used for future research studies on the same topic.

The main limitation of the project is missing data. It is likely that some potential candidate predictors will not be available in data of included studies and could not be included in our predictive models due to missing data in more than 50% of the studies. However, using available candidate predictors and using multiple imputation when applicable, the large sample size available in the IPD set will provide a unique opportunity to identify potential predictors explaining the variance of effect on tinnitus impact.

Despite additional efforts spent to gather and standardize the IPD, an IPD meta-analysis is the best way to estimate the overall effect on understudied populations, such as patients seeking help for tinnitus. We hope that this study will lead to a higher level of evidence and a better understanding of the effect of electrical stimulation as an effective treatment option for tinnitus.

Author contributions

KKSA, ALS and IS conceptualized, designed the study and developed the protocol. All authors (KKSA, ALS and IS) critically revised the draft of the protocol. IS provided statistical expertise in clinical trial design. KKSA drafted the manuscript. All other authors revised the manuscript. All authors read and approved the final version.

Competing interests

KKSA received funding from the European Union's Horizon 2020 research and innovation program under the Marie Sklodowska-Curie grant (agreement number 764604). KSSA is employed at Cochlear Technology Centre Belgium, Mechelen, Belgium. The content of the study belongs to the authors alone and do not reflect Cochlear Technology Centre Belgium policy. No further conflict of interest is reported by the authors.

Data statement

The data that support the findings of this study will be available from the corresponding author, KKSA, upon reasonable request.

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References

1. Baguley, D. M., McFerran, D. & Hall, D. Tinnitus. in The Lancet (2013). doi:10.1016/S0140-6736(13)60142-7.
2. De Ridder, D. et al. Tinnitus and tinnitus disorder : Theoretical and operational definitions (an international multidisciplinary proposal). in Progress in Brain Research vol. 260 1–25 (Elsevier B.V., 2021).
3. McCormack, A., Edmondson-Jones, M., Somerset, S. & Hall, D. A systematic review of the reporting of tinnitus prevalence and severity. Hearing Research (2016) doi:10.1016/j.heares.2016.05.009.
4. Martins, M. L. et al. Effect of transcranial Direct Current Stimulation for tinnitus treatment : A systematic review and meta-analysis. Neurophysiol. Clin. 52, 1–16 (2022).
5. Chen, J.-J. et al. Efficacy of pharmacologic treatment in tinnitus patients without specific or treatable origin : A network meta-analysis of randomised controlled trials. EClinicalMedicine 39, 101080 (2021).
6. Dong, C. et al. Low-Frequency Repetitive Transcranial Magnetic Stimulation for the Treatment of Chronic Tinnitus : A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Biomed Res. Int. 2020, 3141278 (2020).
7. Han, M., Yang, X. & Lv, J. Efficacy of tinnitus retraining therapy in the treatment of tinnitus : A meta-analysis and systematic review. Am. J. Otolaryngol. 42, 103151 (2021).
8. Chen, J.-J. et al. Association of Central Noninvasive Brain Stimulation Interventions With Efficacy and Safety in Tinnitus Management : A Meta-analysis. JAMA Otolaryngol. Head Neck Surg. 146, 801–809 (2020).
9. Nondahl, D. M. et al. Tinnitus and its risk factors in the Beaver Dam Offspring Study. Int. J. Audiol. (2011) doi:10.3109/14992027.2010.551220..
10. Eggermont, J. J. & Roberts, L. E. Tinnitus : animal models and findings in humans. Cell Tissue Res. 361, 311–336 (2015).
11. Quaranta, N., Wagstaff, S. & Baguley, D. M. Tinnitus and cochlear implantation. International Journal of Audiology vol. 43 245–251 (2004).
12. Baguley, D. M. & Atlas, M. D. Cochlear implants and tinnitus. in Tinnitus : Pathophysiology and Treatment (eds. Langguth, B., Hajak, G., Kleinjung, T., Cacace, A. & Møller, A. R. B. T.-P. in B. R.) vol. 166 347–355 (Elsevier, 2007).
13. Peter, N., Liyanage, N., Pfiffner, F., Huber, A. & Kleinjung, T. The Influence of Cochlear Implantation on Tinnitus in Patients with Single-Sided Deafness : A Systematic Review. Otolaryngol. - Head Neck Surg. (2019) doi:10.1177/0194599819846084.
14. Ramakers, G. G. J., Van Zon, A., Stegeman, I. & Grolman, W. The effect of cochlear implantation on tinnitus in patients with bilateral hearing loss : A systematic review. Laryngoscope 125, 2584–2592 (2015).
15. Dixon, Ã. P. R. et al. Predicting Reduced Tinnitus Burden After Cochlear Implantation in Adults. (2019) doi:10.1097/MAO.0000000000002481.

16. Kim, D. K. et al. Prospective, Multicenter Study on Tinnitus Changes after Cochlear Implantation. Audiol. Neurotol. 21, 165–171 (2016).

17. Ramakers, G. G. J. et al. Development and internal validation of a multivariable prediction model for tinnitus recovery following unilateral cochlear implantation : A cross-sectional retrospective study. BMJ Open 8, 1–9 (2018).

18. Kloostra, F. J. J., Arnold, R., Hofman, R., Burgerhof, J. G. M. & Dijk, P. Models to predict positive and negative effects of cochlear implantation on tinnitus. Laryngoscope Investig. Otolaryngol. 1–5 (2018) doi:10.1002/lio2.224.

19. Assouly, K. K. S. et al. Systematic Review on Intra- and Extracochlear Electrical Stimulation for Tinnitus. Brain Sci. 11, (2021).

20. Assouly, K. K. S., van Heteren, J. A. A., Stokroos, R. J., Stegeman, I. & Smit, A. L. Cochlear implantation for patients with tinnitus - A systematic review. Prog. Brain Res. 260, 27–50 (2021).

21. Tudur Smith, C. et al. Individual participant data meta-analyses compared with meta-analyses based on aggregate data. Cochrane database Syst. Rev. 9, MR000007 (2016)

22. Tierney, J., Stewart, L. & Clarke, M. Chapter 26 : Individual participant data. in Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.2 (updated February 2021). Cochrane, 2021. (2021).

23. Moher, D. et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Rev. Esp. Nutr. Humana y Diet. 20, 148–160 (2016).

24. Stewart, L. A. et al. Preferred reporting items for a systematic review and meta-analysis of individual participant data : The PRISMA-IPD statement. JAMA - J. Am. Med. Assoc. 313, 1657–1665 (2015).

25. Fackrell, K., Hall, D. A., Barry, J. G. & Hoare, D. J. Psychometric properties of the Tinnitus Functional Index (TFI) : Assessment in a UK research volunteer population. Hear. Res. 335, 220–235 (2016).

26. Newman, C. W., Sandridge, S. A. & Jacobson, G. P. Psychometric adequacy of the Tinnitus Handicap Inventory (THI) for evaluating treatment outcome. J. Am. Acad. Audiol. 9, 153–60 (1998).

27. Goebel, G. & Hiller, W. [The tinnitus questionnaire. A standard instrument for grading the degree of tinnitus. Results of a multicenter study with the tinnitus questionnaire]. HNO 42, 166–172 (1994).

28. Figueiredo, R. R., Azevedo, A. A. de & Oliveira, P. de M. Correlation analysis of the visual-analogue scale and the Tinnitus Handicap Inventory in tinnitus patients. Braz. J. Otorhinolaryngol. 75, 76–79 (2009).

29. Ouzzani, M., Hammady, H., Fedorowicz, Z. & Elmagarmid, A. Rayyan-a web and mobile app for systematic reviews. Syst. Rev. 5, 1–10 (2016).

30. Sterne, J. et al. ROBINS-I : A tool for assessing risk of bias in non-randomised studies of interventions. BMJ 355, 4–10 (2016).

31. Hall, D. A. et al. The COMiT'ID Study : Developing Core Outcome Domains Sets for Clinical Trials of Sound-, Psychology-, and Pharmacology-Based Interventions for Chronic Subjective Tinnitus in Adults. Trends Hear. 22, 1–16 (2018).

32. Rademaker, M. M., Essers, B. A. B., Stokroos, R. J. & Smit, A. L. What Tinnitus Therapy Outcome Measures Are Important for Patients ?– A Discrete Choice Experiment. 12, 1–10 (2021).

33. Quartagno, M. & Carpenter, J. R. Multiple imputation for IPD meta-analysis : allowing for heterogeneity and studies with missing covariates. Stat. Med. 35, 2938–2954 (2016).

34. Fisher, D. J. Two-stage Individual Participant Data Meta-analysis and Generalized Forest Plots. Stata J. 15, 369–396 (2015).

35. Simmonds, M. C. et al. Meta-analysis of individual patient data from randomized trials : a review of methods used in practice. Clin. Trials 2, 209–217 (2005).

36. Debray, T. P. A. et al. Get real in individual participant data (IPD) meta-analysis : A review of the methodology. Res. Synth. Methods 6, 293–309 (2015).

37. Baguley, D. M., Humphriss, R. L. & Hodgson, C. A. Convergent validity of the tinnitus handicap inventory and the tinnitus questionnaire. J. Laryngol. Otol. 114, 840–843 (2000).

38. Zenner, H. P., De Maddalena, H. & Zalaman, I. M. Validity and reliability study of three tinnitus self-assessment scales : Loudness, annoyance and change. Acta Otolaryngol. 125, 1184–1188 (2005).

39. Huang, C. Y. et al. Relationships among speech perception, self-rated tinnitus loudness and disability in tinnitus patients with normal pure-tone thresholds of hearing. ORL (2006) doi:10.1159/000096713.

40. Zeman, F. et al. Tinnitus assessment by means of standardized self-report questionnaires : Psychometric properties of the Tinnitus Questionnaire (TQ), the Tinnitus Handicap Inventory (THI), and their short versions in an international and multi-lingual sample. Health Qual. Life Outcomes 10, 1–10 (2012).

41. Müller, K. et al. Validation of online versions of tinnitus questionnaires translated into Swedish. Front. Aging Neurosci. 8, (2016)

42. Hoff, M. & Kähäri, K. A Swedish cross-cultural adaptation and validation of the Tinnitus Functional Index. Int. J. Audiol. 56, 277–285 (2017).

43. Nascimento, I. da P. et al. Tinnitus evaluation : relationship between pitch matching and loudness, visual analog scale and tinnitus handicap inventory. Braz. J. Otorhinolaryngol. 85, 611–616 (2019).

44. Jacquemin, L. et al. Sensitivity to change and convergent validity of the Tinnitus Functional Index (TFI) and the Tinnitus Questionnaire (TQ) : Clinical and research perspectives. Hear. Res. 382, 107796 (2019).

45. Boecking, B., Brueggemann, P., Kleinjung, T. & Mazurek, B. All for One and One for All? – Examining Convergent Validity and Responsiveness of the German Versions of the Tinnitus Questionnaire (TQ), Tinnitus Handicap Inventory (THI), and Tinnitus Functional Index (TFI). Front. Psychol. 12, (2021).

46. Dixon, P. R. et al. Predicting Reduced Tinnitus Burden after Cochlear Implantation in Adults. Otol. Neurotol. 41, 196–201 (2020).

47. Manchaiah, V., Granberg, S., Grover, V., Saunders, G. H. & Ann Hall, D. Content validity and readability of patient-reported questionnaire instruments of hearing disability. Int. J. Audiol. 58, 565–575 (2019).

48. Granberg, S., Swanepoel, D. W., Englund, U., Möller, C. & Danermark, B. The ICF core sets for hearing loss project : International expert survey on functioning and disability of adults with hearing loss using the international classification of functioning, disability, and health (ICF). Int. J. Audiol. 53, 497–506 (2014).

49. Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen : The Nordic Cochrane Centre, The Cochrane Collaboration. (2014).

50. Chandra, N., Chang, K., Lee, A., Shekhawat, G. S. & Searchfield, G. D. Psychometric validity, reliability, and responsiveness of the tinnitus functional index. J. Am. Acad. Audiol. 29, 609–625 (2018).

4

Cochlear implantation for tinnitus in adults with bilateral hearing loss : *protocol of a randomised controlled trial*

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Abstract

Introduction

Tinnitus is the perception of sound without an external stimulus, often experienced as a ringing or buzzing sound. Subjective tinnitus is assumed to origin from changes in neural activity caused by reduced or lack of auditory input, for instance due to hearing loss. Since auditory deprivation is thought to be one of the causes of tinnitus, increasing the auditory input by cochlear implantation might be a possible treatment. In studies assessing cochlear implantation for patients with hearing loss, tinnitus relief was seen as a secondary outcome. Therefore, we will assess the effect of cochlear implantation in patients with primarily tinnitus complaints.

Method and analysis

In this randomised controlled trial starting in January 2021 at the ENT department of the UMC Utrecht (the Netherlands), patients with a primary complaint of tinnitus will be included. Fifty patients (Tinnitus Functional Index (TFI) > 32, Beck's Depression Index < 19, pure tone average at 0.5, 1, 2 kHz: bilateral threshold between ≥ 40 and ≤ 80 dB and hearing thresholds in the ear to be implanted (≥ 4 kHz) ≥ 50 dB) will be randomised towards cochlear implantation or no intervention. Primary outcome of the study is tinnitus burden as measured by the TFI. Outcomes of interest are tinnitus severity, hearing performances (tinnitus pitch and loudness, speech perception), quality of life, depression and patient-related changes. Outcomes will be evaluated prior to implantation and at 3 and 6 months after the surgery. The control group will receive questionnaires at 3 and 6 months after randomisation. We expect a significant difference between the cochlear implant recipients and the control group for tinnitus burden.

Ethics and dissemination

This research protocol was approved by the Institutional Review Board of the University Medical Center (UMC) Utrecht (NL70319.041.19, V5.0, January 2021). The trial results will be made accessible to the public in a peer-review journal.

Trial registration number NL8693; Pre-results.

Strengths and limitations of the study

- → The randomised controlled study allows for high quality assessment of outcomes of cochlear implantation for patients suffering primarily from tinnitus and secondarily from moderate to moderately severe bilateral hearing loss.
- → Outcomes of interest are not limited to tinnitus burden but also consider anxiety and depression, quality of life and patient-related changes.
- → The intervention can induce risks associated with surgery and a residual hearing deterioration in the ear implanted which will be monitored by electrocochleography measurement.
- → This study is a further step towards evidence-based medicine for the clinical efficacy of cochlear implants as a tinnitus treatment.

Background

Tinnitus is the perception of sound without an external stimulus, often experienced as a ringing or buzzing sound[1,2]. It is a common symptom with an approximate prevalence of 10-30%, depending on the selected population[3], increasing to 30% of adults over the age of 50 years[4]. Tinnitus can be chronic and disabling for those individuals affected by it. It is a complex condition, in which many components are responsible for perceived burden, like loudness, comorbidity and sleep problems. The heterogeneous aspect of the disease is also accountable for differences in the tinnitus itself: localization, sound characteristics, temporal course and underlying cause. The tinnitus burden and the individual needs of patients for tinnitus related health care are various. While the underlying aetiology of tinnitus is still debated, one hypothesis is that the tinnitus arises from changes in neural activity caused by reduced or lack of auditory input due to hearing loss which often accompanies the tinnitus[5,6]. To date, the only evidence-based therapy for the reduction of tinnitus burden is cognitive behavioural therapy (CBT)[5,7–9] which is offered as standard clinical care in many countries in people with bothersome tinnitus[10]. However, this therapy only improves tinnitus distress but does not reduce tinnitus loudness[11]. Sound therapy is also considered as a recommendation for patients with hearing loss according to European guidelines but there is a lack of conclusive evidence[10,12,13].

Since auditory deprivation is thought to be one of the causes of tinnitus, increasing the auditory input by cochlear implantation might be a possible treatment option. This hypothesis is confirmed by observations in studies

assessing the effectiveness of cochlear implantation to restore hearing function in case of bilateral deafness, where tinnitus reduction is one of the secondary outcomes[14]. Analyzing the effect of intracochlear electrical stimulation with a cochlear implant (CI) on primarily tinnitus complaints has been investigated by only few studies. All studies assessing the effect of cochlear implantation for tinnitus concerned cases with single-sided deafness[15–20] or patients with asymmetrical hearing loss[6]. They all reported a significant tinnitus reduction after implantation. So far, there is no high level of evidence of the effect of intracochlear stimulation as an intervention for primary tinnitus complaint in case of bilateral moderate to severe hearing loss[14].

Above mentioned studies provide the first evidence of possible effectiveness of cochlear implantation for the reduction of tinnitus burden. To provide clear evidence of the effectiveness of cochlear implantation for the suppression of tinnitus complaints, a statistically powered study is needed aiming at patients with tinnitus as their primary complaint instead of hearing loss. To what extent electrical stimulation can reduce tinnitus in patients with bilateral moderate to severe hearing loss (just below the current CI indication), but with primary complaint of tinnitus, is unknown[21]. Therefore, we aim to study the effect of cochlear implantation on tinnitus burden in patients suffering primarily from tinnitus and failed standard clinical care. For these patients which also have a bilateral moderate to severe hearing loss, a randomized controlled trial (RCT) will be conducted in which cochlear implantation will be compared to no intervention.

Method and analysis

STUDY OBJECTIVES

The primary objective of this study is to assess the effect of electrical stimulation by a CI on tinnitus burden, measured with the Tinnitus Functional Index (TFI) at 6 months after cochlear implantation. Secondary outcomes are to assess the effect of CI on tinnitus severity, tinnitus pitch and loudness, auditory function, speech recognition, quality of life, symptoms of depression and anxiety, patient reported change in order to attest treatment-related differences.

PATIENT INVOLVEMENT

Patients were not involved in the design, or conduct, or reporting or dissemination plans of the study.

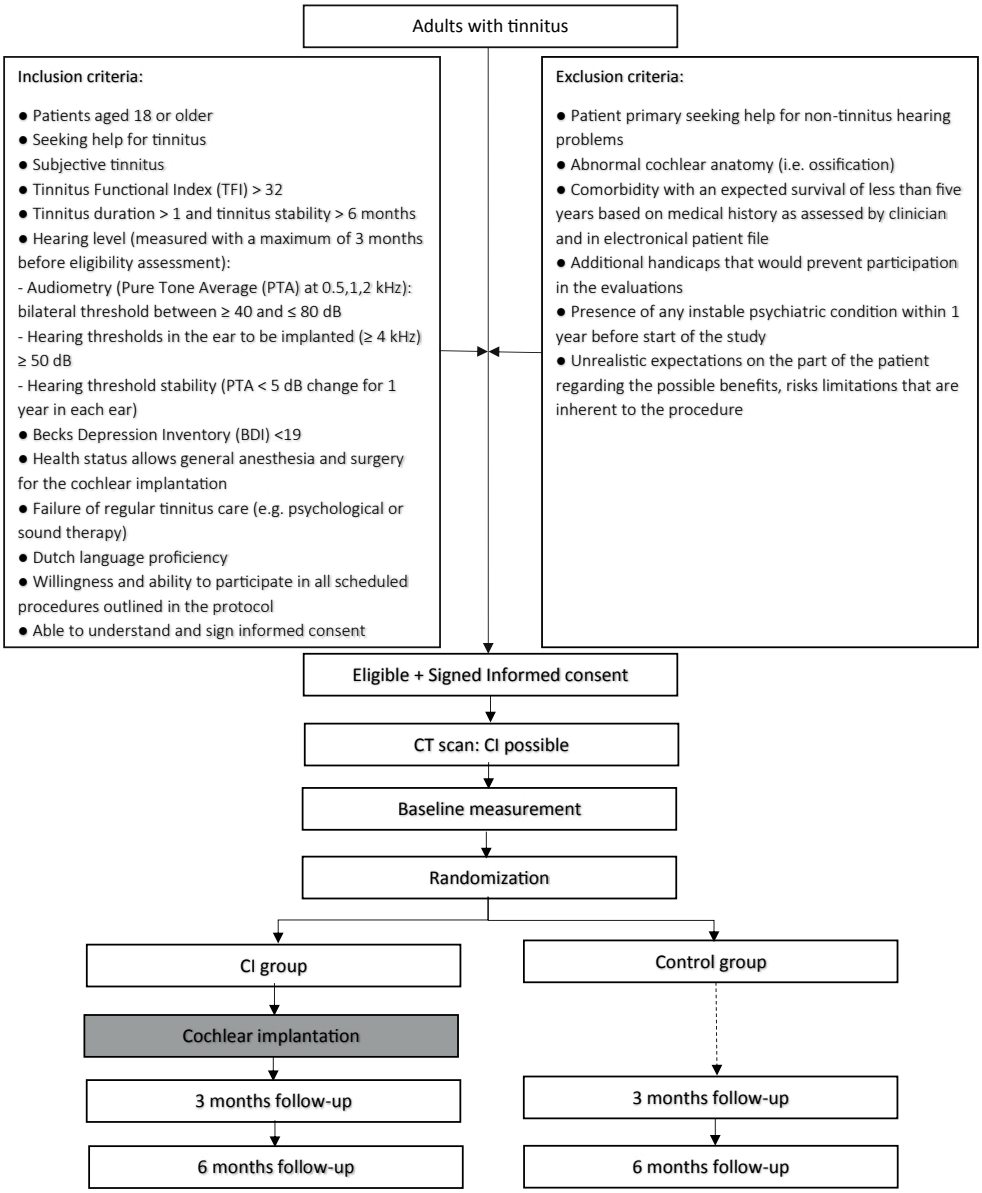
STUDY DESIGN AND SETTING

The study is a monocenter clinical trial performed in a tertiary referral clinic (university hospital) in the Netherlands (University Medical Center Utrecht). The protocol is reported according to the Standard Protocol Items: Recommendations for Interventional Trials statement statement[22]. In this RCT, patients will be randomized into groups: a CI group and a control group (Figure 1). Twenty-five patients (CI group) shall receive a CI in the ear mostly affected by tinnitus. The other 25 patients (control group) shall follow a follow up period of 6 months with no intervention. The follow-up sessions will take place 3 and 6 months after implantation to assess the primary outcome of tinnitus burden and secondary outcomes of quality of life, treatment related outcomes and auditory function.

STUDY POPULATION

The study population consists of patients seeking help for tinnitus, presenting at the outpatient clinic of Ear, Nose and Throat (ENT) of the UMC Utrecht, The Netherlands. Fifty patients aged 18 or older with moderate to severe tinnitus and moderate to severe hearing loss will be included after fulfilling eligibility and informed consent. They must meet the following criteria to be eligible for the study at randomisation.

Figure 1. Study flowchart. CI, cochlear implant group; control, control group.



INCLUSION CRITERIA

The eligibility criteria for patients are:

- Patients aged 18 or older.
- Seeking help for tinnitus.
- Subjective tinnitus.
- Moderate to catastrophic tinnitus burden: TFI > 32.
- Tinnitus duration > 1 year and tinnitus stability > 6 months.
- Hearing level (measured with a maximum of 3 months before eligibility assessment):
  - Audiometry (pure tone average (PTA) at 0.5, 1, 2 kHz): bilateral threshold between ≥ 40 and ≤ 80 dB.
  - Hearing thresholds in the ear to be implanted (≥ 4 kHz) ≥ 50 dB.
  - Hearing threshold stability (PTA < 5 dB change for 1 year in each ear).
- No to mild depression: Becks Depression Inventory (BDI) < 19.
- Health status allows general anaesthesia and surgery for the cochlear implantation.
- Failure of regular tinnitus care (eg, psychological or sound therapy).
- Dutch language proficiency.
- Willingness and ability to participate in all scheduled procedures outlined in the protocol.
- Able to understand and sign informed consent.

EXCLUSION CRITERIA

A potential patient who meets any of the following criteria will be excluded from participation in this study:

- Patient primary seeking help for non-tinnitus hearing problems.
- Abnormal cochlear anatomy (ie, ossification).
- Comorbidity with an expected survival of less than 5 years based on medical history as assessed by clinician and in electronical patient file.
- Additional handicaps that would prevent participation in the evaluations.

- Presence of any unstable psychiatric condition within 1 year before start of the study.
- Unrealistic expectations on the part of the patient regarding the possible benefits, risks and limitations that are inherent to the procedure.

If a patient is eligible for the study, his/her otorhinolaryngologist will ask him/her to participate. The content of the study will be explained by the patient's otorhinolaryngologist who will provide him/her written patient information and the informed consent form. Patients will be given 2 weeks to consider participation. If a patient meets the criteria for inclusion and exclusion and wants to take part in the study, the patient will be asked to come to the UMC Utrecht for a CT scan to visualise the anatomy of the mastoid. If the patient's CT scan shows normal cochlear anatomy, he will, during the same visit, sign the informed consent with a member of the research team and receive a copy of the consent. After inclusion, baseline measurement will be performed where after randomisation will take place.

Recruitment status and trial dates

Patient enrolment started in January 2021 and will be completed in June 2022. The surveys and measurement will be performed until January 2023.

RANDOMIZATION

After inclusion and baseline measurement, patients will be randomly allocated into one of the two groups: CI group or control group. The randomization will be computer-generated with block sizes of 4 and 6 and stratified for TFI score. A website randomization program, developed by Castor EDC23 will be used for randomization. A study database was set up in Castor EDC to support allocation and concealment. Investigators enter information for each eligible patient and the randomization assignment is revealed once the investigators validate the inclusion of the patient. The block design is unavailable to those who assign participants until the moment of assignment. Blinding is not possible during this study since both patients and caregivers will be able to see from outside whether patients have a CI or not.

INTERVENTION

Patients allocated to the intervention group will receive a CI. The CI will be implanted on the most affected tinnitus side, and if equal tinnitus in the two ears, in the ear with the worst hearing loss. Hearing aid will be allowed in the contralateral ear. The cochlear implantation will be carried out under general anaesthesia after consent of the anesthesiologist and after determination of general health status. The standard surgical procedures for cochlear implantation will be followed. A retro-auricular incision will be made to expose the mastoid. The electrode will be inserted via a posterior tympanotomy and round window implantation by soft-surgery techniques. Intraoperatively, normal functioning of the device will be checked by measurement of impedance and neural response telemetry. Electrocochleography will also be recorded intraoperatively using Cochlear™ Research Platform (V.1.1). The CI used for the study consists of a Nucleus [7] sound processor and a CI622 implant with a slim straight electrode from Cochlear (or similar). Serial numbers of the CIs will be registered in the operating room report by the surgeon (standard clinical care for cochlear implantation) and in the master study file (product accountability). A post-operative Cone Beam CT of the mastoid will be planned to detail the electrode location within the cochlea.

One week after surgery patients from the intervention group will be checked at the outpatient department of the ENT to check for wound healing. The rehabilitation phase will start 4 weeks after surgery with a visit of the patient to the department of Audiology to custom fit the processor software and then (bi) weekly till week 11 after surgery to fine tune the programming of the implant and improve speech perception. The CI fitting will not differ from the standard of care and will be optimized for every patient.

In the follow-up phase, the patients with CI will return to the UMC Utrecht 3 and 6 months after implantation to assess study outcome by the research team. The patients of the control group will come to the UMC Utrecht 3 and 6 months after randomization to assess the same study outcome. A questionnaire will have to be filled in at home by the patients before every follow-up session at 3 and 6 months, as well as 2 weeks after surgery for the intervention group.

Participants are not allowed to start another tinnitus treatment during the study.

SAMPLE SIZE

To detect a clinically relevant difference of one grade (15 points) change measured with the TFI[24], in tinnitus burden at 6 months after cochlear implantation compared to the control group, with a power of 90% and alpha of 0.05, 23 patients are needed in both arms of the study. An acceptable standard deviation (SD) was set at 15, based on the results of a previous pilot study assessing CI for tinnitus patients[20]. We will include 25 patients per arm, a 10% margin, to include for possible lost to follow up. Thereby, we expect patients to have a mean TFI at baseline of 50 points on TFI (Grade 3) and a TFI decrease of 15 points at 6 months after intervention with a mean endpoint of 35 points on TFI (Grade 2).

OUTCOMES

The following outcomes will be assessed at the baseline visit and follow-up visits at 3 and 6 months after randomisation (Table 1). All measurements will be performed by the research team following the same protocol procedures.

Primary outcome measure

Our primary outcome is tinnitus burden as measured with the validated Tinnitus Functional Index. The Tinnitus Functional Index (TFI) is a 25-item containing questionnaire with statements/questions about tinnitus burden[24,25]. The index is divided in eight subscale items: intrusive, sense of control, cognitive, sleep, auditory, relaxation and quality of life. Possible answers are ranging between 0 and 10, resulting in a maximum score of 100, representing a maximum burden of tinnitus. This total score is then categorized into five different grades, indicating low to high burden.

Secondary outcome measure

Audiological tests

Five audiological measurements are included in the study and are performed by an audiologist according to the ISO 16832:2006[26].

→ Pure tone audiometry

The first evaluation is a pure tone audiometry at 0.25, 0.5, 1, 1.5, 2, 4 kHz. This standard measurement evaluates the audible threshold of the patient by having patients indicating audibility for frequency-specific pure tone stimuli at different loudness level. The evaluation results in an audiogram which provides information about the hearing level of the patients.

→ Speech recognition test in quiet and noise

The second evaluation is a speech recognition test in quiet and noise. For the patients receiving a CI, post-intervention assessments will be applied with the CI. The participant is listening at digits, Dutch words and sentences in a sound-treated booth. The loudness of the speech will change during the test in steps of 2 dBs, but the noise signal will be presented at a constant level of 65 dB Sound Pressure Level (SPL). The patient is asked to repeat back the words. The patient will perform the same test in two different conditions: with or without noise. This test results in a speech reception threshold obtained by averaging the signal-to-noise ratio over the list of words presented in order to obtain a 50% correct score. The outcome will permit to set up a rehabilitation programme with a speech therapist for the intervention group.

→ Electrocochleography

Electrocochleography (ECochG) is a technique to record electrical potentials generated in the inner ear and auditory nerve in response to acoustic stimulation. ECochG measurement will be performed intraoperatively and at 3 and 6 months after cochlear implantation. The measure will be followed by conventional audiological examination. During the measurement postoperatively, the patient will be asked to sit comfortably on a chair and not move. The operator will install the earplug in the patient's ear and connect it to an audio cable attached to a sound processor. The sound processor will generate acoustic stimulation through the audio cable and the electrical responses will be recorded in real time via the Cochlear Research Platform (V.1.1, Cochlear ltd). The ECochG provides a measure of the cochlear function.

Table 1. Schedule of visits and assessments to measure study outcome per group.

	Baseline	CI group				Control group	
	Rx	CI	2 w post CI	3 m post CI	6 m post CI	Rx + 3 m	Rx + 6 m
CI (surgery)		X					
CT scan	X	X					
Electro-cochleography		X		X	X		
Hearing level				X	X	X	X
Speech perception	X			X	X	X	X
Tinnitus pitch match	X			X	X	X	X
Tinnitus loudness match	X			X	X	X	X
TFI*	X			X	X	X	X
VAS Tinnitus *	X		X	X	X	X	X
SSQ*	X			X	X	X	X
EQ5D*	X			X	X	X	X
HADS*	X			X	X	X	X
BDI*					X		X
GBI*					X		
CGI*				X	X		
ESIT-SQ*	X						

*Questionnaires (Q) will be filled in at home.

BDI, Beck Depression Inventory; CGI, Clinical Global Impression; CI, cochlear implantation; e.o.s, end of study; EQ5D, Euro-Quality-of-life 5D; ESIT-SQ, ESIT Screening Questionnaire; GBI, Glasgow Benefit Inventory; HADS, Hospital Anxiety and Depression Scale; Rx, randomization; SSQ, Speech, Spatial and Qualities Hearing Scales; TFI, Tinnitus Functional Index; VAS, Visual Analogue Scale.

→ Pitch match experiment

Pitch match of tinnitus is performed to find the pitch corresponding to the tinnitus pitch of the patient. An acoustic pitch matching and an electric pitch matching will be performed in a sound-treated booth. The acoustic pitch matching will provide information about the frequency of the tinnitus perceived whereas the electric pitch matching will provide information about the pitch-matched electrode. The patient will be asked to concentrate on the predominant pitch of their tinnitus. Two tones will be presented at the same intensity level previously matched with tinnitus. The patient will indicate which option, the first or the second, sounds the closest in pitch by manipulating the response switch forward and backward. The difference between the first and the second will become smaller and smaller, until there is one frequency that matches best. Each stimulation will be performed twice (apical-to-basal and basal-to-apical to prevent octave-confusion). The pitch matched will be identified as the pitch resulting of the two runs. If the result of the two runs is not the same, the procedure will be repeated until finding a consistent result at least two times[27].

→ Loudness match experiment

Loudness match of tinnitus is performed to find the loudness corresponding to the tinnitus acoustically and electrically[28]. The experiment uses the tinnitus pitch matched. The pure tones are initially presented at 6 dB above threshold. The patient is instructed to adjust the loudness of the comparison tones to match that of their tinnitus. The adjustment of the intensity is made in a range of 5dB for rough determination and then 1 dB steps until a satisfactory loudness match in obtained.

→ CI usage

The history of several user characteristics will be logged from the processor. This provides the following outcome parameters :

- Time on air, providing the time the device was used in speech environment or the device was off
- Scenes, providing the time spending in different environments: quiet, speech, noise, speech in noise, music and wind
- Level of the environmental sound in dBA
- Program usage, providing a daily average on program usage.

Questionnaires

Questionnaires will be sent by e-mail to the study participants through the data management program Castor EDC[23]. If participants do not want to perform online questionnaires, they will receive paper versions of the questionnaires by postal services. All questionnaires will be in the Dutch language.

→ Tinnitus questionnaire

- The Visual Analogue Scale (VAS) tinnitus has two items. The patient answers two questions about tinnitus severity and intrusiveness using a visual analogue scale that ranges from 0 (not at all) to 10 (extremely).

→ Tinnitus history

- The ESIT Screening Questionnaire (ESIT-SQ)[29] consists of 39 items relevant for tinnitus profiling including 17 general and 22 tinnitus-specific questions. Every question present multiple choice. The test is used a baseline questionnaire and takes approximately 10 minutes to fill in.

→ Patient reported benefits

- The Clinical Global Impression (CGI) consists of a one-item observer-rated scale that measures global improvement or change (CGIC)[30]. The question is scored on a scale from 1 to 7, 1 meaning "Very much improved" to 7 meaning "Very much worse".
- The Glasgow Benefit Inventory (GBI) is a validated questionnaire reporting change in health-related quality of life post-intervention[31]. It consists of 18 questions scored on a 5-points Likert scale where 1 indicates "much worse" and 5 is for "much better". The questionnaire presents three different items: general subscale, social support and physical health.

→ Quality-of-life questionnaires

- The Euro-Quality-of-life 5D (EQ5D) is a standardized measure of generic health status. It contains only five questions. Each question deals with a specific domain: mobility, self-care, usual activities, pain/discomfort and anxiety/depression[32]. The patient must choose between different sentences which corresponds to his/her health condition. The last question is a self-report of the overall health status using a visual analogue scaling from 0 (the worst health you can imagine) to 100 (the best health you can imagine).

- The Speech, Spatial and Qualities Hearing Scale (SSQ) measures hearing-related quality of life and consists of three scales that assess different domains of hearing: (1) the speech hearing subscale consists of 15 questions that assess the ability to separate speech from competing noise in a wide range of listening contexts, (2) the spatial hearing subscale consists of 17 questions that assess the ability to locate sound sources and their direction of movement, (3) the quality of hearing subscale consists of 19 questions that assess naturalness and clarity of sound sources[33]. Possible answers are scored using a visual analogue scale ranging from 0 (not at all) to 10 (excellent).

→ Comorbid symptom scores

- The Beck Depression Inventory (BDI) is a 21-item questionnaire used as an indicator of the severity of depression[34]. Each question is scored on four points ranged between 0 (for example 'I do not feel sad') and 3 ('I am so sad') with a maximum of total score of 63.
- The Hospital Anxiety and Depression Scale (HADS) is a 14-item screening tool for anxiety and depression symptoms in non-psychiatric clinical populations[35,36]. Each sentence is scored between 0 and 3 where 0 confirms the sentence and 3 disagrees with it.

STATISTICAL ANALYSIS

Baseline characteristics per group will be described as means or medians, depending on the normality of the data and SD. Between-group mean differences will be calculated with 95% CIs. A p value < 0.05 is considered statistically significant.

The primary outcome will be the difference in TFI score between the intervention at 6 months after cochlear implantation and the control group after 6 months of no intervention, a continuous variable. Differences between the control and intervention group will be calculated using the unpaired t-test and the Mann-Whitney U test. The secondary outcome measures will be the performances on the auditory tests and the questionnaires. Differences between groups will be calculated using the unpaired t-test and the Mann-Whitney U test. Within-subject comparisons will entail differences of mean values. These will be analysed using paired t-tests for continuous measures.

Interim analyses on the safety data will be performed and reviewed by an external data safety monitoring board (DSMB). An interim analysis will be

done every 6 months starting after the five first patients reached 6 months of follow-up. A statistician will perform non-parametric test on the aided speech perception of the implanted ear only, performed 6 months post-implantation to monitor functional hearing performance. The DSMB will advise on stopping the study if there is a risk for the patient's safety based on tinnitus worsening and deterioration of functional hearing.

Potential missing data will be handled using multiple imputation. Complete cases analyses will be done as a sensitivity analysis. All analyses will be performed on an intention-to-treat basis.

Ethics and dissemination

PROTOCOL VERSION

The study will be conducted according to the principles of the Declaration of Helsinki (version 2013, Fortaleza) and in accordance with the Medical Research Involving Human Subjects Act (WMO). The research protocol was approved by the Institutional Review Board (IRB) of the UMC Utrecht (NL70319.041.19) and the Dutch competent authorities.

PROTOCOL AMENDMENT

All amendments will be notified to the local Medical Research Ethics Committee (MREC). The data from this study will be used for publication in peer-reviewed international journals, preferably open-access. To diminish possible chance on publication bias, the study will be reported using the Consolidated Standards of Reporting Trials guidelines[37].

CONFIDENTIALITY

All data will be treated confidentially. The data will be encrypted by using an unique patient identification number. The analysis will be performed with these coded patient data. The key code will be safeguarded by the investigators. The paper data files and informed consents will be stored in a locked cabin in a locked room. The data will be stored on the investigator's computer as well, which is secured by a password and situated in a locked room. The handling of personal data will comply with the EU General Data Protection Regulation and the Dutch Act on Implementation of the General Data Protection Regulation, the Uitvoeringswet AVG, UAVG.

The final trial dataset will be safeguarded and available to the principal investigator and approved members of the research team.

DATA MONITORING AND AUDITING

The investigator will submit a summary of the progress of the trial to the accredited MREC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events (SAEs)/serious adverse reactions, other problems and amendments. Trial quality will be monitored independently by the Julius Clinical Centre (UMC Utrecht, the Netherlands) according to regulations by the UMC Utrecht and the Dutch government. The local monitor will check 50% of signed informedconsents, inclusion and exclusion criteria, source data and SAEs. Due to the high-risk nature of the study, an external DSMB will be in place to perform ongoing safety surveillance. An interim analysis will be performed by the statistician of the research group and will be analysed by the DSMB every 6 months after the fifth first inclusions.

ADVERSE EVENTS

Besides the normal risks associated with surgery and general anaesthesia, adverse events related to cochlear implantation will be monitored by assessment and documentation of intraoperative and postoperative complications and device failures. Deterioration of the hearing < 30 dBs (PTA) is expected after implantation because of the cochlear trauma and should not be considered as an adverse event[38,39]. All adverse events will be followed until they have abated or until a stable situation has been reached. All cases of serious adverse events will be reported to the local IRB and the Dutch competent authorities.

TRIAL STATUS

The study is currently in recruitment phase.

Author contributions

All authors (KA, ALS, IS, KSR, RS and BvD) developed the protocol. IS provided statistical expertise in clinical trial design. KA drafted the manuscript. All other authors revised the manuscript. All authors read and approved the final version.

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Competing interests

KA received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Sklodowska-Curie Grant (agreement number 764604). KA and BvD are employed at Cochlear Technology Centre, Mechelen, Belgium.

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting or dissemination plans of this research.

Ethics approval

This research protocol was approved by the Institutional Review Board (IRB) of the UMC Utrecht (NL70319.041.19, V5, January 2021).

References

1. Van den Berge, M. J. C. et al. Cluster analysis to identify possible subgroups in tinnitus patients. Front. Neurol. 8, 1–7 (2017).
2. Moller, A. R., Salvi, R., De Ridder, D., Kleinjung, T. & Vanneste, S. Pathology of Tinnitus and Hyperacusis-Clinical Implications. Biomed Res. Int. 2015, 608437 (2015).
3. Møller, A. R. Epidemiology of Tinnitus in Adults BT - Textbook of Tinnitus. in (eds. Møller, A. R., Langguth, B., De Ridder, D. & Kleinjung, T.) 29–37 (Springer New York, 2011). doi:10.1007/978-1-60761-145-5_5.
4. Davis, A. E. . The epidemiology of tinnitus. Handb. Tinnitus (R. Tyler,ed) Singluar, 1–23 (2000).
5. Hoare, D. J., Kowalkowski, V. L., Kang, S. & Hall, D. A. Systematic review and meta-analyses of randomized controlled trials examining tinnitus management. Laryngoscope 121, 1555–1564 (2011).
6. Mertens, G., De Bodt, M. & Van de Heyning, P. Cochlear implantation as a long-term treatment for ipsilateral incapacitating tinnitus in subjects with unilateral hearing loss up to 10 years. Hear. Res. 331, 1–6 (2016).
7. Dobie, R. A. A Review of Randomized Clinical Trials in Tinnitus. Laryngoscope 109, 1202–1211 (1999).
8. Hoare, D. J., Edmondson-Jones, M., Sereda, M., Akeroyd, M. A. & Hall, D. Amplification with hearing aids for patients with tinnitus and co-existing hearing loss. Cochrane Database of Systematic Reviews (2014) doi:10.1002/14651858.CD010151.pub2.
9. Martinez-Devesa, P., Perera, R., Theodoulou, M. & Waddell, A. Cognitive behavioural therapy for tinnitus. Cochrane Database Syst. Rev. (2010) doi:10.1002/14651858.cd005233.pub3.
10. Cima, R. F. F. et al. A multidisciplinary European guideline for tinnitus: diagnostics, assessment, and treatment. HNO 67, 10–42 (2019).
11. Fuller, T. et al. Cognitive behavioural therapy for tinnitus. Cochrane Database Syst. Rev. 2017, (2017).
12. Sereda, M., Xia, J., El Refaie, A., Hall, D. A. & Hoare, D. J. Sound therapy (using amplification devices and/or sound generators) for tinnitus. Cochrane Database of Systematic Reviews (2018) doi:10.1002/14651858.CD013094.pub2.
13. Hobson, J., Chisholm, E. & El Refaie, A. Sound therapy (masking) in the management of tinnitus in adults. Cochrane Database Syst. Rev. (2012) doi:10.1002/14651858.cd006371.pub3.
14. Ramakers, G. G. J., Van Zon, A., Stegeman, I. & Grolman, W. The effect of cochlear implantation on tinnitus in patients with bilateral hearing loss: A systematic review. Laryngoscope 125, 2584–2592 (2015).
15. Ramos Macías, A. et al. One-Year Results for Patients with Unilateral Hearing Loss and Accompanying Severe Tinnitus and Hyperacusis Treated with a Cochlear Implant. Audiol. Neurotol. 23, 8–19 (2018).
16. Van De Heyning, P. et al. Incapacitating unilateral tinnitus in single-sided deafness treated by cochlear implantation. Ann. Otol. Rhinol. Laryngol. 117, 645–652 (2008).

17. Poncet-Wallet, C. et al. Prospective Multicentric Follow-up Study of Cochlear Implantation in Adults With Single-Sided Deafness : Tinnitus and Audiological Outcomes. 0, (2019).

18. Kleine Punte, A., De Ridder, D. & Van De Heyning, P. On the necessity of full length electrical cochlear stimulation to suppress severe tinnitus in single-sided deafness. Hear. Res. 295, 24–29 (2013).

19. Ahmed, M. F. & Khater, A. Tinnitus suppression after cochlear implantation in patients with single-sided deafness. Egypt. J. Otolaryngol. 33, 61 (2017).

20. Arts, R. A. G. J. et al. Tinnitus Suppression by Intracochlear Electrical Stimulation in Single Sided Deafness – A Prospective Clinical Trial: Follow-Up. PLoS One 11, e0153131 (2016).

21. Sampaio, A. L. L., Araújo, M. F. S. & Oliveira, C. A. C. P. New Criteria of Indication and Selection of Patients to Cochlear Implant. Int. J. Otolaryngol. 2011, 1–13 (2011).

22. Chan, A. W. et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. BMJ (2013) doi:10.1136/bmj.e7586.

23. BV, C. Castor electronic data capture. Amsterdam, The Netherlands (2018).

24. Meikle, M. B. et al. The tinnitus functional index: Development of a new clinical measure for chronic, intrusive tinnitus. Ear Hear. (2012) doi:10.1097/AUD.0b013e31822f67c0.

25. Rabau, S., Wouters, K. & Van de Heyning, P. Validation and translation of the Dutch tinnitus functional index. B-ENT 10, 251–258 (2014).

26. Valente, D. INTERNATIONAL STANDARD Acoustics — Loudness scaling by means. 2006, (2006).

27. Arts, R. A. G. J., George, E. L. J., Chenault, M. N. & Stokroos, R. J. Optimizing intracochlear electrical stimulation to suppress tinnitus. Ear Hear. 36, 125–135 (2015).

28. Theelen-Van Den Hoek, F. L., Boymans, M., Stainsby, T. & Dreschler, W. A. Reliability of categorical loudness scaling in the electrical domain. Int. J. Audiol. 53, 409–417 (2014).

29. Genitsaridi, E. et al. Standardised profiling for tinnitus research: The European School for Interdisciplinary Tinnitus Research Screening Questionnaire (ESIT-SQ). Hear. Res. 377, 353–359 (2019).

30. Guy, W. CGI Clinical Global Impressions. ECDEU Assess. Man. (1976).

31. Hendry, J., Chin, A., Swan, I. R. C., Akeroyd, M. A. & Browning, G. G. The Glasgow Benefit Inventory: A systematic review of the use and value of an otorhinolaryngological generic patient-recorded outcome measure. Clin. Otolaryngol. 41, 259–275 (2016).

32. Health Policy. EuroQol - a new facility for the measurement of health-related quality of life. (1990) doi:10.1016/0168-8510(90)90421-9.

33. Gatehouse, S. & Noble, I. The Speech, Spatial and Qualities of Hearing Scale (SSQ). Int. J. Audiol. (2004) doi:10.1080/14992020400050014.

34. Beck, A. T., Steer, R. A., Ball, R. & Ranieri, W. F. Comparison of Beck depression inventories -IA and -II in psychiatric outpatients. J. Pers. Assess. (1996) doi:10.1207/s15327752jpa6703_13.

35. Bjelland, I., Dahl, A. A., Haug, T. T. & Neckelmann, D. The validity of the Hospital Anxiety and Depression Scale. J. Psychosom. Res. 52, 69–77 (2002).

36. Zigmond, A. S. & Snaith, R. P. The Hospital Anxiety and Depression Scale. Acta Psychiatr. Scand. (1983) doi:10.1111/j.1600-0447.1983.tb09716.x.

37. Schulz, K. F., Altman, D. C. & Moher, D. CONSORT 2010 Statement: Updated guidelines for reporting parallel group randomised trials. Ital. J. Public Health (2010) doi:10.4178/epih/e2014029

38. Ramos-Macías, A., Borkoski-Barreiro, S. A., Falcón-González, J. C. & Ramos-De Miguel, A. Hearing Preservation with the Slim Modiolar Electrode Nucleus CI532® Cochlear Implant: A Preliminary Experience. Audiol. Neurotol. (2018) doi:10.1159/000486409.

39. Jurawitz, M. C. et al. Hearing preservation outcomes with different cochlear implant electrodes: Nucleus® hybridTM-L24 and nucleus freedomTM CI422. Audiol. Neurotol. 19, 293–309 (2014).

5

Analysis of a cochlear implant database : *changes in tinnitus prevalance and distress after cochlear implantation*

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Abstract

The aim of this study was to estimate the prevalence and distress of tinnitus pre- and post-cochlear implantation in patients with bilateral severe to profound hearing loss. In this retrospective study, we included patients from a cochlear implant clinic in Perth, Western Australia. Pre- and post-cochlear implantation data from 300 implant recipients were collected on self-reported presence of tinnitus, tinnitus distress using the Tinnitus Reaction Questionnaire (TRQ), hearing-related quality of life using the Abbreviated Profile of Hearing Aid Benefit (APHAB), and consonant-nucleus vowel-consonant (CNC) word recognition test scores. Retrospectively, patients were grouped into those with or without tinnitus, and the grade of tinnitus distress. The potential factors associated with post-implantation changes in the presence of tinnitus and its distress were evaluated. Tinnitus prevalence was 55.8% pre-operatively and 44.3% post-implantation with a median TRQ score respectively of 12.0 (IQR: 1.0–28.0) and 3.5 (IQR: 0.0–16.2) points. Among the 96 patients experiencing tinnitus pre-implantation, 14.6% patients experienced moderate to catastrophic tinnitus distress pre-implantation compared to 6.3% post-implantation. To conclude, the pre- and post-implantation median TRQ score for the cohort population showed that tinnitus was a "slight" handicap. Tinnitus prevalence and its associated tinnitus distress decreased post-implantation. Patients with tinnitus post-implantation were significantly younger and had less severe pre-implantation hearing loss in the non-implanted ear than patients without tinnitus. Further research is needed to understand the factors influencing changes in tinnitus.

Introduction

Tinnitus is the perception of a sound in the ears or head without an external auditory input[1]. It has a prevalence ranging from 10 to 30% of the general population with up to 3% of people with tinnitus experiencing severe and bothersome tinnitus resulting in a substantial reduction of the quality of life[1–3]. The cause and mechanisms of tinnitus are still not well understood. However, hearing loss has often been associated with tinnitus, and identified as a most common risk factor[4,5]. In a recent retrospective cohort study, it was found that around 20% of adult patients having an initial hearing consultation at a single tertiary hearing institute report tinnitus as a primary complaint[6]. Amongst cochlear implant (CI) candidates, tinnitus prevalence has been reported at levels up to 52% to 86%[7–9].

The CI is a device that partially restores hearing for people with severe-to-profound hearing loss by electrical stimulation of the auditory nerve. While some studies show that tinnitus loudness, distress or annoyance can be reduced or suppressed after cochlear implantation, others report that tinnitus can also be worsened in up to 10% of recipients[7,10]. Induction of tinnitus has been reported in up to 4% of patients receiving a CI for bilateral severe to profound hearing loss[7]. To date, no randomized controlled trials investigating cochlear implantation and its effect on tinnitus as a primary complaint have been reported. In several systematic reviews, authors were unable to definitively comment upon the effect of cochlear implantation on tinnitus due to the high degree of heterogeneity in study designs and studied populations, limited sample sizes, short follow-up durations, and differences in CI types and outcomes measures[10–12]. As the effect of cochlear implantation on tinnitus distress seems to vary widely between studies, it is of clinical importance to understand the factors underlying this variability. The variability of tinnitus outcomes following cochlear implantation may be associated with patient characteristics, trauma provoked by the implantation procedure, and the presence of tinnitus and/or tinnitus distress prior to surgery[13–15]. A few researchers have addressed this issue and attempted to find predictive factors for the effect of cochlear implantation on tinnitus perception amongst individuals with bilateral severe-to-profound hearing loss. Poorer pre-implantation hearing thresholds[13], or speech perception[16] were identified as potential predictive factors for tinnitus improvement after cochlear implantation.

Some pre-implantation patient characteristics have also been reported to predict clinically relevant tinnitus improvement or suppression after cochlear implantation: unilateral localization of tinnitus[16], higher pre-implantation tinnitus severity[13,15] or a less severe depression state[15]. A larger deterioration of residual hearing at 250 Hz, i.e. the difference in hearing threshold before and after surgery at this frequency, has also been associated with tinnitus suppression (presence of tinnitus pre-implantation and complete absence of tinnitus post-implantation)[16]. In contrast, Kloostra et al. were not able to find predictors for a positive tinnitus outcome, using speech comprehension scores and pre-operative tinnitus distress, personality characteristics, anxiety and depression, and hearing handicap questionnaires, although they did find predictors that negatively influence tinnitus outcome in terms of lower pre-implantation tinnitus handicap and hearing handicap[17]. None of the factors identified in the abovementioned studies were consistent among the various prediction models, which might be partly due to the small sample sizes of studies, high risk of bias of the presented models and lack of validation of these models. Therefore, no consensus has been reached on factors predictive of tinnitus outcome post-implantation.

Since there is uncertainty on tinnitus prevalence post-implantation and there is no clear prediction model for presence of tinnitus and associated distress, this topic must be further investigated. Identifying key factors which can characterize tinnitus changes after implantation will help clinicians to counsel CI candidates on the risk of developing or improving tinnitus after implantation and thus help to manage patient expectations. Therefore, the primary aim of the study was to estimate the prevalence and distress of tinnitus pre- and post-implantation in patients with bilateral severe to profound hearing loss. The secondary aim was to assess potential factors associated with post-implantation changes in the presence of tinnitus and its distress. Finally, we compared patient and hearing-related factors between patients with and without tinnitus.

Methods

STUDY POPULATION

A retrospective, longitudinal study was conducted. For this purpose, we reviewed a dataset gathered from 300 adult CI recipients with bilateral severe to profound hearing loss who were surgically implanted unilaterally or bilaterally with a CI between 2000 and 2017 at the Ear Science Clinic, Perth, Western

Australia. The dataset is the same as the one used for a report on the association between tinnitus after cochlear implantation and hearing-related quality of life[18]. This population consisted of patients with pre-lingual and post-lingual deafness; pre-lingual deafness was defined as hearing loss occurring prior to three years of age. Patients followed a rehabilitation and follow-up plan after implantation that included auditory evaluations and questionnaires. Only patients who replied to the question about the presence or absence of tinnitus pre-operatively were included in the study.

DATA COLLECTION AND HANDLING

This study used data gathered from the patient records including outcomes of standardized questionnaires. Data were extracted from electronic databases by an authorized member of the research team and anonymized prior to viewing and analyses by other members of the research team. Data were captured pre-implantation and at 6 and 12 months after implantation, and then annually. Due to missing data for recipients at some follow-up time points, the data from the latest available time point after implantation were used for the analysis as the post-implantation follow-up. We considered the first implantation date as the surgery date for all questionnaires and measurements follow-up. In case of bilaterally implanted recipients, the post-implantation follow-up used in the analysis for tinnitus outcome was always when bilaterally implanted recipients had received both implants. Six bilaterally implanted recipients reported tinnitus suppression before their second implantation and did not have post-second implant score available. Two bilaterally implanted recipients did not have post-second implant scores available. We considered the post-implantation outcomes of these eight bilaterally implanted recipients as missing data.

OUTCOME ASSESSMENT

As part of the pre- and post-implantation assessments, patients were asked to answer two single questions: “Are you currently experiencing tinnitus or have you experienced tinnitus in the past month?” and “How often have you experienced tinnitus in the past month?”. If the answer to the first question was positive, and the answer to the second question indicated that tinnitus was experienced more than very occasionally, then the patient was included in the self-reporting tinnitus group and was asked to complete the TRQ. Otherwise, the patient was included in the no tinnitus group and was not asked to complete the TRQ.

DESCRIPTIONS OF VARIABLES

Outcome variables

The Tinnitus Reaction Questionnaire (TRQ) is a measure of the psychological distress associated with tinnitus. The TRQ contains 26 questions divided in four subscales: general distress, interference with daily activities, severity of tinnitus, and avoidance[19,20]. Possible answers are: not at all (scored 0), a little of the time (scored 1), some of the time (scored 2), a good deal of the time (scored 3), and almost all of the time (scored 4). A total score can range from 0 to 104 points which are classified into five grades of severity[19]: slight (0 to 16 points), mild (18 to 36 points), moderate (38 to 56 points), severe (58 and 76 points) and catastrophic (78 and 104 points). In addition to completion of the TRQ, patients were asked about the characteristics of their tinnitus: tinnitus side, regularity, awareness, and volume. Ipsilateral or contralateral tinnitus was determined based on comparison between the post-implant tinnitus side and the CI side. For bilaterally implanted recipients, we always considered it to be ipsilateral tinnitus. A patient was deemed to have a TRQ score of 0 at any of the pre-operative or post-operative points at which they self-reported the absence of tinnitus.

Hearing-related quality of life of CI recipients was assessed pre-implantation and at each post-implantation follow-up visit using the Abbreviated Profile of Hearing Aid Benefit (APHAB). The APHAB is a 24 item questionnaire comparing the difficulties of aided and unaided listening in everyday situations[21]. This questionnaire has been validated for hearing aid users[21]. The APHAB has often been used in CI recipients without being validated for the clinical population of CI recipients. The APHAB assesses the outcome in four domains: Ease of Communication (EC), Reverberation (RV), Background Noise (BN) and Aversiveness (AV). In the three first subscales (EC, RV and BN), speech communication in different environments is scored whereas the last subscale (AV) negative reactions to environmental sound are assessed. Seven answers are possible: always (99% of the time), almost always (87% of the time), usually (75% of the time), half-the-time (50% of the time), sometimes (25% of the time), hardly ever (12% of the time) and never (1% of the time). An overall score as well as four sub-domain scores were obtained based on the addition of scores of negative descriptors and reversed scores for positive descriptors. The higher the score, the greater the perceived hearing disability and thus the lower the hearing-related quality of life[21].

Speech recognition performance was evaluated using the consonant-nucleus-consonant (CNC) test[22]. The CNC test is a validated and common measure in the

CI standard of care[23]. The patient was presented with a list of 25 words at 65 dBA in quiet, with the speaker 1 meter in front of the patient, at zero degrees azimuth, in a soundproof booth. Pre- and post-implantation tests were performed aided, with the device used by the patient at the time of the test. Responses were scored as the percentage of correct repeated words by the patient for each list. The test was performed pre-implantation and at each post-implantation follow-up visit.

Demographic information regarding sex, age at implantation, etiology of hearing impairment of the implanted ear, laterality of implantation and pre- or post-lingual onset of hearing loss were collected. Existence of balance concerns was assessed pre-implantation using a binary question. Clinical guidelines of the Ear Science clinic (Perth, Western Australia) are to consider bilateral implantation where medically and audiologically appropriate at 6 months post initial implant. Apart from questionnaires, audiometric data were retrieved from the patients' medical files. The pre-implantation pure tone average (PTA) was calculated for each ear using the four-frequency average hearing loss (4FAHL, average of 0.5, 1, 2 and 4 kHz) in unaided condition, as well as the pre-implantation high frequency pure tone average (PTAHF) using the mean of the hearing thresholds at 4, 6, 8 kHz. Pure tone averages were classified by side of implantation (implanted or non-implanted ear). In case of bilateral implantation, the pure tone averages of both implanted ears were calculated.

Substantial TRQ change classification

We distinguished six categories of change in tinnitus status: no tinnitus reported (either pre- or post-implantation), total tinnitus suppression (tinnitus reported pre-implantation but not post-implantation), tinnitus induction (no tinnitus reported pre-implantation but reported post-implantation), tinnitus reduction, tinnitus worsening, and no tinnitus change.

Tinnitus reduction and tinnitus worsening are determined based on the difference in TRQ score pre- and post-implantation. A difference in TRQ score of 17 points between pre- and post-implantation, corresponding to a change of at least one severity grade on the TRQ score, was defined as a substantial TRQ change. A tinnitus worsening was characterized by an increase in TRQ score of more than 17 points post-implantation. Conversely, tinnitus reduction was considered when the patient reported a TRQ score of 17 points or more decrease than previous reports.

No change is reported when the difference in TRQ score did not exceed 17 points. No change is reported when the difference in TRQ score did not exceed 17 points.

Statistical analysis

Descriptive statistics were used to summarize patient characteristics in the tinnitus and no tinnitus groups. Normally distributed data were presented using mean and standard deviation (SD). Not normally distributed data were reported using median and interquartile range (IQR). APHAB, TRQ and CNC scores were considered as continuous outcome variables.

Wilcoxon signed rank tests were used to determine significant difference in TRQ scores between pre- and post-implantation time periods in the tinnitus group.

We used univariate linear regressions to assess the association between patient characteristics (tinnitus experience before implantation, age at implantation, sex, onset of deafness, balance concerns, lateralization of implantation, averaged hearing thresholds PTA and PTAHF in the implanted and non-implanted ear respectively) and the TRQ scores at 12 months post-implantation. The laterality of implantation was reported based on the situation of each recipient at 12 months after the first implantation.

Group differences, pre- and post-implantation, were also evaluated between the tinnitus and the no tinnitus groups in order to identify features that could statistically distinguish one group from another. Wilcoxon rank sum tests were used for continuous variables. Pearson chi square tests were used to assess the difference between categorical variables.

Statistical analysis between different tinnitus change groups were not performed because of the small sample size within each group. Missing data imputation was not used because we were not able to verify the nature of the missing data i.e. random or not.

All analyses were performed using R Studio version 1.3.1073 (®R Studio). A p-value lower than 0.05 indicated a statistically significant result. Corrections for multiple comparison correction were not performed.

Results

COHORT CHARACTERISTICS

A total of 300 adults who underwent cochlear implantation between 2001 and 2016 were reviewed for the purpose of the study. The cohort characteristics are summarized in Table 1. The cohort APHAB and CNC outcomes are summarized in Table A1. The median age was 65.0 years (IQR: 52.2–74.5), 52.3% (157/300) were men and 47.7% (143/300) were women. A high proportion of these were unilaterally implanted recipients (77.3%, 232/300). For these unilaterally implanted recipients, pre-implantation median PTA hearing thresholds were 92.5 dB HL (IQR: 80.9–103.8) and 77.5 dB HL (IQR: 60.0–90.6) in the implanted and non-implanted ear respectively. Overall, 75% (169/225) of CI users had post-lingual deafness and 33% (99/300) reported pre-implantation balance concerns. The mean time between the implantation date and the latest post-implantation follow-up was 468 days, i.e., 15.4 months, for unilaterally implanted recipients.

For the 68 bilaterally implanted recipients, the median interval between the two implantations was 746 days, i.e., 24.6 months, and the mean time between the second implantation date and the latest post-implantation follow-up was 590 days, i.e., 19.3 months. All bilaterally implanted recipients were implanted sequentially, except one who had been implanted simultaneously. Pre-implantation median PTA hearing thresholds were 101.2 dB HL (IQR: 85.0–113.1) and 105.0 dB HL (IQR: 86.2–117.5) in the left and right ears, respectively.

Table 1. Cohort baseline characteristics.

Characteristic	Cohort (n = 300, %)
Age at implantation, median (IQR)	65.0 (52.2-74.5)
Sex, n (%)	
Male	157 (52.3)
Female	143 (47.7)
Onset of hearing loss	
Pre-lingual, n (%)	56 (18.7)
Post-lingual, n (%)	169 (56.3)
Missing, n (%)	75 (25.0)
Balance concerns, n (%)	99 (33.0)
Etiology	
Congenital, n (%)	60 (20.0)
Hereditary, n (%)	60 (20.0)
Meniere's, n (%)	20 (6.7)
Noise exposure, n (%)	31 (10.3)
Otosclerosis, n (%)	20 (6.7)
Other, n (%)	70 (23.3)
Unknown, n (%)	16 (5.3)
Missing, n (%)	23 (7.7)
Laterality of implantation	
Unilateral	232 (77.3)
Bilateral	68 (22.7)
Pre-operative PTA in dB HL, median (IQR)	
Implanted ear (unilateral) (164)	92.5 (80.9-103.8)
Missing, n (%)	68 (29.3)
Non-implanted ear (unilateral) (215)	77.5 (60.0-90.6)
Missing, n (%)	17 (7.3)
Implanted ear (bilateral) (57)	
Left	101.2 (85.0-113.1)
Right	105.0 (86.2-117.5)
Missing, n (%)	11 (16.2)
Pre-operative PTAHF in dB HL, median (IQR)	
Implanted ear (unilateral) (111)	108.3 (96.7-115.0)
Missing, n (%)	121 (52.2)
Non-implanted ear (unilateral) (141)	96.7 (75.0-110.0)
Missing, n (%)	91 (39.2)
Implanted ear (bilateral) (38)	
Left	113.3 (108.3-116.7)
Right	113.3 (107.1-116.7)
Missing, n (%)	30 (44.1)

TINNITUS PREVALENCE

Of the 300 patients, 172 (57.3%), 195 (65.0%), 124 (41.3%), 145 (40.3%), and 97 (32.3%) patients answered the single question about the presence of tinnitus at pre-implantation, 6, 12, 24, and 36 months post-implantation, respectively. Before implantation, 96 out of 172 (55.8%) patients reported tinnitus. The proportion of patients reporting tinnitus decreased over time (Table 2), with a prevalence decreasing from 55.8% pre-implantation to 44.3% 36 months post-implantation. Of the 96 patients who reported tinnitus preimplantation, 27 (28.1%) did not report tinnitus at a later timepoint (Figure A1). Of the 76 patients who did not report tinnitus prior to implantation, 14 (18.4%) reported tinnitus post-implantation (Figure A1).

TINNITUS CHARACTERISTICS

Of the 96 patients reported pre-implantation tinnitus, prior to implantation, 34 patients (35.4%) had unilateral tinnitus whilst 35 patients (36.4%) had bilateral tinnitus, and 14 (14.6%) reported central tinnitus (in the head). At the latest available time point post-implantation, 124 recipients were included in the self-reported tinnitus group, where 98 were unilaterally implanted and 26 were bilaterally implanted (Table 2). Of the 98 unilaterally implanted recipients, 29 had unilateral post-implantation tinnitus (25 ipsilateral tinnitus, 4 contralateral tinnitus), 64 had bilateral or central tinnitus (19 in both ears but worse in the ipsilateral ear, 9 in both ears but worse in the contralateral ear, 19 both ears equally and, 17 in the head), and 5 were unsure about the tinnitus location. Of the 26 bilaterally implanted recipients, 6 had unilateral tinnitus, 10 had bilateral tinnitus, 9 had central tinnitus, and 1 did not report his/her tinnitus location.

Post-implantation, variations in tinnitus volume, described as “goes softer and louder”, occurred in 85 patients (68.5%) whereas 39 patients (31.4%) reported a stable volume (Table 2). Sixty-six patients (53.2%) experienced constant tinnitus while the rest (46.8%) experienced tinnitus intermittently. Tinnitus awareness pre-implantation was reported as “all the time” by 18 (18.75%) of the participants, “most of the time” by 32 (33.3%), “some of the time” by 32 (33.3%) and “hardly ever” by 14 (14.6%). Post-implantation, 64 (51.6%) patients described their tinnitus awareness as “some of the time” and 12 (9.7%) described it as “all the time”.

TINNITUS DISTRESS

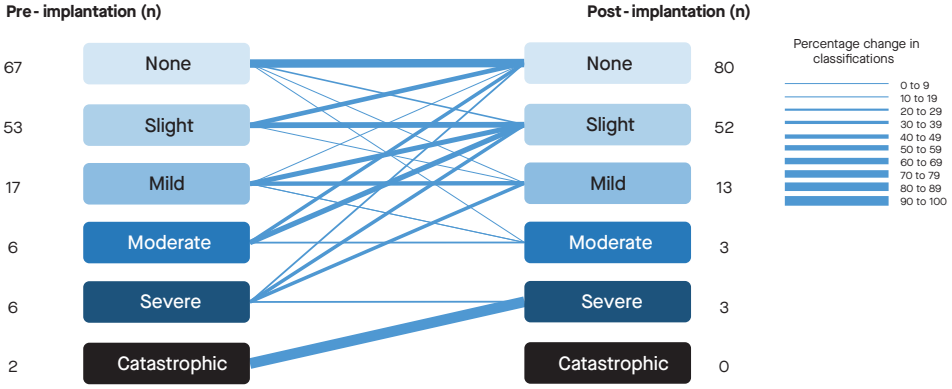
TRQ score

A statistically significant reduction in TRQ score between pre-implantation and the latest available time point post-implantation was found (pre-implantation: 12.0 (IQR: 1.0–28.0); post-implantation: 3.5 (IQR: 0.0–16.3), Wilcoxon signed rank test, $z = 1583$, $p < 0.001$) (Table 2, Figure A2). Statistically significant changes in TRQ score were found at all individual post-implantation follow-up timepoints, except at 36 months post-implantation where the sample size was smaller (pre-implantation: 12.0 (IQR: 1.0–28.0); 6 months post-implantation: 2.0 (IQR: 0.0–12.0), Wilcoxon signed rank test, $z = 973.5$, $p < 0.001$; 12 months post-implantation: 4.0 (IQR: 1.0–13.8), Wilcoxon signed rank test, $z = 463$, $p < 0.001$; 24 months post-implantation: 4.0 (IQR: 0.0–11.0), Wilcoxon signed rank test, $z = 380$, $p < 0.001$; 36 months post-implantation: 3.0 (IQR: 0.0–9.0), Wilcoxon signed rank test, $z = 86.5$, $p = 0.14$) (Table 2).

Tinnitus severity grade

The outcomes of the TRQ severity grades classification at the pre- and the latest available time point post-implantation are illustrated in Figure 1. Improvement in tinnitus severity grade was observed in 44 (28.9%) cases comparing pre-implantation versus post-implantation. Among the 6 patients with severe tinnitus prior to surgery, 5 (83.3%) reported a two grades reduction (severe to mild tinnitus). Sixteen (10.6%) patients scored a worsening of the tinnitus from none to a mild tinnitus grade.

Figure 1. Pre- and post-implantation outcomes of the TRQ severity grades.



TRQ severity grade classification: slight (0 to 16 points), mild (18 to 36 points), moderate (38 to 56 points), severe (58 and 76 points) and catastrophic (78 and 104 points).

Substantial TRQ change

Pre- and post-implantation TRQ scores were available for a subset of 152 patients (Table 3). An examination of the substantial TRQ change showed that 27 (17.8%) had a total suppression of tinnitus (tinnitus reported pre-implantation but not post-implantation), 15 (9.9%) had a reduction of at least 17 points in TRQ score, 53 (34.9%) did not report tinnitus pre- or post-implantation, 14 (9.2%) had an induction of tinnitus, and 2 (1.3%) had a worsening of their tinnitus of at least 17 points in TRQ score compared to pre-implantation. The remaining 41 (27%) patients reported a change in TRQ score of less than 17 points, which was considered as no change (Table 3).

Table 2. Tinnitus reported, TRQ score and tinnitus characteristics associated at different evaluation time.

Variable	Pre-CI	6 months post-CI	12 months post-CI	24 months post-CI	36 months post-CI	Post-CI
N	172	195	124	145	97	280
Tinnitus, n (%)	96 (55.8)	98 (50.25)	61 (50.8)	67 (46.2)	43 (44.3)	124 (44.3)
No tinnitus, n (%)	76 (44.2)	97 (49.75)	63 (49.2)	78 (53.8)	54 (55.7)	156 (55.7)
Missing, n (%)	128 (42.7)	105 (35.0)	176 (58.7)	155 (51.7)	203 (67.7)	20 (6.7)
TRQ, median (IQR)	12.0 (1.0-28.0)	2.0 (0.0-12.0)	4.0 (1.0-13.8)	4.0 (0.0-11.0)	3.0 (0.0-9.0)	3.5 (0.0-16.3)
p-value		<0.001*	<0.001*	<0.001*	0.14	<0.001*
Tinnitus side (unilateral CI), n (%)						
In both ears but worse in my left ear	6 (7.1)	11 (12.9)	8 (16.0)	6 (10.9)	5 (15.6)	14 (14.3)
In both ears but worse in my right ear	10 (11.9)	9 (10.6)	7 (14.0)	7 (12.7)	4 (12.5)	14 (14.3)
In both ears equally	12 (14.3)	15 (17.6)	8 (16.0)	12 (21.8)	9 (28.1)	19 (19.4)
In my head	11 (13.1)	13 (15.3)	6 (12.0)	7 (12.7)	3 (9.4)	17 (17.3)
Only in my left ear	20 (23.8)	11 (12.9)	4 (8.0)	12 (21.8)	6 (18.8)	14 (14.3)
Only in my right ear	14 (16.7)	19 (22.4)	12 (24.0)	8 (14.6)	5 (15.6)	15 (15.3)
Missing	11 (13.1)	7 (8.2)	5 (10.0)	3 (5.5)	0 (0.0)	5 (5.1)
Tinnitus side (bilateral CI), n (%)						
In both ears but worse in my left ear	1 (8.3)	1 (7.7)	0 (0.0)	1 (8.3)	0 (0.0)	3 (11.5)
In both ears but worse in my right ear	1 (8.3)	0 (0.0)	1 (9.1)	1 (8.3)	1 (9.1)	1 (3.8)
In both ears equally	5 (41.7)	5 (38.5)	1 (9.1)	4 (33.3)	4 (36.4)	6 (23.1)
In my head	3 (25.0)	0 (0.0)	6 (54.5)	3 (25.0)	4 (36.4)	9 (34.6)
Only in my left ear	0 (0.0)	0 (0.0)	1 (9.1)	1 (8.3)	2 (18.2)	4 (15.4)
Only in my right ear	0 (0.0)	3 (23.1)	0 (0.0)	1 (8.3)	0 (0.0)	2 (7.7)
Missing	2 (16.7)	4 (30.8)	2 (18.2)	1 (8.3)	0 (0.0)	1 (3.8)
Tinnitus regularity, n (%)						
Constant (is there all the time)	53 (55.2)	48 (49.0)	26 (42.6)	32 (47.8)	19 (44.2)	66 (53.2)
Intermittent (comes and goes)	43 (47.8)	50 (51.0)	35 (57.4)	35 (52.2)	24 (55.8)	58 (46.8)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Tinnitus volume, n (%)						
Changes in volume (goes softer and louder)	62 (64.6)	65 (66.3)	40 (65.6)	44 (65.7)	27 (62.8)	85 (68.5)
Stays at the same volume	34 (35.4)	33 (33.7)	21 (34.4)	23 (34.3)	16 (37.2)	39 (31.5)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Tinnitus awareness, n (%)						
All of the time	18 (18.8)	11 (11.2)	6 (9.8)	5 (7.5)	5 (11.6)	12 (9.7)
Most of the time	32 (33.3)	22 (22.4)	15 (25.6)	13 (19.4)	8 (18.6)	30 (24.2)
Some of the time	32 (33.3)	47 (48.0)	30 (48.2)	37 (55.2)	7 (16.3)	64 (51.6)
Hardly ever	14 (14.6)	18 (18.4)	10 (16.4)	12 (17.9)	23 (53.5)	18 (14.5)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Post-CI corresponds to the latest available time point after implantation for every patient.

CI: cochlear implantation; IQR: interquartile range; n: number of patients; TRQ: Tinnitus Reaction Questionnaire.

N corresponds to the number of patients answering the question about tinnitus experienced. The p-value reported results from the Wilcoxon signed rank test between the TRQ score pre-implantation

and the TRQ score post-implantation for every evaluation time.
*indicates variables that showed a significant difference with the TRQ score pre-implantation ($p < 0.05$).

Table 3. Distribution of characteristics and scores between tinnitus changes groups.

Tinnitus changes	Induction	No change	No tinnitus	Reduction	Suppression	Worsening
Total, n (%)	14 (9.2)	41 (27.0)	53 (34.9)	15 (9.9)	27 (17.8)	2 (1.3)
Age (152), median (IQR)	65.8 (58.4-75.8)	68.5 (58.3-74.6)	71.9 (65.1-76.8)	58.2 (43.1-65.3)	62.5 (57.2-75.5)	45.3 (39.4-51.2)
Sex (152), n (%)						
Female	6 (42.9)	22 (53.7)	27 (50.9)	4 (26.7)	15 (55.6)	2 (100.0)
Male	8 (57.1)	19 (46.3)	26 (49.1)	11 (73.3)	12 (44.4)	
Laterality of implantation (152), n (%)						
Unilateral	12 (85.7)	33 (80.5)	44 (83.0)	15 (100.0)	25 (92.6)	2 (100.0)
Bilateral	2 (14.3)	8 (19.5)	9 (17.0)	0 (0.0)	2 (7.4)	0 (0.0)
Balance concerns (152), n (%)						
No	12 (85.7)	29 (70.7)	40 (75.5)	7 (46.7)	20 (74.1)	2 (100.0)
Yes	2 (14.3)	12 (29.3)	13 (24.5)	8 (53.3)	7 (25.9)	
Onset of hearing loss (120), n (%)						
Post-lingual	7 (87.5)	29 (87.9)	35 (81.4)	10 (83.3)	16 (72.7)	
Pre-lingual	1 (12.5)	4 (12.1)	8 (18.6)	2 (16.7)	6 (27.3)	
Pre-operative PTA, median (IRQ)						
Implanted ear (107)	88.8 (78.1-98.8)	93.8 (82.8-104.1)	88.8 (80.6-105.6)	76.2 (70.0-96.2)	98.8 (89.1-105.0)	80.0 (68.1-91.9)
Non-implanted ear (121)	75.6 (56.9-85.9)	66.2 (38.8-85.0)	79.4 (65.3-91.2)	63.8 (15.0-80.0)	80.6 (63.4-95.3)	88.8 (88.8-88.8)
Pre-operative PTAHF, median (IRQ)						
Implanted ear (78)	103.3 (95.8-111.6)	98.3 (83.3-111.2)	109.4 (95.0-115.0)	90.0 (85.0-106.7)	111.7 (100.8-114.2)	106.7 (104.2-109.2)
Non-implanted ear (75)	96.7 (88.3-113.3)	81.7 (55.8-113.3)	103.3 (81.2-112.1)	75.0 (15.0-100.0)	91.7 (76.7-104.2)	103.3 (103.3-103.3)
Total ear (176), n (%)	16 (9.1)	49 (27.8)	63 (35.8)	15 (8.5)	31 (17.6)	2 (1.1)
CNC word, median (IQR)						
Pre-implantation (145)	10.0 (0.0-20.0)	0.0 (0.0-15.2)	8.0 (0.0-24.5)	4.0 (0.0-9.0)	4.0 (0.0-15.0)	24.5 (20.2-28.8)
6 months post (146)	32.0 (12.0-60.0)	40.0 (21.5-51.2)	25.0 (15.0-45.0)	27.0 (11.5-53.0)	37.5 (23.0-50.0)	17.5 (16.2-18.8)
12 months post (85)	35.0 (20.0-45.0)	40.0 (17.5-53.5)	30.0 (20.0-44.5)	24.5 (19.0-35.0)	34.0 (12.0-64.0)	12.0 (12.0-12.0)
Post-implantation (156)	35.0 (20.0-45.0)	40.0 (20.0-52.0)	32.0 (15.0-46.2)	24.5 (8.5-48.2)	42.5 (25-56.0)	7.5 (3.8-11.2)
APHAB, median (IQR)						
Pre-implantation (163)	72.0 (55.1-78.6)	55.2 (45.0-69.6)	60.7 (49.1-71.9)	65.8 (53.0-69.3)	54.1 (46.7-62.7)	49.2 (48.6-49.9)
6 months post (154)	45.3 (36.7-57.9)	36.0 (27.6-48.2)	40.8 (25.9-51.1)	49.2 (31.8-55.8)	38.0 (23.3-52.6)	53.3 (50.4-56.2)
12 months post (118)	44.1 (40.4-55.0)	33.2 (26.3-45.2)	34.5 (29.0-47.1)	41.6 (31.0-49.8)	36.4 (23.9-43.8)	45.3 (45.3-45.3)
Post-implantation (176)	39.4 (30.0-57.2)	35.5 (24.7-45.1)	36.9 (25.9-48.5)	42.6 (31.5-59.5)	34.9 (20.7-38.8)	46.4 (45.9-47.0)

The post-implantation scores correspond to the scores at the last available time point after implantation for every patient.
CI: cochlear implantation; IQR: interquartile range; n: number of patients; PTA: pure tone average; PTAHF: high frequency pure tone average.

Positive substantial TRQ changes

Patients experiencing tinnitus reduction or suppression after cochlear implantation demonstrated respectively a median pre-operative PTA of 76.2 dB and 98.8 dB and a median PTAHF of 90.0 dB and 111.7 dB in the implanted ear (Table 3). Patients experiencing positive substantial TRQ changes showed improvement in CNC word score post-implantation: tinnitus reduction group (baseline: 4.0 (IQR: 0.0–9.0); 12 months post- implantation: 24.5 (IQR: 19.0–35.0)) and tinnitus suppression group (baseline: 4.0 (IQR: 0.0–15.0); 12 months post-implantation:

34.0 (IQR: 12.0–64.0)). Improvement in APHAB scores post-implantation was observed for the tinnitus reduction group (baseline: 65.8 (IQR: 53.0–69.3); 12 months post-implantation: 41.6 (IQR: 31.0–49.8)) and the tinnitus suppression group (baseline: 54.1 (IQR: 46.7–62.7); 12 months post-implantation: 36.4 (23.9–43.8)) (Table A3). For all APHAB subscales, an improvement was found post-implantation in the two groups with positive substantial TRQ changes (Table A3).

Negative substantial TRQ changes

Patients experiencing tinnitus worsening or induction after cochlear implantation demonstrated respectively a median pre-operative PTA of 80.0 dB and 88.8 dB and a median PTAHF of 106.7 dB and 103.3 dB in the implanted ear (Table 3). The two patients experiencing tinnitus worsening had bilateral tinnitus and worsening in CNC word score post-implantation (baseline: 24.5 (IQR: 20.2–28.8); 12 months post-implantation: 12.0 (IQR: 12.0–12.0)). The APHAB AV subscale score increased in patients reporting an induction or tinnitus worsening after implantation: tinnitus induction group (baseline: 26.1 (IQR: 16.4–41.7); 6 months post-implantation: 52.0 (IQR: 23.8–70.2); 12 months post-implantation: 47.8 (IQR: 40.2–56.2)) and tinnitus worsening group (baseline: 2.8 (IQR: 1.9–3.8); 6 months post-implantation: 14.6 (IQR: 11–17.5); 12 months post-implantation: 1.0 (1.0–1.0)) (Table A3). In the two individuals with worsening tinnitus, the post-implantation APHAB RV scores were higher than the pre-implantation (baseline: 68.5 (IQR: 67.5–69.5); 6 months post-implantation: 81.8 (IQR: 77.1–86.4); 12 months post-implantation: 76.7 (IQR: 76.7–76.7)) (Table A3). The APHAB EC and APHAB BN scores decreased over time for patients experiencing negative substantial TRQ change (Table A3).

Associations between patient characteristics and TRQ score at 12 months post-implantation

There was no significant association between the TRQ score 12 months post-implantation and other factors: tinnitus absence/presence pre-implantation, age at implantation, onset of hearing loss, pre-implantation balance concerns, laterality of implantation and pure tone averages in the implanted and the non-implanted ear (Table 4). More than 40% of subjects had missing data for the pure tone averages (24 (40.0%) for PTA and 34 (56.7%) for PTAHF in the implanted ear; 22 (40.0%) for PTAHF in the non-implanted ear).

DIFFERENCE BETWEEN TINNITUS AND NO TINNITUS GROUP

Pre-implantation

Patients with tinnitus pre-implantation were statistically significantly younger than patients without tinnitus (tinnitus group: 62.6 years (IQR: 45.3–74.3); no tinnitus group: 70.7 years (IQR: 59.7–76.7); Wilcoxon rank sum test, w = 4493, p = 0.009). Patients with tinnitus pre-implantation had statistically significantly less severe high-frequency hearing loss in the non-implanted ear (tinnitus group: 84.2 dB PTA (IQR: 61.7–110.0); no tinnitus group: 101.7 dB PTA (IQR: 85.0–111.7); Wilcoxon rank sum test, w = 1154.5, p = 0.03). There were no other statistically significant differences in all other patient characteristics between patients with and without tinnitus pre-implantation (Table 5).

Post-implantation

Patients with tinnitus post-implantation were statistically significantly younger than patients without tinnitus (tinnitus group: 61.3 years (IQR: 47.7–72.0); no tinnitus group: 68.2 years (IQR: 57.3–76.2); Wilcoxon rank sum test, w = 11657, p = 0.002) (Table 5). Sex, laterality of implantation, balance concerns and onset of hearing loss did not differ significantly between groups. The non-tinnitus group had a statistically significantly more severe pre-implantation hearing loss in the non-implanted ear (tinnitus group: 70.0 dB PTA (IQR: 50.0–85.0); no tinnitus group: 80.6 dB PTA (IQR: 68.4–95.0); Wilcoxon rank sum test, w = 6138.5, p < 0.001). The same observation can be found in the high frequencies for both ears: implanted ear (tinnitus group: 102.5 dB PTA (IQR: 85.0–112.5); no tinnitus group: 108.3 dB PTA (IQR: 96.7–115.0); Wilcoxon rank sum test, w = 3948.5, p = 0.02), nonimplanted ear (tinnitus group: 85.8 dB PTA (IQR: 63.3–109.6); no tinnitus group: 103.3 dB PTA (IQR: 83.3–110.0); Wilcoxon rank sum test, w = 2626.5, p = 0.01).

The APHAB and CNC word scores were not statistically significant discriminant factors between groups (Table A2).

Table 4. Relative importance of patient characteristics on tinnitus distress at 12 months post-implantation measured using outcomes of univariable association analysis.

Characteristic	Missing, n (%)	Cohort (n=60)	OR (95% CI)	p-value
Tinnitus pre-implantation, n (%)	0 (0.0)		-1.63 (-12.86-9.59)	0.77
Yes		36 (60.0)		
No		24 (40.0)		
Age at implantation, median (IQR)	0 (0.0)	67.6 (57.1-74.5)	-0.09 (-0.38-0.19)	0.52
Sex, n (%)	0 (0.0)		-1.22 (-9.18-6.75)	0.76
Male		33 (55.0)		
Female		27 (45.0)		
Onset of hearing loss, n (%)	13 (21.7)		-3.01 (-15.27-9.26)	0.62
Pre-lingual		8 (13.3)		
Post-lingual		39 (65.0)		
Balance concerns pre-implantation, n (%)	0 (0.0)		1.40 (-6.91-9.71)	0.74
Yes		21 (35.0)		
No		39 (65.0)		
Laterality of implantation, n (%)	0 (0.0)		-2.67 (-17.01-	0.71
Unilateral		55 (91.7)	11.67)	
Bilateral		5 (8.3)		
Pre-operative PTA in the implanted ear, median (IQR)	24 (40.0)	90.0 (80.0-98.8)	0.07 (-0.32-0.45)	0.73
Pre-operative PTA in the non-implanted ear, median (IQR)	4 (7.3)	72.5 (46.9-85.0)	0.05 (-0.10-0.20)	0.54
Pre-operative PTAHF in the implanted ear, median (IQR)	34 (56.7)	100.8 (91.2-110.0)	-0.33 (-0.76-0.10)	0.13
Pre-operative PTAHF in the non-implanted ear, median (IQR)	22 (40.0)	86.7 (65.0-111.7)	-0.02 (-0.17-0.13)	0.78

CI: confidence intervals; IQR: interquartile range; n: number of patients; PTA: pure tone average; PTAHF: high frequency pure tone average; TRQ: Tinnitus Reaction Questionnaire. The p-value reported results from the univariate linear regression modelling the TRQ score at 12 months post-implantation.

Table 5. Distribution of characteristics between tinnitus and no tinnitus reported pre- and post-CI.

	Pre-CI			Post-CI		
Characteristic	**No tinnitus 76 (44.2%)**	**Tinnitus 96 (55.8%)**	**p-value**	**No tinnitus 156 (55.7%)**	**Tinnitus 124 (44.3%)**	**p-value**
Age, median (IQR)	70.7 (59.7-76.7)	62.6 (45.3-74.3)	0.009*	68.2 (57.3-76.2)	61.3 (47.7-72.0)	0.002*
Sex, n (%)			0.85			0.18
Female	40 (52.6)	48 (50.0)		79 (50.6)	52 (41.9)	
Male	36 (47.4)	48 (50.0)		77 (49.4)	72 (58.1)	
Laterality of implantation, n (%)			0.41			0.37
Unilateral	64 (84.2)	86 (89.6)		115 (73.7)	98 (79.0)	
Bilateral	12 (15.8)	10 (10.4)		41 (26.3)	26 (21.0)	
Balance concerns, n (%)			0.24			0.31
No	60 (78.9)	67 (69.8)		107 (68.6)	77 (62.1)	
Yes	16 (21.1)	29 (30.2)		49 (31.4)	47 (37.9)	
Onset of hearing loss, n (%)			0.77			0.20
Post-lingual	44 (80.0)	58 (76.3)		86 (72.9)	78 (81.2)	
Pre-lingual	11 (20.0)	18 (23.7)		32 (27.1)	18 (18.8)	
Pre-operative PTA, median (IQR)						
Implanted ear	92.5 (80.0-108.8)	93.8 (80.0-103.8)	0.96	95.0 (84.4-107.5)	93.8 (78.8-103.8)	0.09
Non-implanted ear	80.0 (62.5-91.2)	73.8 (43.8-90.0)	0.15	80.6 (68.4-95.0)	70.0 (50.0-85.0)	0.001*
Pre-operative PTAHF, median (IQR)						
Implanted ear	106.7 (95.0-114.7)	105.0 (91.2-113.2)	0.30	108.3 (96.7-115.0)	102.5 (85.0-112.5)	0.02*
Non-implanted ear	101.7 (85.0-111.7)	84.2 (61.7-110.0)	0.03*	103.3 (83.3-110.0)	85.8 (63.3-109.6)	0.01*

CI: cochlear implantation; IQR: interquartile range; n: number of patients; PTA: pure tone average; PTAHF: high frequency pure tone average.

The p-value reported results from statistical comparison test between the no tinnitus group and the tinnitus group. The Wilcoxon rank sum test was used for continuous variables and Person chi square test was used for categorical variables.

* indicates variables that showed a significant difference between the groups ($p < 0.05$).

Discussion

In this retrospective cohort study, we gathered data to estimate the prevalence and distress of tinnitus pre- and post-implantation among 300 patients with bilateral severe to profound hearing loss. Two hundred thirty-two (77.3%) patients underwent unilateral cochlear implantation, and 68 (22.7%) patients underwent bilateral cochlear implantation. Tinnitus prevalence was 55.8% preoperatively and 44.3% post-implantation. The median TRQ score was 12.0 (IQR: 1.0–28.0) points pre-implantation and 3.5 (IQR: 0.0–16.2) points post-implantation. Among the 96 patients experiencing tinnitus pre-implantation, 14.6% patients experienced moderate to catastrophic tinnitus distress pre-implantation. Post-implantation, 6.3% patients reported moderate to severe tinnitus distress.

Patients with tinnitus post-implantation were statistically significantly younger and had less severe pre-implantation hearing loss in the nonimplanted ear than patients without tinnitus.

About half of the CI patients (55.8%) experienced tinnitus pre-implantation in our cohort study. This finding suggests that tinnitus is more prevalent in CI candidates than in the general population (up to 30%)[2]. The estimate of the present study is in line with the prevalence of 52% reported in a sample of 211 UK adults identified as potential candidates for cochlear implantation[9]. Quaranta et al. reviewed studies on tinnitus experiences in patients undergoing cochlear implantation, which reported between 66% and 86% of CI recipients experiencing tinnitus before implantation[7]. However, studies included in this review presented some considerable risks of bias including methodological limitations and heterogeneous populations. Post-implantation, we found an estimate of 44.3% CI users reported experiencing tinnitus. This is marginally lower than the 50% of tinnitus estimated in a UK Biobank resource[9]. One possible explanation for these discrepancies in tinnitus estimation is the differences in the study setting or the use of different definitions of tinnitus when assessing the presence of tinnitus[24]. The scale of the 'problem' of tinnitus in CI patients should not be defined by prevalence alone. Most patients in our cohort (80/151) experienced no distress post-implantation and only 6 out 151 patients experienced moderate to severe handicap. However, our finding may motivate stakeholders in the implementation of tinnitus counselling as part of the CI standard of care.

As described above, in the studied population of CI recipients, the experienced tinnitus distress was generally low. The median post-implantation TRQ score for our study population was 3.5, interpreted as no to slight handicap. Using the TRQ severity grade classification, 6.3% had moderate to severe tinnitus distress. Andersson et al. investigated the tinnitus handicap in 111 CI recipients with tinnitus, in which 24.5% experienced a moderate to severe handicap based on the classification of Tinnitus Handicap Inventory[25]. Among CI recipients, there might be a subgroup of users experiencing tinnitus as a problem after implantation. As such, attention should be paid to further characterize this group which could benefit from tinnitus specific therapy.

Comparing differences in patient characteristics between patients with post-implantation tinnitus and without post-implantation tinnitus revealed that patients with tinnitus were statistically significantly younger at implantation than patients without tinnitus. Previous studies did not find age at implantation

as a discriminant factor[13,15–17] Patients reporting tinnitus pre-implantation were also younger than patients without tinnitus. As most of patients reporting tinnitus pre-implantation were also in the group of patients reporting tinnitus post-implantation, this observation might be specific to the study sample. Thereby, this finding could be related to hearing levels. Baseline pure tone average was found as a discriminant factor between patients with tinnitus and without tinnitus pre- and post-implantation. The tinnitus group had better baseline hearing on average than no tinnitus group. Within the tinnitus groups, patients experiencing a tinnitus reduction had better hearing thresholds pre-implantation. This outcome is not in agreement with the observation of Kompis et al. who reported that patients who develop tinnitus post-operatively had slightly better preoperative hearing thresholds in the implanted ear[26]. Further research with higher quality data is needed to assess whether pre-operative hearing loss could be meaningful for effect on tinnitus, especially at high frequencies. Speech perception, measured by CNC word score, was not significantly different between patients with tinnitus and without tinnitus. This observation is consistent with previous research on unilateral cochlear implantation[27].

No association was found between the TRQ score 12 months post-implantation and patient characteristics. Previous models predicting the effect of cochlear implantation on tinnitus distress assessed similar patient characteristics and did find significant associations. Dixon et al. (n = 358) showed that pure tone thresholds per 10-dB increase at 1kHz (OR: 1.11 (95% CI: 1.00, 1.22)) and at 2kHz (OR: 1.11 (95% CI: 1.01, 1.23)) in the contralateral ear were significantly associated with tinnitus improvement, defined as a reduction of at least 7 points in the Tinnitus Handicap Questionnaire, in unilateral CI users[13]. Further research is needed to identify key factors modelling the positive and negative effects of cochlear implantation on tinnitus and to direct clinical decision making and patient counselling, especially on the risk of tinnitus onset after implantation.

The prevalence of negative effects of cochlear implantation on experienced tinnitus, based on worsening of 17 points in TRQ score and induced tinnitus, was 10.5% in our study. These proportions are in agreement with previous studies, reporting any worsening in tinnitus distress scores in 4 to 13.7%[7,17,26,28]. The impact of tinnitus on cochlear implant performance and quality of life after implantation, as well as the risk of implantation inducing or worsening tinnitus is not well understood.

A novel finding of the present study was the absence of tinnitus severity grade worsening in patients with moderate or more severe tinnitus pre-implantation (Figure 1). This finding is in agreement with the association found between higher pre-implantation tinnitus burden, assessed by the Tinnitus Handicap Inventory, and tinnitus improvement in two studies attempting to predict the positive effect of cochlear implantation on tinnitus[13,15]. This observation suggests that tinnitus burden or distress should be an important criterion to consider when counselling about tinnitus worsening as a complication of cochlear implantation.

Our study has a relatively large sample size when compared with previous studies on tinnitus changes following cochlear implantation[7,13,15–17,26]. The data were systematically collected at defined follow-up time points according to a strict process of data collection integrated in the standard of care of the clinic. We evaluated substantial tinnitus change based on a minimum difference in TRQ scores of 17 points (equivalent to a change in severity grade). This method enabled us to investigate substantial positive and negative effect on tinnitus and to classify tinnitus changes in five different categories: tinnitus suppression, tinnitus reduction, no tinnitus change, tinnitus worsening and tinnitus induction.

The most important limitation of this study is the lack of a pre-defined protocol, and the retrospective nature of this study. Data were collected in clinical care. This is also reflected in the high proportion of missing post-operative data at late follow-up time point (missing self-reported tinnitus: 58.7% (12 months post-CI); 51.7% (24 months post-CI); 67.7% (36 months post-CI)). We therefore choose to select data available of the latest follow-up point as the post-implantation data to compare it with the pre-implantation data collected.

In the present study, we assessed tinnitus based on two complementary variables: self-reported presence of tinnitus and TRQ score. This combination of outcomes highlights a limitation in the interpretation of the TRQ score. In fact, we encountered cases where patients reported they were experiencing tinnitus but had a TRQ score of 0 i.e. they reported no distress from their tinnitus. These cases would have been difficult to interpret based only on the TRQ questionnaire score. Furthermore, the TRQ questionnaire is a measure focusing on psychological distress associated with tinnitus and does not assess a broader construct of the impact of tinnitus or treatment-related changes, as could be measured using the Tinnitus Handicap Inventory (THI) or the Tinnitus Functional Index (TFI)[29,30].

Another limitation in our analysis was the interpretation of the difference in TRQ score. Previous studies have used the criteria of an improvement in

TRQ score of 40% or greater as a clinically relevant tinnitus change[31,32]. We think this criterion is meaningful for clinically relevant improvement but there is a missing criterion for clinically relevant increase in tinnitus distress. For this reason, we defined a new criteria equivalent to a change in tinnitus distress instead of a change in percentages. For our classification of tinnitus change categories, we used a difference in TRQ score of 17 points between two times of assessment, which corresponds to at least a change in tinnitus severity grade, as a substantial TRQ change. Conversely, no change is reported when the change in TRQ score does not exceed 17 points. The criterion must be validated before being extended to further studies using the TRQ as a measure of treatment-related change. Furthermore, since significant tinnitus worsening was not specifically defined in literature, tinnitus worsening is usually not considered during tinnitus questionnaire development. There is a need to develop research quantifying tinnitus worsening, which is an essential aspect in tinnitus treatment-related change.

Our study confirms the high prevalence of tinnitus in CI candidates and current CI recipients. Most CI recipients experienced no to slight tinnitus distress. The post-implantation median tinnitus distress was 3.5 on a TRQ scale of 100, which is in line with earlier studies in similar patient groups[10,25,33]. However, there is a subgroup of CI recipients experiencing tinnitus burden. Identifying these patients and addressing their needs should be a priority to ensure the benefit of cochlear implantation. Among the studied outcomes, no factor was associated with post-implantation tinnitus changes. Fully understanding tinnitus worsening and induction after cochlear implantation requires further research, which is essential to allow clinicians to be confident in clinical decision making and provide realistic expectations on tinnitus changes after implantation.

Multi-center studies with a larger data set may provide further information about tinnitus in patients with CIs. These may give insights in the importance of patient characteristics on tinnitus, its distress, and the possibilities to minimize negative outcomes after implantation. Perhaps more importantly, better quality data is required i.e. fewer missing data, agreement on definitions, standard tools to assess and grade tinnitus. To avoid selection bias, prospective data collection should aim not only to assess hearing performance in CI recipients but also to collect tinnitus information as a standard in implant clinics.

Conclusion

Tinnitus prevalence was 55.8% preoperatively and 44.3% post-implantation. The median TRQ score was 12.0 (IQR: 1.0–28.0) points pre-implantation and 3.5 (IQR: 0.0–16.2) points post-implantation, interpreted as a "slight" tinnitus distress (TRQ < 17 points). A small proportion of recipients (6.3%) experienced tinnitus as moderate to severe post-implantation. Although, tinnitus distress in those reporting tinnitus pre-implantation improved statistically significantly post-implantation, there is no association between speech performance, measured by CNC word, and tinnitus distress, measured by TRQ. None of the patients reporting moderate to catastrophic tinnitus distress prior to implantation experienced worsening of tinnitus after implantation. The need to conduct research to fully understand tinnitus worsening and induction after cochlear implantation is important to extend our knowledge in order to allow clinicians to be confident in clinical decision making and provide realistic expectations on tinnitus changes after implantation. There is a need to combine the experiences of patients and clinical specialists involved in tinnitus management with evidence from around the world to better understand the impact of tinnitus on CI users.

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Data availability statement

The data that support the findings of this study are available the corresponding author, Kelly K.S. Assouly, upon reasonable request and agreement from Ear Science Institute Australia.

Conflicts of interest

Kelly K.S. Assouly is employee at Cochlear Technology Centre, Belgium. The other authors declare no conflict of interest.

Ethical approval

Data privacy protection practices were implemented. All patient data were deidentified and meet data compliance requirements for local patient data privacy laws following the Australian Privacy Act 1988 and international law for General Data Protection Regulation (GDPR). Ethical review and approval were not required for this type of observational studies containing no directly identifiable data (art. 24 GDPR Implementation Act).

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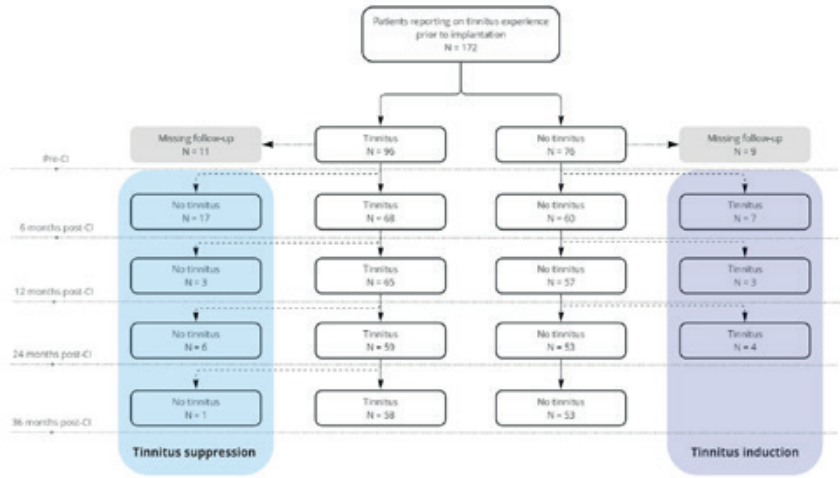
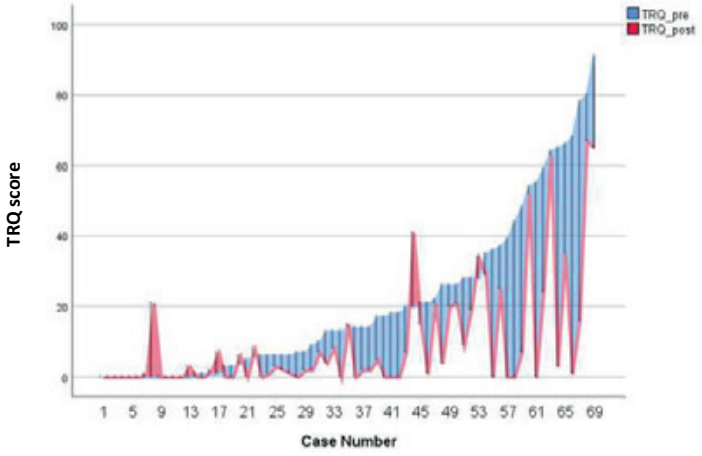
Appendix

Figure A1. Distribution of tinnitus reporting pre-implantation and at 6, 12, 24 and 36 months post-implantation.



CI: cochlear implantation; N: number of patients.

Figure A2. Pre- and post-implantation TRQ score of 68 patients who reported tinnitus pre- and post-implantation. Case number corresponds to individual ranged from 1 to 68.



The area in blue corresponds to a decrease in TRQ scores between pre- and post-implantation and the area in red corresponds to an increase in TRQ score between pre- and post-implantation.

Table A1. Cohort APHAB and CNC outcomes pre-implantation and at 6, 12, 24 and 36 months post-implantation.

Outcomes	Ears (n = 567)
Abbreviated Profile of Hearing Aid Benefit (APHAB), median (IQR)	
Pre-implantation	60.6 (48.2-70.4)
Missing, n (%)	178 (31.4)
6 months post-implantation	38.2 (25.9-51.5)
Missing, n (%)	279 (49.2)
12 months post-implantation	35.6 (26.0-49.3)
Missing, n (%)	355 (62.6)
24 months post-implantation	35.4 (24.1-48.2)
Missing, n (%)	305 (53.8)
36 months post-implantation	36.8 (24.9-49.4)
Missing, n (%)	395 (69.7)
CNC word score, median (IQR)	
Pre-implantation	4.0 (0.0-16.0)
Missing, n (%)	167 (29.5)
6 months post-implantation	36.0 (20.0-53.5)
Missing, n (%)	171 (30.2)
12 months post-implantation	40.0 (25.0-60.0)
Missing, n (%)	289 (51.0)
24 months post-implantation	45.0 (32.0-60.0)
Missing, n (%)	261 (46.0)
36 months post-implantation	48.0 (35.0-60.0)
Missing, n (%)	374 (66.0)

Table A2. Distribution of characteristics and scores between tinnitus and no tinnitus reported post-implantation.

Characteristic	No tinnitus post-CI	Tinnitus post-CI	p-value
Total ears (355), n (%)	203 (57.2)	152 (42.8)	
CNC word, median (IQR)			
Pre-implantation (274)	5.0 (0.0 to 15.0)	4.0 (0.0 to 16.0)	0.56
6 months post (280)	35.0 (16.0 to 50.5)	32.5 (20.0 to 52.8)	0.79
12 months post (191)	40.0 (24.0 to 60.0)	35.0 (21.0 to 55.0)	0.39
Post-implantation (318)	42.0 (25.0 to 60.0)	40.0 (23.0 to 52.8)	0.17
APHAB, median (IQR)			
Pre-implantation (255)	57.4 (47.7 to 67.6)	62.7 (47.4 to 73.5)	0.17
6 months post (240)	38.5 (24.2 to 50.9)	39.8 (29.8 to 53.3)	0.14
12 months post (181)	36.4 (26.8 to 49.8)	34.9 (27.4 to 45.6)	0.59
Post-implantation (350)	37.3 (23.5 to 51.5)	38.5 (25.2 to 49.3)	0.58
Ease of Communication (EC)			
Pre-implantation (255)	54.0 (30.5 to 74.8)	54.1 (31.2 to 81.0)	0.62
6 months post (239)	22.8 (12.0 to 37.5)	25.8 (16.3 to 38.9)	0.37
12 months post (181)	24.6 (14.2 to 29.3)	18.5 (12.0 to 27.0)	0.03*
Post-implantation (350)	20.7 (12.0 to 37.4)	20.5 (12.3 to 33.2)	0.96
Background Noise (BN)			
Pre-implantation (255)	74.5 (57.7 to 84.8)	77.8 (64.3 to 91.0)	0.05
6 months post (240)	54.0 (29.7 to 67.8)	55.2 (41.5 to 72.2)	0.07
12 months post (181)	49.8 (37.5 to 64.3)	52.0 (37.5 to 62.3)	0.77
Post-implantation (350)	49.7 (29.0 to 64.5)	54.2 (39.5 to 64.5)	0.11
Reverberation (RV)			
Pre-implantation (254)	76.7 (58.3 to 93.0)	76.7 (61.2 to 93.0)	0.71
6 months post (239)	50.0 (33.3 to 72.5)	50.0 (37.5 to 71.3)	0.78
12 months post (181)	50.8 (31.7 to 71.9)	49.7 (39.3 to 62.5)	0.50
Post-implantation (348)	50.0 (28.5 to 70.7)	46.8 (33.3 to 70.0)	0.63
Aversiveness (AV)			
Pre-implantation (255)	21.0 (10.2 to 42.6)	29.4 (11.9 to 50.5)	0.15
6 months post (239)	17.2 (8.7 to 35.2)	22.8 (11.2 to 45.9)	<0.05*
12 months post (181)	20.8 (8.8 to 35.5)	22.8 (9.6 to 40.1)	0.46
Post-implantation (350)	18.7 (8.7 to 37.2)	21.0 (7.6 to 39.5)	0.54

APHAB : Abbreviated Profile of Hearing Aid Benefit ; CI : cochlear implantation ; CNC : consonant nucleus consonant ; IQR : interquartile range ; n : number of patients ; PTA : pure tone average.
* indicates variables that showed a significant difference between the groups ($p<0.05$)

Table A3. Distribution of APHAB total and subscales scores between tinnitus changes groups.

Tinnitus changes	Induction	No change	No tinnitus	Reduction	Suppression	Worsening
Total ear (176), n (%)	16 (9.1)	49 (27.8)	63 (35.8)	15 (8.5)	31 (17.6)	2 (1.1)
APHAB, median (IQR)						
Pre-implantation (163)	72.0 (55.1-78.6)	55.2 (45.0-69.6)	60.7 (49.1-71.9)	65.8 (53.0-69.3)	54.1 (46.7-62.7)	49.2 (48.6-49.9)
6 months post (154)	45.3 (36.7-57.9)	36.0 (27.6-48.2)	40.8 (25.9-51.1)	49.2 (31.8-55.8)	38.0 (23.3-52.6)	53.3 (50.4-56.2)
12 months post (118)	44.1 (40.4-55.0)	33.2 (26.3-45.2)	34.5 (29.0-47.1)	41.6 (31.0-49.8)	36.4 (23.9-43.8)	45.3 (45.3-45.3)
Post-implantation (176)	39.4 (30.0-57.2)	35.5 (24.7-45.1)	36.9 (25.9-48.5)	42.6 (31.5-59.5)	34.9 (20.7-38.8)	46.4 (45.9-47.0)
Ease of communication (EC)						
Pre-implantation (163)	72.7 (41.1-86.0)	53.0 (30.5-77.4)	57.2 (33.2-78.3)	50.2 (33.0-72.8)	52.1 (29.0-69.7)	44.8 (38.2-51.5)
6 months post (154)	33.3 (20.6-38.5)	22.8 (16.3-33.3)	22.8 (12.8-39.0)	27.0 (11.6-35.3)	29.2 (11.2-41.7)	41.2 (38.0-44.4)
12 months post (118)	22.4 (18.5-27.4)	20.6 (12.3-30.3)	22.7 (14.4-33.3)	18.5 (12.3-29.0)	18.5 (12.0-27.5)	37.2 (37.2-37.2)
Post-implantation (176)	17.6 (10.8-38.4)	22.5 (14.2-33.2)	18.7 (13.5-39.5)	27.0 (14.2-36.5)	16.3 (12.0-24.9)	36.0 (35.4-36.6)
Background Noise (BN)						
Pre-implantation (163)	88.0 (71.1-93.5)	74.7 (59.5-86.9)	78.7 (66.2-86.4)	87.0 (74.5-93.0)	71.5 (58.2-80.8)	80.8 (76.8-84.9)
6 months post (154)	64.5 (39.6-70.5)	54.2 (40.0-64.5)	56.2 (41.8-72.0)	56.2 (42.7-75.7)	45.7 (29.2-67.0)	74.7 (67.5-81.8)
12 months post (118)	54.0 (45.8-70.5)	51.0 (34.7-62.3)	49.8 (37.5-65.3)	60.2 (52.0-66.5)	45.9 (31.8-59.3)	66.5 (66.5-66.5)
Post-implantation ()	43.8 (38.4-64.5)	54.2 (35.3-64.5)	58.2 (38.5-66.3)	57.8 (44.8-72.5)	41.5 (23.0-56.2)	63.4 (61.9-65.0)
Reverberation (RV)						
Pre-implantation (163)	87.8 (73.7-97.0)	70.7 (55.7-89.5)	79.7 (62.9-94.8)	72.7 (57.9-90.0)	74.7 (55.0-83.5)	68.5 (67.5-69.5)
6 months post (153)	60.3 (45.2-68.5)	50.0 (34.2-62.3)	54.0 (37.5-74.5)	47.8 (37.5-59.2)	49.5 (35.5-84.6)	81.8 (77.1-86.4)
12 months post (118)	50.0 (41.3-62.5)	44.2 (37.5-60.9)	54.2 (29.2-67.5)	50.0 (48.0-54.8)	47.6 (26.5-56.7)	76.7 (76.7-76.7)
Post-implantation (176)	47.7 (25.0-77.3)	41.7 (33.3-66.5)	50.0 (28.3-70.6)	50.0 (33.4-67.4)	41.7 (29.1-72.7)	74.6 (73.5-75.6)
Aversiveness (AV)						
Pre-implantation (163)	26.1 (16.4-41.7)	28.2 (13.1-38.1)	16.8 (7.3-30.7)	47.7 (25.9-66.3)	32.4 (17.4-41.5)	2.8 (1.9-3.8)
6 months post (154)	52.0 (23.8-70.2)	14.2 (8.3-24.8)	15.1 (8.1-31.3)	45.5 (26.3-64.4)	17.8 (11.2-41.8)	14.6 (11-17.5)
12 months post (118)	47.8 (40.2-56.2)	22.4 (10.1-28.3)	14.5 (4.8-27.1)	25.2 (14.2-35.2)	26.9 (10.4-42.0)	1.0 (1.0-1.0)
Post-implantation (176)	41.5 (30.2-54.8)	16.3 (8.3-26.8)	14.2 (5.8-31.1)	35.3 (18.7-57.1)	12.3 (4.7-29.2)	10.8 (5.9-15.6)

References

1. Baguley, D. M., McFerran, D. & Hall, D. Tinnitus. in The Lancet (2013). doi:10.1016/S0140-6736(13)60142-7.
2. McCormack, A., Edmondson-Jones, M., Somerset, S. & Hall, D. A systematic review of the reporting of tinnitus prevalence and severity. Hearing Research (2016) doi:10.1016/j.heares.2016.05.009.
3. Stegeman, I. et al. Tinnitus and its associations with general health and hearing loss. Prog. Brain Res. Press. (2021).
4. Nondahl, D. M. et al. Tinnitus and its risk factors in the Beaver Dam Offspring Study. Int. J. Audiol. (2011) doi:10.3109/14992027.2010.551220.
5. Eggermont, J. J. & Roberts, L. E. Tinnitus: animal models and findings in humans. Cell Tissue Res. 361, 311–336 (2015).
6. Lewis, R. M., Jahn, K. N., Parthasarathy, A., Goedicke, W. B. & Polley, D. B. Audiometric Predictors of Bothersome Tinnitus in a Large Clinical Cohort of Adults With Sensorineural Hearing Loss. Otol. Neurotol. Off. Publ. Am. Otol. Soc. Am. Neurotol. Soc. [and] Eur. Acad. Otol. Neurotol. 41, e414–e421 (2020).
7. Quaranta, N., Wagstaff, S. & Baguley, D. M. Tinnitus and cochlear implantation. International Journal of Audiology vol. 43 245–251 (2004).
8. Baguley, D. M. & Atlas, M. D. Cochlear implants and tinnitus. in Tinnitus: Pathophysiology and Treatment (eds. Langguth, B., Hajak, G., Kleinjung, T., Cacace, A. & Møller, A. R. B. T.-P. in B. R.) vol. 166 347–355 (Elsevier, 2007).
9. Pierzycki, R. H. et al. Tinnitus and Sleep Difficulties after Cochlear Implantation. Ear Hear. (2016) doi:10.1097/AUD.0000000000000341.
10. Ramakers, G. G. J., Van Zon, A., Stegeman, I. & Grolman, W. The effect of cochlear implantation on tinnitus in patients with bilateral hearing loss: A systematic review. Laryngoscope 125, 2584–2592 (2015).
11. Peter, N., Liyanage, N., Pfiffner, F., Huber, A. & Kleinjung, T. The Influence of Cochlear Implantation on Tinnitus in Patients with Single-Sided Deafness: A Systematic Review. Otolaryngol. - Head Neck Surg. (2019) doi:10.1177/0194599819846084.
12. Assouly, K. K. S., van Heteren, J. A. A., Stokroos, R. J., Stegeman, I. & Smit, A. L. Cochlear implantation for patients with tinnitus - A systematic review. Prog. Brain Res. 260, 27–50 (2021)..
13. Dixon, P. R. et al. Predicting Reduced Tinnitus Burden after Cochlear Implantation in Adults. Otol. Neurotol. 41, 196–201 (2020).
14. Hoekstra, C. E. L., Wesdorp, F. M. & van Zanten, G. A. Socio-demographic, health, and tinnitus related variables affecting tinnitus severity. Ear Hear. (2014) doi:10.1097/AUD.0000000000000045.
15. Kim, D. K. et al. Prospective, Multicenter Study on Tinnitus Changes after Cochlear Implantation. Audiol. Neurotol. 21, 165–171 (2016).

16. Ramakers, G. G. J. et al. Development and internal validation of a multivariable prediction model for tinnitus recovery following unilateral cochlear implantation: A cross-sectional retrospective study. BMJ Open 8, 1–9 (2018).Multicenter Study on Tinnitus Changes after Cochlear Implantation. Audiol. Neurotol. 21, 165–171 (2016).

17. Kloostra, F. J. J., Arnold, R., Hofman, R., Burgerhof, J. G. M. & Dijk, P. Models to predict positive and negative effects of cochlear implantation on tinnitus. Laryngoscope Investig. Otolaryngol. 1–5 (2018) doi:10.1002/lio2.224..

18. Opperman, E., le Roux, T., Masenge, A. & Eikelboom, R. H. The effect of tinnitus on hearing-related quality of life outcomes in adult cochlear implant recipients. Int. J. Audiol. 0, 1–9 (2020).

19. Wilson, P. H., Henry, J., Bowen, M. & Haralambous, G. Tinnitus reaction questionnaire: psychometric properties of a measure of distress associated with tinnitus. J. Speech Hear. Res. 34, 197–201 (1991).

20. Meric, C., Pham, E. & Chery-Croze, S. Validation of French translation of the 'Tinnitus Reaction Questionnaire', Wilson et al. 1991. Encephale. 23, 442–446 (1997).

21. Cox, R. M. & Alexander, G. C. The abbreviated profile of hearing aid benefit. Ear Hear. (1995) doi:10.1097/00003446-199504000-00005.

22. Peterson, G. E. & Lehiste, I. Revised CNC lists for auditory tests. J. Speech Hear. Disord. 27, 62–70 (1962).

23. Luxford, W. M. Minimum speech test battery for postlingually deafened adult cochlear implant patients. Otolaryngol. neck Surg. Off. J. Am. Acad. Otolaryngol. Neck Surg. 124, 125–126 (2001).

24. De Ridder, D. et al. Tinnitus and tinnitus disorder: Theoretical and operational definitions (an international multidisciplinary proposal). in Progress in Brain Research vol. 260 1–25 (Elsevier B.V., 2021).

25. Andersson, G., Freijd, A., Baguley, D. M. & Idrizbegovic, E. Tinnitus distress, anxiety, depression, and hearing problems among cochlear implant patients with tinnitus. J. Am. Acad. Audiol. (2009) doi:10.3766/jaaa.20.5.5.

26. Kompis, M. et al. Tinnitus before and 6 months after cochlear implantation. Audiol. Neurotol. 17, 161–168 (2012).

27. Amoodi, H. A. et al. The effects of unilateral cochlear implantation on the tinnitus handicap inventory and the influence on quality of life. Laryngoscope 121, 1536–1540 (2011).

28. Pan, T. et al. Changes in the tinnitus handicap questionnaire after cochlear implantation. Am. J. Audiol. (2009) doi:10.1044/1059-0889(2009/07-0042).

29. Boecking, B., Brueggemann, P., Kleinjung, T. & Mazurek, B. All for One and One for All? – Examining Convergent Validity and Responsiveness of the German Versions of the Tinnitus Questionnaire (TQ), Tinnitus Handicap Inventory (THI), and Tinnitus Functional Index (TFI). Front. Psychol. 12, (2021).

30. Jacquemin, L. et al. Sensitivity to change and convergent validity of the Tinnitus Functional Index (TFI) and the Tinnitus Questionnaire (TQ): Clinical and research perspectives. Hear. Res. 382, 107796 (2019).

31. Hazell, J. The TRT method in practice. Proc. SixthInternational Tinnitus Semin. London Tinnitus Hyperacusis Centre. 92–98 (1999).

32. McKinney, C., Hazell, J. & Graham, R. An evaluation of the TRTmethod. Proc. Sixth Int. Tinnitus Semin. London Tinnitus Hyperacusis Centre. 99–105 (1999).

33. Ramakers, G. G. J. et al. Tinnitus after Simultaneous and Sequential Bilateral Cochlear Implantation. Front. Surg. 4, 65 (2017).


PART 02
related factors
cochlear implant
Influence of

Influence of cochlear implant related factors on tinnitus outcomes

PART 02

6

Relationship between cochlear implant electrode position and tinnitus outcomes in patients with single-sided deafness

Submitted

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Abstract

OBJECTIVE

We aimed to assess the relationship between the tinnitus characteristics and impact on daily life and the cochlear implant (CI) array types and positions in single-sided deaf (SSD) patients at three months post-activation.

METHODS

Twenty-five SSD patients (12 lateral wall electrode array, 13 perimodiolar electrode array) completed tinnitus questionnaires pre-implantation and at three months post-activation. The electrode position was determined using the radius of the most apical electrode, the angular spacing position of the most apical electrode and the angular spacing position of the most basal electrode on high resolution computed tomography scans.

RESULTS

We did not identify any statistical difference in tinnitus impact or characteristics post-activation when comparing the two electrode array types. For the lateral wall group, a higher angular spacing position of the most apical electrode was statistically significantly associated with a higher tinnitus pitch (when the CI was off), and a higher angular spacing position of the most basal electrode was statistically significantly associated with a higher tinnitus pitch and number of sounds (when the CI was active).

CONCLUSION

Besides a weak but statistically significant association between angular spacing positions and tinnitus characteristics in lateral wall electrodes, no influence of electrode design or position was found on tinnitus impact and characteristics in SSD patients implanted with a CI.

Introduction

Tinnitus is the perception of sound in the ears or in the head in absence of an external stimulus[1]. It has a prevalence ranging from 10 to 30% in the general population and up to 52% or even 86% in people with severe to profound hearing loss[2]. Tinnitus characteristics can vary in the nature of the sound, but also in the location, pitch and loudness. It can be bothersome and result in a substantial reduction of the quality of life[3]. So far, the cause and mechanisms of tinnitus are still not fully understood. However, hearing loss has often been identified as the most common risk factor for tinnitus[4,5].

Single-sided deafness (SSD) is a unilateral hearing impairment defined as a mean pure-tone hearing threshold (averaged over 0.5, 1, 2, 4 kHz) of at least 70 dB hearing level (HL) in the poor ear and less than 30 dB HL in the better ear[6]. Patients with SSD often experience poor sound localization, reduced speech understanding in noise and reduced quality of life[7,8]. A significant proportion of SSD patients may have incapacitating tinnitus[9]. Current SSD treatments focus on providing hearing input in the contralateral ear with hearing devices such as contralateral routing of sound hearing aid (CROS-HA) or bone conduction devices (BCD). Neither of these hearing devices stimulate the deprived auditory pathway of the impaired ear as a potential mechanism to reduce ipsilateral tinnitus[6,10].

A cochlear implant (CI) is an auditory prosthesis that can restore hearing capabilities in case of a severe to profound sensorineural hearing loss by electrical stimulation of the cochlea. Previous studies have shown that electrical stimulation of the cochlea in patients with SSD can also result in tinnitus reduction[10–17]. However, in some cases, cochlear implantation can induce tinnitus or the provided electrical stimulation could result in tinnitus worsening[18,19].

So far, it is unclear which surgical or patient related characteristics influence tinnitus outcomes after cochlear implantation in SSD patients. Also, device and stimulation characteristics might be related to the change in tinnitus experienced by SSD patients receiving a CI. For example, the electrode array position partly determines the neural interface between the spiral ganglion cells and the implant. Perimodiolar electrode arrays are pre-curved, which results in electrode contacts close to the modiolus and the spiral ganglion cells. Lateral wall electrode arrays have electrode contacts further away from the modiolus. The difference in electrode position may influence the channel interaction due to spread of stimulation leading to differences in tinnitus outcomes.

Understanding the factors that can explain tinnitus outcomes after CI placement might lead to optimization of patient selection, implantation procedures, patient counselling, and at the end, better outcomes. Our aim is to assess the possible relationship between tinnitus characteristics and impact on daily life and electrode position in SSD patients implanted with a lateral wall electrode array or a perimodiolar electrode array. In addition, we examined the relationship between the angular spacing position of the most apical electrode, the radius of the most apical electrode and the angular spacing position of the most basal electrode and the tinnitus outcomes.

Materials and methods

STUDY SAMPLE AND RECRUITMENT PROCESS

This study is a part of a randomized controlled trial on treatments for SSD patients[20]. For this study, SSD patients were recruited between July 2014 and January 2019. Inclusion criteria were having a pure tone average of 500, 1000, 2000, and 4000 kHz (PTA) threshold ≥ 70 dB in the deaf ear and ≤ 30 dB in the contralateral ear, an air bone gap ≤ 10 dB, a duration of deafness > 3 months and ≤ 10 years and no (retro)cochlear abnormalities[20.] After inclusion, patients were randomized to a CI group, a BCD and a CROS-HA trial group. As a part of the study, 27 patients received a Nucleus CI (Cochlear Limited, Australia). For further details about recruitment, inclusion and exclusion criteria, and the randomization procedure, we refer to the complete study protocol[20]. Due to the long inclusion period of the study, newer versions of the CI became available during the study. The first patients were implanted with a Nucleus® CI422 or CI522 (lateral wall electrode array), while later patients were implanted with a Nucleus® CI512 (perimodiolar electrode array). All patients in the CI group underwent a post-operative computed tomography (CT) scanning. For the current study, to relate electrode position to tinnitus outcomes, we only included patients in which a full insertion into the cochlea by the electrode array was achieved, i.e. without signs of tip fold-over on CT scan or electrode position outside the cochlea.

STUDY PROCEDURES

After cochlear implantation, all participants followed rehabilitation. Three months after activation, a computed tomography (CT) of the petrous bone according to standard procedures was taken using a Philips Brilliance iCT scanner (Koninklijke Philips N.V., The Netherlands).

Pre-implantation and three months after activation of the CI, tinnitus outcomes

were assessed including scores of the impact of tinnitus on daily life and tinnitus characteristics. A part of the outcomes on tinnitus for the total group of CI recipients were already published[21]. For the current study, we focussed on the comparison between electrode array type and position in relation to the impact of tinnitus on daily life and tinnitus characteristics.

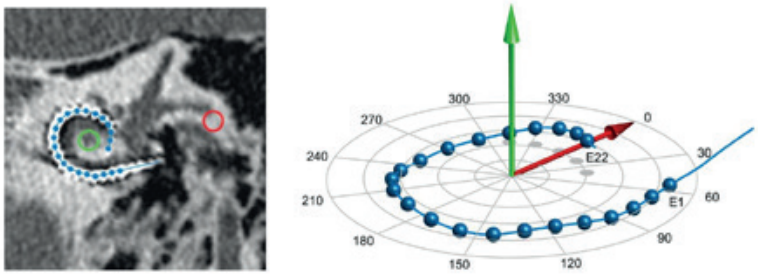
OUTCOME ASSESSMENT

Electrode position

The Nucleus® CI422 or CI522 has a Slim Straight electrode array of 18.75 mm long, which is a lateral wall electrode array. The Nucleus® CI512 has a Contour Advance perimodiolar electrode array of 11.70 mm long. Both electrode array types consist of 22 electrode contacts, where the most basal electrode in the cochlea is electrode contact number 1 (E1), and the most apical electrode is electrode contact number 22 (E22).

The intracochlear electrode array position was imaged using post-operative high-resolution CT scans three months after activation. The CT scans were reconstructed to 0.1 mm in-plane pixel spacing and 0.4-mm slice spacing using a high-resolution convolution kernel. The position of each cochlear implant electrode array was determined using the method developed and validated by Bennink et al. (2017). In short, after filtering CT scans, a three dimension bounding box was manually positioned on the cochlea, in which the centreline of the electrode array was automatically tracked. Then, the resulting CT coordinates were transformed to a cylindrical coordinate system (insertion angle, radius, elevation) by fitting a plane through the basal turn of the cochlea and the manual selection of the top of the modiolus and the most lateral point of the horizontal semicircular canal by an experienced radiologist[23]. The top of the modiolus defines the centre of the cylindrical coordinate system, whereas the line between this point and the most lateral point of the horizontal semi-circular canal defines the −34.6° angle with respect to the position of the round window[24].

The electrode position factors explored in the current study were the type of electrode array used, the radius of the most apical electrode (E22) in millimeters (mm), the angular spacing position of the most apical electrode (E22) in degrees (°), as well as the angular spacing position of the most basal electrode (E1) in degrees (°) (Figure 1).



A B

Figure 1. (A) A reformatted CT slice through the basal turn of the cochlea (25×25 mm). The green circle is of the top of the modiolus. The red circle is the most lateral point of the horizontal semi-circular canal. The 22 blue dots indicate the location of the electrode contacts. (B) The CT-based cylindrical coordinate system as defined by the plane trough the basal turn of the cochlea and the two reference points : the top of the modiolus (green point) and the most lateral point of the horizontal semi-circular canal (red point). The top of the modiolus defines the centre of the cylindrical coordinate system, whereas the line between the two reference points defines the -34.6° angle with respect to the position of the round window[24]. The 5-mm green arrow is in the direction of the top of the modiolus (elevation) and the 5-mm red arrow is toward the most lateral point of the horizontal semi-circular canal (0° angle). The polar gridlines have a radial spacing of 1 mm and an angular spacing of 30°. Electrode contact positions are marked by blue spheres ; E1 is the most basal electrode contact and E22 is the most apical electrode contact. The radius of the most apical electrode is the distance in mm between the reference point of the coordinate system and the most apical electrode contact (blue sphere E22) on the axis of the red arrow. The angular spacing position of the most apical electrode contact is the angle in degrees between the modiolus axis (red arrow) and the most apical electrode contact (blue sphere E22), which is the maximum insertion depth angle of the array. The angular spacing position of the most basal electrode is the angle between the modiolus axis (red arrow) and the most basal electrode contact (blue sphere E1), which is the minimum insertion depth angle of the array. Figures were extracted from the publication[22] with the consent from Bennink et al.
CT : computed tomography.

Tinnitus outcomes

Pre-implantation and at three months post-activation, patients indicated whether they had tinnitus or not. If they indeed reported to have tinnitus, they were asked to fill out tinnitus questionnaires on impact and characteristics. If they reported not to have tinnitus, tinnitus questionnaires were not completed. If a patient reported tinnitus and completed tinnitus questionnaires at one assessment time point, but reported not to have tinnitus at another time point, he/she was deemed to have tinnitus questionnaire scores of zero when not reporting tinnitus.

Several questionnaires were used to score the impact of tinnitus on daily life and the tinnitus characteristics. The Tinnitus Handicap Inventory (THI) contains 25 questions characterizing the effect of tinnitus on a patient's emotions and daily life. Possible answers are 'no' (0 points), 'sometimes' (2 points) and 'yes' (4 points). An overall THI scores can be calculated with a maximum of 100 points, representing a maximum of tinnitus burden[25].

The Tinnitus Questionnaire (TQ) measures distress caused by tinnitus with 52 questions divided in six domains : emotional and cognitive distress, intrusiveness, auditory perceptual difficulties, sleep disturbances and associated somatic complaints[26]. Three answers are possible for every question : 'true' (0 point), 'partly true' (1 point) or 'not true' (2 points). A total TQ score from 0 to 84 points can be reached, where a higher score indicates a more distressing tinnitus. For the study, we used the validated Dutch version of the TQ[27].

The Tinnitus Burden Questionnaire (TBQ) is a self-developed questionnaire assessing various aspects of tinnitus. It contains seven visual analogue scales (VAS) asking about tinnitus impact on daily life (tinnitus burden, tinnitus impact on annoyance, concentration, sleep, social life, family life and work) and five VAS assessing tinnitus characteristics (tinnitus loudness, tinnitus pitch, tinnitus occurrence, tinnitus stability, number of tinnitus sounds). The VAS ranges from '0' (no burden) to '100' (maximum burden) for all VAS TBQ questions characterizing tinnitus impact. The VAS tinnitus loudness ranges from '0' (not audible) to '100' (extremely loud), VAS tinnitus pitch ranges from '0' (extremely low) to '100' (extremely high), VAS tinnitus occurrence ranges from '0' (constantly absent) to '100' (constantly present), VAS tinnitus stability ranges from '0' (not varying) to '100' (extremely varying) and the VAS related to the number of tinnitus sounds ranges between '0' and '10'. For every VAS, two conditions were assessed : when the CI was on (CI on) and when the CI was turned off (CI off).

Tinnitus impact on daily life was characterized using the THI, TQ, TBQ VAS tinnitus burden as well as TBQ VAS tinnitus related impact on concentration, sleep, annoyance, social life, family life and work single question scores. Tinnitus characteristics were defined by TBQ VAS tinnitus loudness, pitch, number of sounds, occurrence and stability single question scores.

Demographics

Demographic data included sex, age at CI activation, etiology of deafness, duration of deafness and the hearing level of both ears (PTA) at time of inclusion.

STATISTICS

Descriptive statistics were used to summarize patient characteristics and electrode position characteristics per electrode array group.

Tinnitus outcomes were analyzed and reported in two categories : tinnitus impact on daily life and tinnitus characteristics. We compared tinnitus outcome scores at three months post-activation between the lateral wall electrode group and the perimodiolar electrode group. Differences between the two electrode arrays were statistically assessed using the Mann-Whitney u test. Within-subject comparisons were performed using the Wilcoxon signed-rank test. For the TBQ, we also assessed the difference in individual VAS outcomes between the two different conditions post-activation : CI on and CI off.

Additionally, univariate linear regressions were performed to assess the relation between tinnitus outcomes and electrode position characterized by the angular spacing position of the most apical electrode, the radius of the most apical electrode, and the angular spacing position of the most basal electrode.

Data analysis was performed using R version 4.1.2 and R Studio version 1.3.1073 (®R Studio). A p-value < 0.05 was considered statistically significant.

Results

PATIENT CHARACTERISTICS

From the initially 27 patients receiving a CI, 25 were included in this study (2 patients were excluded : 1 patient had a tip fold-over and another patient had four electrodes outside the cochlea). Of the 25 patients included, 12 patients were implanted with a perimodiolar electrode array (Nucleus® CI512) and 13 patients were implanted with a lateral wall electrode array (Nucleus® CI422 or CI522). The group characteristics are summarized per group in Table 1.

Table 1. Group characteristics.

Characteristics	Levels	Perimodiolar (CI512)	Lateral wall (CI422/CI522)
Total, n (%)		13 (52.0)	12 (48.0)
Sex, n (%)	Female	8 (61.5)	4 (33.3)
	Male	5 (38.5)	8 (66.7)
Age at CI activation (year), mean (SD)		50.9 (13.4)	54.4 (13.7)
Duration of deafness (years), mean (SD)		2.7 (3.2)	3.5 (2.8)
Hearing level (PTA in dB HL), mean (SD)	Best ear	14.0 (6.1)	15.9 (8.0)
	Poor ear	98.7 (12.4)	91.7 (14.3)
Etiology, n (%)	Iatrogenic	0 (0.0)	1 (8.3)
	Labyrinthitis	2 (15.4)	2 (16.7)
	Ménière's disease	1 (7.7)	2 (16.7)
	Sudden deafness	8 (61.5)	4 (33.3)
	Unknown	2 (15.4)	3 (25.0)
Tinnitus presence, n (%)	Pre-implantation	12 (92.3)	11 (91.7)
	Post-implantation	11 (84.6)	9 (75.0)
Radius of E22 (mm), mean (SD)		1.6 (0.3)	1.8 (0.2)
Angular insertion depth (°), mean (SD)		344.6 (28.7)	455.5 (62.7)
Angular position of E1 (°), mean (SD)		44.9 (10.5)	70.6 (19.3)

CI : cochlear implant ; E1 : most basal electrode ; E22 : most apical electrode ; PTA : pure tone average (dB hearing loss) at 0.5, 1, 2, and 4 kHz ; SD : standard deviation.

ELECTRODE POSITION CHARACTERISTICS

The mean radius of the most apical electrode of the perimodiolar group was 1.6 (SD : 0.3) mm compared to 1.8 (SD : 0.2) mm in the lateral wall group. The mean angular spacing position of the most apical electrode of the perimodiolar group was 344.6° ± 28.7° whereas the mean angular spacing position of the most apical electrode of the lateral wall group was 455.5° ± 62.7°. The mean angular spacing position of the most basal electrode was 44.9° ± 10.5° for the perimodiolar group and 70.6° ± 19.3° for the lateral wall group.

TINNITUS PRESENCE

Of the total study group, 23 out of the 25 included patients reported tinnitus pre-implantation (12 out of 13 in the perimodiolar implanted group and 11 out of 12 in the lateral wall implanted group) (Table 1). One of the 12 patients in the perimodiolar group and two out of 11 patients of the lateral wall group reported total tinnitus suppression three months after activation. Two out of the 12 patients with perimodiolar electrode arrays did not complete the THI and TQ post-activation, which were considered as missing. No tinnitus induction (i.e., no tinnitus reported pre-implantation, but tinnitus reported post-activation) was reported.

TINNITUS IMPACT ON DAILY LIFE

THI

There was a statistically significant reduction in median THI scores between pre-implantation and post-activation for the perimodiolar group (*pre-implant :* 26.0 (IQR : 16.0 – 43.5), *3 months post-activation :* 4.0 (IQR : 0.0 – 4.0), *Wilcoxon singed-rank test,* p = 0.01) (Figure 2). No statistically significant reduction was found for the lateral wall group (*pre-implant :* 14.0 (IQR : 7.0-40.0), *3 months post-activation :* 8.0 (IQR : 2.0-33.0), Wilcoxon singed-rank test, p = 0.22).

TQ

There was a statistically significant reduction in median TQ scores between pre-implantation and post-activation for the perimodiolar group (*pre-implant :* 26.5 (IQR : 13.0-40.0), *3 months post-activation :* 4.0 (IQR : 3.0 – 11.0), *Wilcoxon singed-rank test,* p = 0.01) and for the lateral wall group (*pre-implant :* 21.0 (IQR : 9.0 – 32.5), *3 months post-activation :* 10.0 (IQR : 3.0 – 23.0), Wilcoxon singed-rank test, p = 0.02) (Figure 2).

TBQ

There was a statistically significant reduction in median TBQ VAS tinnitus burden score between pre-implantation and post-activation when the CI was on for the perimodiolar group (*pre-implant :* 70.0 (IQR : 60.0 – 80.0), *CI on :* 10.0 (IQR : 0.0 – 20.0), *Wilcoxon singed-rank test, p* = 0.002) and for the lateral wall group (pre-implant : 50.0 (IQR : 22.5 – 75.0), CI on : 0.0 (IQR : 0.0 – 30.0), Wilcoxon singed-rank test, p = 0.007) (Figure 2). There was a statistically significant reduction in median TBQ VAS tinnitus burden score between pre-implantation and post-activation when the CI was off for the perimodiolar group (*pre-implant :* 70.0 (IQR : 60.0 – 80.0), *CI off :* 25.0 (IQR : 17.5 – 52.5), *Wilcoxon singed-rank test, p* = 0.003). No statistically significant reduction was found for the lateral wall group when the CI was off (*pre-implant :* 50.0 (IQR : 22.5 – 75.0), *CI off :* 30.0 (IQR : 10.0 – 40.0), *Wilcoxon singed-rank test, p* = 0.13). When the CI was on, both perimodiolar and lateral wall groups had significantly lower median values in TBQ VAS tinnitus burden, compared to when the CI was off (perimodiolar : CI on : 10.0 (IQR : 0.0 – 20.0), CI off : 25.0 (IQR : 17.5 – 52.5), *Wilcoxon singed-rank test, p* = 0.005 ; lateral wall : *CI on :* 0.0 (IQR : 0.0 – 30.0), CI off : 30.0 (IQR : 10.0 – 40.0), *Wilcoxon singed-rank test, p* = 0.024) (Figure 2).

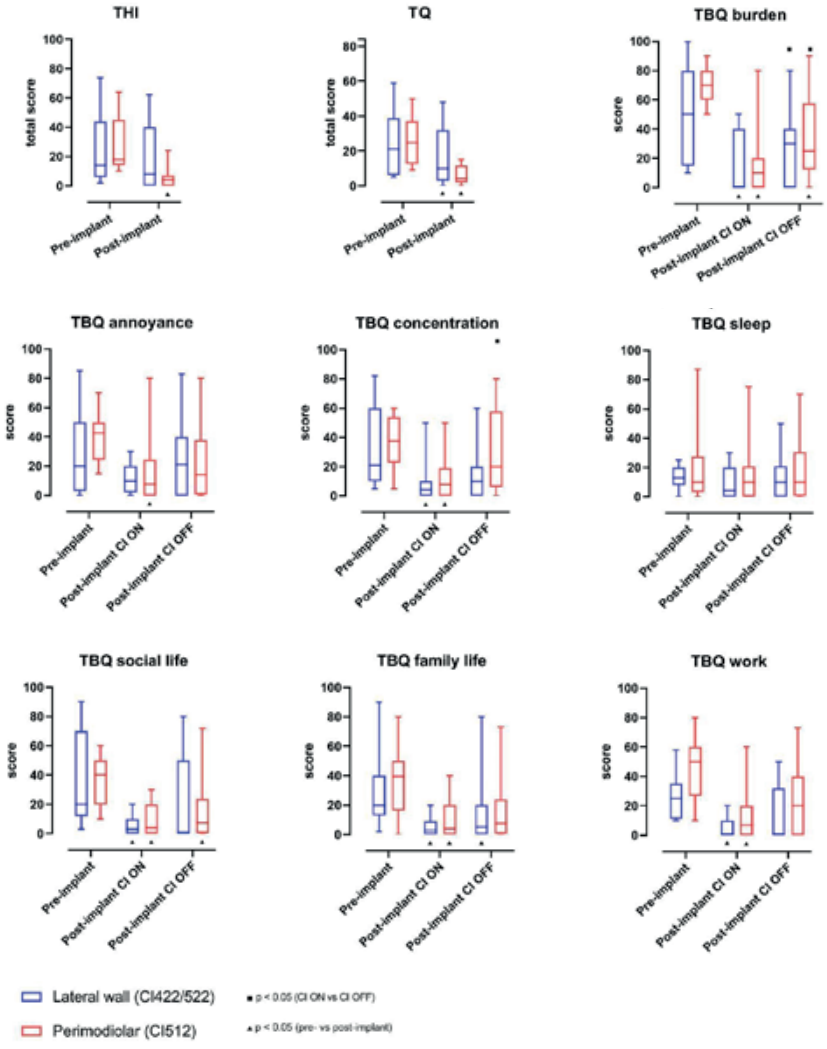
For both groups, there were statistically significant reductions in tinnitus related concentration, social life, family life and work between pre-implantation and post-implantation when the CI was on (Figure 2). Only in the perimodiolar group, a statistically significant reduction in tinnitus annoyance was found between pre-implantation and post-implantation when the CI was on. The perimodiolar implanted group also showed significantly lower median values in tinnitus related concentration when the CI was on compared to when the CI was off. See Figure 2 and Table A1 for further information on tinnitus impact TBQ scores per group.

TINNITUS CHARACTERISTICS

There was a statistically significant reduction in median TBQ VAS tinnitus loudness when the CI was on, for both perimodiolar (*pre-implant :* 65.0 (IQR : 50.0 – 70.8), *CI on :* 7.5 (2.2 – 12.5), *Wilcoxon singed-rank test, p* = 0.002) and lateral wall group (*pre-implant :* 59.0 (IQR : 51.0 – 63.0), *CI on :* 22.0 (1.0 – 32.0), *Wilcoxon singed-rank test, p* = 0.005). When the CI was on, both groups had significantly lower median values in TBQ tinnitus loudness, compared to when the CI was off (perimodiolar : *CI on :* 7.5 (2.2 – 12.5), *CI off :* 26.5 (17.5 – 41.0), *Wilcoxon singed-rank test, p* = 0.036 ; lateral wall : *CI on :* 22.0 (1.0 – 32.0), *CI off :* 50.0 (15.5 – 70.0), *Wilcoxon singed-rank test, p* = 0.028) (Figure 3).

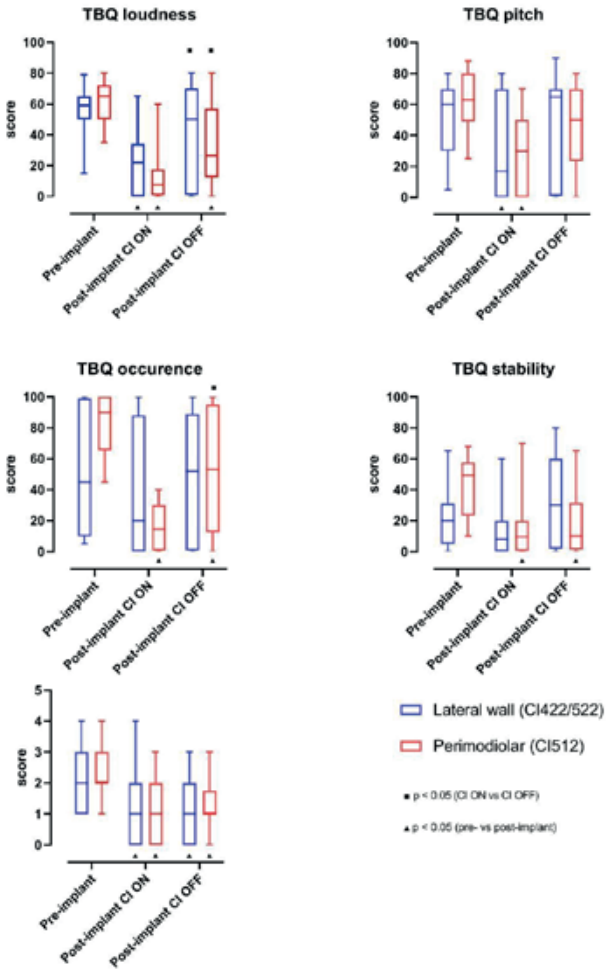
For both groups, there were statistically significant reductions in tinnitus pitch and number of sounds between pre-implantation and post-implantation when the CI was on (Figure 3). When the CI was on, the perimodiolar implanted group had significantly lower median values in tinnitus occurrence compared to when the CI was off. See Figure 3 and Table A1 for further information on other TBQ scores on tinnitus characteristics per group.

Figure 2. Tinnitus impact scores per group and per condition.



↙ CI on : situation assessed when the cochlear implant is on ; CI off : situation assessed when the cochlear implant is off ; TBQ : Tinnitus Burden Questionnaire ; THI : Tinnitus Handicap Inventory ; TQ : Tinnitus Questionnaire. The p-value reported results from within-subject comparisons using the Wilcoxon singed-rank tests.

Figure 3. Tinnitus characteristics scores per group and per condition.



CI on : situation assessed when the cochlear implant is on ; CI off : situation assessed when the cochlear implant is off ; TBQ : Tinnitus Burden Questionnaire ; THI : Tinnitus Handicap Inventory ; TQ : Tinnitus Questionnaire. The p-value reported results from within-subject comparisons using the Wilcoxon singed-rank tests.

COMPARISON BETWEEN ELECTRODE ARRAY TYPE ON TINNITUS IMPACT AND CHARACTERISTICS

Figure 2 and Figure 3 show respectively the tinnitus impact and tinnitus characteristics outcomes relative to the time of assessment per group. No significant difference in post-activation TBQ, THI and TQ scores was found between the two electrode array type groups (Mann-Whitney u test, $p > 0.05$).

COMPARISON BETWEEN ELECTRODE POSITION ON TINNITUS IMPACT AND CHARACTERISTICS

Radius of the most apical electrode

In patients reporting pre-implantation tinnitus, the median radius of the most apical electrode was 1.5mm in the perimodiolar group and 1.8mm in the lateral wall group (Table 2).

There was no statistically significant association between the radius of the most apical electrode and tinnitus impact and characteristics outcomes post-activation (Table 2).

Angular spacing position of the most apical electrode

In patients reporting pre-implantation tinnitus the median angular spacing position of the most apical electrode was 348.9° in the perimodiolar group and 467.5° in the lateral wall group (Table 2).

There was no statistically significant association between the angular spacing position of the most apical electrode and tinnitus burden and impact outcomes post-activation (Table 2).

A statistically significant positive association was found between the angular spacing position of the most apical electrode of the lateral wall electrode array and the tinnitus pitch score assessed when the CI was off (β (regression coefficient) = 0.4, 95% confidence intervals (CI) (0.1-0.8)). No other statistically significant association was found between the angular spacing position of the most apical electrode and tinnitus characteristics outcomes.

Angular spacing position of the most basal electrode

In patients reporting pre-implantation tinnitus the median angular spacing position of the most basal electrode was 42.2° in the perimodiolar group and 78.4° in the lateral wall group (Table 2).

There was no statistically significant association between the angular spacing position of the most basal electrode and tinnitus impact outcomes post-activation (Table 2).

A statistically significant positive association was found between the angular spacing position of the most basal electrode of the lateral wall electrode array and the tinnitus pitch score, independently of the CI on or off situation (when the CI is on : β = 1.1, 95% CI (0.04-2.2) ; when the CI is off : β = 1.3, 95% CI (0.04-2.5)) (Table 2). For the lateral wall group, the angular spacing position of the most basal electrode was statistically significantly associated with the number of tinnitus sounds only when the CI was on post-activation (β = 0.05, 95% CI (0.00-0.09)). No other association was found between the angular spacing position of the most basal electrode and tinnitus characteristics outcomes.

Table 2. Outcomes of univariable linear regression on tinnitus outcomes by electrode position parameters.

	Radius of E22 (mm)		**Angular insertion depth (°)**		**Angular position of E1 (°)**	
	Perimodiolar (n = 12)	Lateral wall (n = 11)	Perimodiolar (n = 12)	Lateral wall (n = 11)	Perimodiolar (n = 12)	Lateral wall (n = 11)
Median (IQR)	1.5 (1.5 – 1.7)	1.8 (1.6 – 1.9)	348.9 (332.9 – 365.9)	467.5 (428.9 – 481.2)	42.2 (40.3 – 47.6)	78.4 (61.3 – 83.7)
Tinnitus impact on daily life						
THI, β (95% CI)	11.6 (-6.4 – 29.6)	-35.1 (-106.0 – 35.9)	-0.1 (-0.3 – 0.02)	0.04 (-0.24 – 0.32)	-0.05 (-0.6 – 0.5)	-0.5 (-1.3 – 0.4)
TQ, β (95% CI)	4.0 (-9.9 – 17.9)	-25.5 (-84.1 – 33.0)	-0.01 (-0.2 – 0.1)	0.04 (-0.19 – 0.27)	0.1 (-0.2 – 0.5)	-0.3 (-1.0 – 0.4)
TBQ, β (95% CI)						
Burden						
CI on	-0.2 (-48.6 – 48.2)	-8.47 (-79.67 –62.18)	0.20 (-0.31 – 0.71)	-0.06 (-0.3 – 0.2)	0.02 (-1.4 – 1.4)	-0.07 (-0.9 – 0.8)
CI off	-16.1 (-0.3 – 0.9)	-31.59 (-120.00 – 56.83)	0.33 (-0.27 – 0.93)	0.01 (-0.3 – 0.4)	0.3 (-1.4 – 2.1)	0.1 (-1.0 – 1.2)
Tinnitus characteristics						
TBQ, β (95% CI)						
Loudness						
CI on	27.5 (-7.6 – 62.6)	23.4 (-50.7 – 97.6)	-0.3 (-0.7 – 0.1)	-0.06 (-0.3 – 0.2)	-0.2 (-1.4 – 0.1)	0.25 (-0.7 – 1.2)
CI off	-27.8 (-78.2 – 22.7)	-37.6 (-152.0 – 76.8)	0.5 (0.0 – 0.1)	0.1 (-0.3 – 0.6)	0.7 (-0.9 – 2.3)	0.13 (-1.3 – 1.6)
Pitch						
CI on	33.5 (-20.4 – 87.4)	-17.8 (-129.7 – 94.1)	-0.3 (-0.9 – 0.3)	0.1 (-0.3 – 0.5)	0.7 (-1.0 – 2.4)	**1.1 (0.04 – 2.2)**
CI off	1.38 (-56.8 – 59.5)	-93.5 (-199.8 – 12.7)	0.3 (-0.3 – 0.9)	**0.4 (0.1 – 0.8)**	1.0 (-0.7 – 2.6)	**1.3 (0.04 – 2.5)**

Occurrence						
CI on	5.1 (-27.8 – 38.0)	34.7 (-111.3 – 180.8)	-0.06 (-0.4 – 0.3)	-0.2 (-0.8 – 0.3)	-0.3 (-1.3 – 0.7)	0.2 (-1.6 – 2.0)
CI off	-60.2 (-137.1 – 16.7)	-8.3 (-1.5 – 2.1)	0.6 (-0.5 – 0.6)	0.06 (-0.5 – 0.6)	0.1 (-2.6 – 2.8)	0.3 (-1.5 – 2.1)
Stability						
CI on	0.9 (-42.4 – 44.2)	-9.3 (-72.9 – 54.4)	0.2 (-0.2 – 0.7)	0.04 (-0.2 – 0.3)	-0.2 (-1.5 – 1.1)	0.6 (-0.1 – 1.2)
CI off	-37.3 (-78.5 – 4.0)	-38.5 (-149.5 – 72.5)	0.4 (-0.1 – 0.8)	0.3 (-0.1 – 0.6)	-0.1 (-1.6 – 1.4)	0.6 (-0.6 – 2.0)
N of sounds						
CI on	0.7 (-1.5 – 2.9)	1.1 (-3.3 – 5.6)	0.00 (-0.03 – 0.02)	0.01 (-0.01 – 0.02)	-0.02 (-0.08 – 0.05)	**0.05 (0.00 – 0.09)**
CI off	0.3 (-1.4 – 1.9)	-1.6 (-0.01 – 0.07)	0.01 (-0.01 – 0.02)	0.01 (-0.01 – 0.02)	-0.01 (-0.06 – 0.04)	0.03 (-0.01 – 0.07)

β : estimated regression coefficients ; CI : confidence intervals ; E1 : most basal electrode ; E22 : most apical electrode ; IQR : interquartile intervals ; n : number of patients ; N : number ; CI on : when the cochlear implant is on ; CI off : when the cochlear implant is off ; TBQ : Tinnitus Burden Questionnaire ; THI : Tinnitus Handicap Inventory; TQ : Tinnitus Questionnaire. Bold indicates statistically significant regression coefficients ($p < 0.05$).

Discussion

In the current study, we compared the tinnitus impact on daily life and tinnitus characteristics at three months after cochlear implant activation in two groups of SSD patients with a cochlear implant : 13 patients implanted with a perimodiolar electrode array and 12 patients implanted with a lateral wall electrode array. There was a significant reduction in TQ scores, TBQ VAS tinnitus burden, TBQ VAS tinnitus-related concentration, social life, family life and work in both electrode array groups between pre- and post-implantation. Tinnitus characteristics such as scores on tinnitus loudness, pitch and number of sounds were also significantly reduced in both groups post-implantation. We found no statistical differences in tinnitus impact on daily life between the perimodiolar electrode array group and the lateral wall electrode array group. There was no association between parameters of the electrode position and outcomes of tinnitus impact on daily life.

First of all, it needs to be noted that the results of our study are based on outcomes of participants to the CINGLE study primarily aimed to assess the effect of CI on hearing restoration, with tinnitus being a secondary outcome. In this study sample, participants scored on average slight to mild tinnitus handicap before implantation and scores were representing no to slight tinnitus handicap three months post-activation. The findings of a significant reduction in THI and TQ scores three months post-implantation in the total study cohort compared to pre-implantation are consistent with previous studies reporting reduction in tinnitus

impact as a benefit of cochlear implantation in SSD patients[10–12,28]. Moreover, for both electrode array groups, we found statistically significant reductions in the TBQ VAS tinnitus burden and loudness when the CI was on compared to when the CI was off in accordance to previous studies[11,12,16]. These findings support the idea that electrical stimulation of the auditory nerve through the cochlear implant could reduce tinnitus impact and influence tinnitus characteristics.

Significant reductions in several tinnitus impact scores post-implantation compared to pre-implantation were demonstrated, whereby no statistically significant difference between the two electrode array groups were found in scores of tinnitus impact and characteristics. Potentially, early effects of different electrical stimulation characteristics -by different electrode lengths or designs- on tinnitus outcome do decrease with time due to brain plasticity[29]. Therefore, the influence of different electrode designs might have disappeared at three months post-implantation. However, the results should be interpreted with caution due to the relatively small sample size of the study, which might have led to a small sample size bias.

Associations between angular spacing positions and tinnitus characteristics were found only in the lateral wall group. Indeed, higher angular spacing position of the most apical electrode was found to be associated with a higher tinnitus pitch when the CI was off, and the angular spacing position of the most basal electrode was also associated with a higher tinnitus pitch and with the numbers of tinnitus sounds assessed when the CI was on. Several factors could explain these findings. First of all, a greater angular spacing position of the most apical electrode is related to more cochlear trauma or mechanical distortion which could explain a changed tinnitus percept. Also, the re-organization of the frequency distribution and the distance between electrode and the spiral ganglion cells might play a role in the tinnitus characteristics changes and could be the reason why outcomes differ between a perimodiolar and a lateral wall electrode position. To detail and in depth explain tinnitus outcomes in relation to electrode design or location further studies are needed, in which also intra-operative electrophysiological measurements, such as electrocochleography, can be used to measure the actual cochlear trauma.

In the lateral wall group, there was a significant reduction in TQ score, but there was no significant reduction in THI score between pre- and post-implantation. This observation can be explained by the fact that these multi-item tinnitus questionnaires weigh psychological, auditory and health related aspects of tinnitus differently[30]. To be noted, these questionnaires were not designed

to measure treatment-related changes[31] although minimal clinically important differences have been defined for both (7 points for the THI[32] and 12 points for the TQ[27]). In our study, the minimal clinically important differences in THI and TQ scores were achieved in the perimodiolar group but not in the lateral wall group.

The current study has several strengths. Firstly, we investigated the association between cochlear electrode placement and positioning in relation to tinnitus impact on daily life and characteristics by using several single-item and multi-item tinnitus outcome measures which enabled us to measure different aspects of the tinnitus as well as its effect on daily life in detail. Secondly, electrode position was determined based on high resolution CT and using a validated semiautomatic method[22], which permits to work with reliable electrode array position data. Finally, our study design provided not only a between-group comparison, but also allowed a within-group comparison.

Our study has also limitations. Firstly, our study is limited by a small sample size and therefore results should be interpreted with caution. Moreover, the two electrode array groups were created based on a shift of electrode design during the course of the study, not by randomization or matching. After inclusion of half of the intended participants, consecutively included participants received no longer the lateral wall array but the perimodiolar array design. This could create selection bias. We consider this risk to be low as the transition of electrode design was only motivated by the technical advancements of the newer electrode designs released during the long course of the study and not by analysis of outcomes. However, besides electrode array position also other factors such as stimulation-related factors or rehabilitation-related factors may influence tinnitus outcomes and be important confounding factors. Our findings should be validated by a randomized controlled trial with tinnitus as a primary outcome and a sample size based on power calculation in order to draw a conclusion on the influence of electrode design and position on tinnitus outcomes in SSD patients. Secondly, ideally, measuring tinnitus outcomes during the first weeks after implantation and during longer follow-up could be advocated to understand the effect of the implantation procedure and effect of short- and long-term activation on outcomes in more detail. Furthermore, one can argue that tinnitus outcomes might change within a longer period of time post-activation. Moreover, outcomes were assessed with single- and multi-item questions. Open interviews might have been more appropriate or could be of additional value to further investigate the tinnitus experience using two different electrode arrays. Finally, the electrode positions were limited to the most basal

and most apical electrode. We should consider other electrode position variables such as the electrode-to-modiolus distance[33]. The cochlear duct length should also be considered taking into account the cochlea anatomy which is patient specific[34,35].

Conclusion

Based on the current study, electrode design and position does not seem to have an influence on the tinnitus impact on daily life in SSD patients with tinnitus and a CI. Tinnitus sonority such as tinnitus pitch or numbers of sounds might be associated with angular spacing positions, although this effect was only statistically significant in our data for the lateral wall electrode array. Understanding these associations and the factors involved in the variation in tinnitus outcomes might lead to a better electrode array selection, implantation, and patient counselling. A randomized controlled trial should be conducted to primarily investigate the influence of electrode position on tinnitus impact and characteristics.

Ethical approval

The research protocol of this study was approved by the Institutional Review Board of the University Medical Center Utrecht (NL45288.041.13) and is registered in the Netherlands Trial Register (www.trialregister.nl, NTR4580).

Informed consent from participants

All patients provided signed Informed Consent between July 2014 and February 2019 for their study participation.

Data availability statement

The data that support the findings of this study are available from the corresponding author, Adriana L. Smit, upon reasonable request.

Competing interests

Kelly K.S. Assouly and Bas van Dijk are employees at Cochlear Technology Center, Belgium. The other authors declared no conflict of interest.

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Appendix

Table A1. Tinnitus outcomes.

Group	Perimodiolar (CI512)	Lateral wall (CI422/CI522)	p-value
Tinnitus impact on daily life			
THI, median (IQR)			
Pre-implant	26.0 (16.0 – 43.5)	14.0 (7.0 – 40.0)	0.25
Post-implant	4.0 (0.0 – 4.0)	8.0 (2.0 – 33.0)	0.15
Missing, n (%)	2 (15.4)	0 (0.0)	
TQ, median (IQR)			
Pre-implant	26.5 (13.0 – 40.0)	21.0 (9.0 – 32.5)	0.44
Post-implant	4.0 (3.0 – 11.0)	10.0 (3.0 – 23.0)	0.34
Missing, n (%)	2 (15.4)	0 (0.0)	
TBQ, median (IQR)			
Burden			
Pre-implant	70.0 (60.0 – 80.0)	50.0 (22.5 – 75.0)	0.10
Post-implant CI on	10.0 (0.0 – 20.0)	0.0 (0.0 – 30.0)	0.85
Post-implant CI off	25.0 (17.5 – 52.5)	30.0 (10.0 – 40.0)	0.87
Annoyance			
Pre-implant	42.5 (33.5 – 49.2)	20.0 (6.5 – 37.5)	0.12
Post-implant CI on	7.5 (0.0 – 21.5)	10.0 (2.5 – 19.5)	0.73
Post-implant CI off	14.0 (1.5 – 32.5)	21.0 (0.5 – 35.0)	0.80
Concentration			
Pre-implant	37.5 (27.5 – 51.2)	21.0 (13.5 – 60.0)	0.78
Post-implant CI on	8.0 (0.0 – 17.0)	4.0 (0.0 – 7.0)	0.51
Post-implant CI off	20.0 (8.8 – 42.5)	10.0 (0.0 – 15.5)	0.19

Sleep			
Pre-implant	10.0 (3.8 – 22.5)	13.0 (9.0 – 20.0)	0.93
Post-implant CI on	7.5 (0.0 – 20.2)	4.0 (0.0 – 20.0)	0.71
Post-implant CI off	10.0 (1.5 – 23.5)	10.0 (0.0 – 20.5)	0.60
Social life			
Pre-implant	40.0 (20.0 – 50.0)	20.0 (16.0 – 55.0)	0.62
Post-implant CI on	4.0 (0.0 – 20.0)	3.0 (0.0 – 10.0)	0.66
Post-implant CI off	7.5 (1.5 – 21.2)	1.0 (0.0 – 35.0)	0.76
Family life			
Pre-implant	39.5 (18.8 – 50.0)	20.0 (16.5 – 35.0)	0.52
Post-implant CI on	4.0 (0.0 – 20.0)	3.0 (0.0 – 7.5)	0.61
Post-implant CI off	7.5 (1.5 – 21.2)	5.0 (0.5 – 15.5)	0.83
Work			
Pre-implant	50.0 (30.0 – 60.0)	25.0 (13.8 – 35.0)	0.06
Post-implant CI on	3.5 (0.0 – 20.0)	2.0 (0.0 – 9.2)	0.70
Post-implant CI off	20.0 (3.0 – 34.0)	1.5 (0.0 – 32.0)	0.47
Tinnitus characteristics			
TBQ, median (IQR)			
Loudness			
Pre-implant	65.0 (50.0 – 70.8)	59.0 (51.0 – 63.0)	0.32
Post-implant CI on	7.5 (2.2 – 12.5)	22.0 (1.0 – 32.0)	0.47
Post-implant CI off	26.5 (17.5 – 41.0)	50.0 (15.5 – 70.0)	0.31
Pitch			
Pre-implant	63.0 (49.8 – 80.0)	55.0 (33.0 – 66.0)	0.12
Post-implant CI on	30.0 (0.0 – 50.0)	17.0 (1.0 – 45.0)	1.00
Post-implant CI off	50.0 (31.2 – 70.0)	65.0 (10.0 – 70.0)	0.95

Occurrence			
Pre-implant	90.0 (76.5 – 100.0)	45.0 (18.5 – 98.5)	0.06
Post-implant CI on	14.5 (2.2 – 30.0)	20.0 (1.0 – 79.0)	0.42
Post-implant CI off	53.0 (17.5 – 95.0)	52.0 (5.5 – 84.5)	0.46
Stability			
Pre-implant	49.5 (24.5 – 52.5)	20.0 (6.5 – 30.5)	**0.03**
Post-implant CI on	9.5 (1.5 – 20.0)	8.0 (0.5 – 15.0)	0.64
Post-implant CI off	10.0 (3.8 – 30.5)	30.0 (2.0 – 55.0)	0.54
Number of sounds			
Pre-implant	2.0 (2.0 – 3.0)	2.0 (1.5 – 2.5)	0.36
Post-implant CI on	1.0 (0.0 – 2.0)	1.0 (0.0 – 2.0)	0.80
Post-implant CI off	1.0 (1.0 – 1.25)	2.0 (0.5 – 2.0)	0.12

IQR : interquartile ; CI on : when the cochlear implant is on ; CI off : when the cochlear implant is off ; TBQ : Tinnitus Burden Questionnaire ; THI : Tinnitus Handicap Inventory ; TQ : Tinnitus Questionnaire. All TBQ items ranged between 0 and 100, except TBQ number of sounds which ranged between 0 and 10.

P-value is from Mann-Whitney u tests between the perimodiolar and the lateral wall groups, excluding the missing category. Bold indicates statistically significant a difference between electrode array groups ($p < 0.05$).

References

1. Baguley, D. M. & Atlas, M. D. Cochlear implants and tinnitus. in Tinnitus : Pathophysiology and Treatment (eds. Langguth, B., Hajak, G., Kleinjung, T., Cacace, A. & Møller, A. R. B. T.-P. in B. R.) vol. 166 347–355 (Elsevier, 2007).
2. Baguley, D. M. & Atlas, M. D. Cochlear implants and tinnitus. in Tinnitus : Pathophysiology and Treatment (eds. Langguth, B., Hajak, G., Kleinjung, T., Cacace, A. & Møller, A. R. B. T.-P. in B. R.) vol. 166 347–355 (Elsevier, 2007).
3. McCormack, A., Edmondson-Jones, M., Somerset, S. & Hall, D. A systematic review of the reporting of tinnitus prevalence and severity. Hearing Research (2016) doi:10.1016/j.heares.2016.05.009.
4. Eggermont, J. J. & Roberts, L. E. Tinnitus : animal models and findings in humans. Cell Tissue Res. 361, 311–336 (2015).
5. Nondahl, D. M. et al. Tinnitus and its risk factors in the Beaver Dam Offspring Study. Int. J. Audiol. (2011) doi:10.3109/14992027.2010.551220.
6. Van de Heyning, P., Távora-vieira, D. & Rompaey, V. Towards a Unified Testing Framework for Single-Sided Deafness Studies : A Consensus Paper. Audiol. Neurotol. 21, 391–398 (2016).
7. Arndt, S. et al. Comparison of pseudobinaural hearing to real binaural hearing rehabilitation after cochlear implantation in patients with unilateral deafness and tinnitus. Otol. Neurotol. Off. Publ. Am. Otol. Soc. Am. Neurotol. Soc. [and] Eur. Acad. Otol. Neurotol. 32, 39–47 (2011).
8. Dwyer, R. T., Firszt, J. B. & Reeder, R. M. Effects of unilateral input and mode of hearing in the better ear : Self-reported performance using the Speech, Spatial and Qualities of Hearing Scale. Ear Hear. 35, 1–24 (2014).
9. Mertens, G., Kleine Punte, A., De Ridder, D. & Van de Heyning, P. Tinnitus in a single-sided deaf ear reduces speech reception in the nontinnitus ear. Otol. Neurotol. 34, 662–666 (2013).
10. Poncet-Wallet, C. et al. Prospective Multicentric Follow-up Study of Cochlear Implantation in Adults With Single-Sided Deafness : Tinnitus and Audiological Outcomes. 0, (2019).
11. Mertens, G., De Bodt, M. & Van de Heyning, P. Cochlear implantation as a long-term treatment for ipsilateral incapacitating tinnitus in subjects with unilateral hearing loss up to 10 years. Hear. Res. 331, 1–6 (2016).
12. Ramos Macías, A. et al. One-Year Results for Patients with Unilateral Hearing Loss and Accompanying Severe Tinnitus and Hyperacusis Treated with a Cochlear Implant. Audiol. Neurotol. 23, 8–19 (2018).
13. Ramos Macías, A. et al. Cochlear Implant in Patients With Sudden Unilateral Sensorineural Hearing Loss and Associated Tinnitus. Acta Otorrinolaringol. (English Ed. 63, 15–20 (2012).
14. Arts, R. A. G. J. et al. Tinnitus Suppression by Intracochlear Electrical Stimulation in Single Sided Deafness – A Prospective Clinical Trial : Follow-Up. PLoS One 11, e0153131 (2016).

15. Ahmed, M. F. & Khater, A. Tinnitus suppression after cochlear implantation in patients with single-sided deafness. Egypt. J. Otolaryngol. 33, 61 (2017).

16. Punte, A. K., De Ridder, D. & Van de Heyning, P. On the necessity of full length electrical cochlear stimulation to suppress severe tinnitus in single-sided deafness. Hearing research vol. 295 24–29 (2013).

17. Van De Heyning, P. et al. Incapacitating unilateral tinnitus in single-sided deafness treated by cochlear implantation. Ann. Otol. Rhinol. Laryngol. 117, 645–652 (2008).

18. Quaranta, N., Wagstaff, S. & Baguley, D. M. Tinnitus and cochlear implantation. International Journal of Audiology vol. 43 245–251 (2004).

19. Kompis, M. et al. Tinnitus before and 6 months after cochlear implantation. Audiol. Neurotol. 17, 161–168 (2012).

20. Peters, J. P. M. et al. CINGLE-trial : Cochlear implantation for siNGLE-sided deafness, a randomised controlled trial and economic evaluation. BMC Ear, Nose Throat Disord. 15, 1–8 (2015).

21. Peters, J. P. M. et al. Short-term outcomes of cochlear implantation for single-sided deafness compared to bone conduction devices and contralateral routing of sound hearing aids — Results of a Randomised controlled trial. PLoS One 16, 1–25 (2021).

22. Bennink, E. et al. Automatic localization of cochlear implant electrode contacts in CT. Ear Hear. 38, e376–e384 (2017).

23. Verbist, B. M. et al. Cochlear coordinates in regard to cochlear implantation : A clinically individually applicable 3 dimensional CT-bBased method. Otol. Neurotol. (2010) doi:10.1097/MAO.0b013e3181d8d3c4.

24. Verbist, B. M. et al. Consensus panel on a cochlear coordinate system applicable in histologic, physiologic, and radiologic studies of the human cochlea. Otol. Neurotol. 31, 722–730 (2010).

25. Newman, C. W., Jacobson, G. P. & Spitzer, J. B. Development of the Tinnitus Handicap Inventory. Arch. Otolaryngol. Neck Surg. 122, 143–148 (1996).

26. Goebel, G. & Hiller, W. [The tinnitus questionnaire. A standard instrument for grading the degree of tinnitus. Results of a multicenter study with the tinnitus questionnaire]. HNO 42, 166–172 (1994).

27. Meeus, O., Blaivie, C. & Van de Heyning, P. Validation of the Dutch and the French version of the Tinnitus Questionnaire. B-ENT 3 Suppl 7, 11–17 (2007).

28. Peter, N. et al. Cochlear implants in single-sided deafness - clinical results of a Swiss multicentre study. Swiss Med. Wkly. 149, w20171 (2019).

29. Büchner, A., Illg, A., Majdani, O. & Lenarz, T. Investigation of the effect of cochlear implant electrode length on speech comprehension in quiet and noise compared with the results with users of electro-acoustic-stimulation, a retrospective analysis. PLoS One 12, e0174900 (2017).

30. Hall, D. A. et al. Systematic review of outcome domains and instruments used in clinical trials of tinnitus treatments in adults. Trials 17, 270 (2016).

31. Kamalski, D. M., Hoekstra, C. E., Van Zanten, B. G., Grolman, W. & Rovers, M. M. Measuring disease-specific health-related quality of life to evaluate treatment outcomes in tinnitus patients : A systematic review. Otolaryngol. - Head Neck Surg. 143, 181–185 (2010).

32. Newman, C. W., Sandridge, S. A. & Jacobson, G. P. Psychometric adequacy of the Tinnitus Handicap Inventory (THI) for evaluating treatment outcome. J. Am. Acad. Audiol. 9, 153–60 (1998).

33. Davis, T. J. et al. Relationship Between Electrode-to-Modiolus Distance and Current Levels for Adults With Cochlear Implants. Otol. Neurotol. Off. Publ. Am. Otol. Soc. Am. Neurotol. Soc. [and] Eur. Acad. Otol. Neurotol. 37, 31–37 (2016).

34. Koch, R. W., Ladak, H. M., Elfarnawany, M. & Agrawal, S. K. Measuring Cochlear Duct Length - a historical analysis of methods and results. J. Otolaryngol. - head neck Surg. = Le J. d'oto-rhino-laryngologie Chir. cervico-faciale 46, 19 (2017).

35. Ketterer, M. C. et al. The influence of cochlear morphology on the final electrode array position. Eur. Arch. oto-rhino-laryngology Off. J. Eur. Fed. Oto-Rhino-Laryngological Soc. Affil. with Ger. Soc. Oto-Rhino-Laryngology - Head Neck Surg. 275, 385–394 (2018).

7

Systematic review on intra- and extracochlear electrical stimulation for tinnitus

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Abstract

Several electrical stimulation patterns of the auditory nerve have been described for tinnitus relief, but there is no consensus on the most effective stimulation pattern. Therefore, we aim to systematically review the literature on the effect of intra- and extracochlear electrical stimulation patterns as a treatment option for patients with tinnitus. Only studies on intra- and extracochlear electrical stimulation for patients with tinnitus were included if the stimulation used did not concern standardized CI stimulation patterns to primarily rehabilitate hearing loss as intervention. A total of 34 studies met the inclusion criteria, with 10 studies (89 patients) on intracochlear electrical stimulation and 25 studies on extracochlear electrical stimulation (1109 patients). There was a high to medium risk of bias in 22 studies, especially due to lack of a non-exposed group and poor selection of the exposed group. All included studies showed subjective tinnitus improvement during or after electrical stimulation, using different stimulation patterns. Due to methodological limitations and low reporting quality of the included studies, the potential of intra- and extracochlear stimulation has not been fully explored. To draw conclusions on which stimulation patterns should be optimized for tinnitus relief, a deeper understanding of the mechanisms involved in tinnitus suppression is needed.

Introduction

Tinnitus is the perception of a sound without an external auditory input, often experienced as a ringing or buzzing sound in the ear or the head. Tinnitus can become severe and disabling, affecting quality of life and causing anxiety, depression and sleep disorders in those affected. The pathophysiology of tinnitus is still not fully understood. One main hypothesis is that tinnitus originates from maladaptive plasticity, causing an increase in spontaneous and synchronous activity in the auditory pathway[1]. So far, there is no curative treatment available, only tinnitus management therapies that reduce the burden.

A cochlear implant (CI) is an invasive device that transmits the external sound environment by electrically stimulating the auditory nerve of a deaf ear through the cochlea, thereby providing auditory sensation. Cochlear implantation aims to partially restore hearing and does not specifically target tinnitus[2]. In patients with severe to profound hearing loss, intracochlear electrical stimulation through CI showed positive effects on pre-operative tinnitus complaints, but tinnitus induction was reported in some cases ; therefore, tinnitus reduction cannot be predicted yet[3–6]. It is still unclear how intra- and extracochlear electrical stimulation applied primarily for hearing improvement leads to tinnitus relief. Optimizing this electrical stimulation could lead to the development of a tinnitus-dedicated device and an efficient treatment for tinnitus relief, which might also be suitable for patients with less than severe hearing loss.

One of the challenges is to develop an electrical stimulation that evokes 'silence' instead of sound. Electrically stimulating neurons of the auditory nerve enables targeting the auditory pathway and thus may counteract tinnitus origins. This can be achieved using intracochlear stimulation by electrodes within the cochlea or, potentially, by extracochlear stimulation applied by electrodes outside the cochlea. In these situations, the major issue now is to identify electrical patterns that induce suitable and substantial tinnitus relief.

So far, several electrical stimulation patterns of the auditory nerve have been described for tinnitus relief, but no consensus on the most effective type of stimulus exists[7,8]. Therefore, in this paper, we aim to systematically review the literature on the effectiveness of intra- and extracochlear electrical stimulation techniques and patterns as a treatment option for patients with tinnitus.

Materials and methods

PROTOCOL AND REGISTRATION

The protocol of this systematic review can be found in PROSPERO with registration number CRD42020180652. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) format for this systematic review[9].

SEARCH STRATEGY

We conducted a systematic search in PubMed, Embase, the Cochrane Library, CINAHL, and Web of Science. Search terms and their synonyms of domain (tinnitus) and determinant (electrical stimulation) were used in title, abstract and medical subject headings (MeSH) terms. The search syntaxes can be found in Table 1. In addition to electronic database searches, reference lists were scanned to identify additional studies. We searched in ClinicalTrials.gov for ongoing trials and protocols. The search was conducted on 7 August 2021.

Table 1. Search syntax (PubMed).

Search	Syntax
1	(((((((tinnitus[Title/Abstract]) OR ringing[Title/Abstract]) OR booming[Title/Abstract]) OR buzzing[Title/Abstract]) OR whizzing[Title/Abstract]) OR whistling[Title/Abstract]) OR blowing[Title/Abstract]) OR clicking[Title/Abstract] OR tinnitus[MeSH Terms])
2	((((((((((electric*[Title/Abstract]) OR intracoch*[Title/Abstract]) OR extracoch*[Title/Abstract]) OR auditory[Title/Abstract]) OR experim*[Title/Abstract]) OR *cochle*[Title/Abstract])))) AND stim*[Title/Abstract])) OR electrical stimulation[MeSH Terms])
3	1 AND 2

ELIGIBILITY CRITERIA

We defined our research question and selected eligibility criteria (Table 2) based on the Participants, Intervention, Comparators and Outcomes (PICO) design[10]. Articles published or accepted for publication in peer-reviewed academic journals and ongoing trials were eligible for screening without publication date restriction. Studies on intra-and extracochlear electrical stimulation for patients with tinnitus were included only if the stimulation used did not concern standardized CI stimulation patterns to primarily rehabilitate hearing loss as intervention.

We excluded studies with a non-original study design, animal studies or studies without an available abstract after the title/abstract screening. Exclusion criteria were studies without an available full text or studies presenting overlapping populations. We contacted corresponding authors to retrieve full text articles if these were not available in our databases or for clarification and further data. In the case of overlap, the most complete publication was included.

Table 2. Inclusion and exclusion criteria for the review.

	Inclusion	**Exclusion**
Participant	Adults (aged ≥18 years) with tinnitus	Studies focusing on children or animals
Interventions	Intra/extracochlear electrical stimulation to reduce tinnitus	Standardized CI stimulation patterns to rehabilitate hearing loss
Comparators	CI recipients with standard CI fitting or controls or no comparison groups	No exclusion restriction
Outcomes	Self-reported results of questions or questionnaires related to the experienced tinnitus	No self-reported measure or not related to the experienced tinnitus
Study designs	Case reports, cohort and randomized controlled trials	No original design, reviews, conference papers No studies presenting overlapping population

STUDY SELECTION

After removal of duplicates, two authors (K.K.S.A. and M.J.D.) independently performed the title/abstract and full text screening of the retrieved studies, according to our inclusion and exclusion criteria (Table 2). The screening tool used was Rayyan[11]. Conflicts about selection were resolved through discussion with two additional reviewers (A.L.S. and I.S.).

DATA COLLECTION AND ANALYSIS

Quality assessment of the studies

Two authors (K.K.S.A. and M.J.D.) independently assessed the risk of bias (RoB). We used the Newcastle–Ottawa quality assessment Scale (NOS) to evaluate risk of bias in cohort studies[12]. The NOS uses three domains to evaluate risk of bias : selection, comparability and exposure for case-control studies and selection, comparability and outcomes for cohort studies (NOS checklist available in Table A1). Items were scored using stars. An overall risk of bias judgment was determined based on the total score : • high risk of bias (0–3), ◐ medium risk of bias ○ (4–6), low risk of bias (7–9). Any discrepancies were resolved through discussion between the two reviewers and then by consulting with two additional reviewers (A.L.S. and I.S.). Case reports and ongoing trials were not applicable for quality assessment.

Data extraction and synthesis

All study characteristics and outcomes were extracted independently and then compared by two authors (K.K.S.A. and M.J.D.). The following information was extracted : study characteristics (first author, publication year and study design), patient characteristics (number of patients, age, gender and inclusion criteria), intervention parameters (stimulation location, stimulation mode, stimulation intensity, pulse rate, polarity and, if available, duration of treatment), tinnitus outcomes, follow-up and adverse effects. We presented outcomes separately by type of stimulation (intracochlear or extracochlear). When the data were incomplete or only reported on a graph, we contacted the corresponding authors for details. If available, outcomes were reported with their corresponding 95% confidence intervals (95% CI) or the standard deviation (SD), and p-value. The p-value is the result of a statistical comparison test between the tinnitus questionnaire scores used at different follow-up period or groups (Table 5) or for specific parameter values (Table 6). The cut-off of the p-value used to indicate a statistically significant result was established as described in the corresponding studies. We did not perform statistical analysis on the extracted data.

Because of the heterogeneity of the studies in methods, inclusion of participants, interventions and assessment of outcomes, we did not conduct a meta-analysis but instead performed a descriptive synthesis of the results.

Outcome measures

The primary outcome of this review is the self-reported experience of tinnitus of specific electrical stimulation parameters, in which tinnitus was measured by general questions or validated questionnaires assessing one or more aspects of the tinnitus (e.g., loudness, severity, distress, annoyance, irritability, awareness, or intrusiveness).

Secondary outcomes were adverse effects. We considered negative effects related to electrode placement or electrical stimulation (e.g., infection, pain or discomfort, facial nerve palsy, dizziness, tinnitus increase) as relevant harms.

Tinnitus outcomes

The tinnitus questionnaires used are the Tinnitus Functional Index (TFI), Tinnitus Handicap Inventory (THI), Tinnitus Handicap Questionnaire (THQ), Tinnitus Questionnaire (TQ) and the Visual Analogue Scale (VAS) for tinnitus experience.

The TFI contains 25 questions about eight domains : intrusiveness, sense of control, cognitive interference, sleep disturbance, auditory difficulties attributed to tinnitus, relaxation, quality of life and emotional distress. Possible answers are rated on a scale of 0 to 10, or 0% to 100%. An overall TFI score of 0 to 100 can be calculated, where a total score of more than 53 indicates severe tinnitus burden. A clinically relevant reduction is characterized by a decrease of 13 points or more[13].

The THI questionnaire contains 25 questions characterizing the effect of tinnitus on a patient's emotions and daily life. Possible answers are 'no' (0 points), 'sometimes' (2 points) and 'yes' (4 points). An overall THI score can be calculated, resulting in five different tinnitus grades : no or slight handicap (0–16 points), mild handicap (18–36 points), moderate handicap (38–56 points), severe handicap (58–76 points) and catastrophic handicap (78–100 points)[14]. A decrease of seven points or more can be interpreted as a clinically relevant reduction of the tinnitus burden[15].

The THQ assesses the handicapping effect of tinnitus with 27 questions organized in a three-factor structure[16]. The three factors reflect the physical, emotional, and social consequences of tinnitus (Factor 1), hearing ability of the patient (Factor 2), and the patient's view of tinnitus (Factor 3). Each question can be scored on a scale from 0 to 100, providing a total score also ranging

from 0 to 100. This questionnaire can be used to compare the patient's tinnitus handicap and to monitor progress with treatment.

The TQ measures distress caused by tinnitus with 52 questions divided into six domains : emotional and cognitive distress, intrusiveness, auditory perceptual difficulties, sleep disturbances and associated somatic complaints[17]. Three answers are possible for every question : 'true' (0 point), 'partly true' (1 point) or 'not true' (2 points). A total TQ score from 0 to 84 points can be reached, where a higher score indicates more distressing tinnitus. A clinically relevant reduction is characterized by a decrease of 12 points or more[18].

Single-item questionnaires based on a visual analogue scale (VAS) can be used to assess only one characteristic of tinnitus : loudness (VAS-L), severity, distress, annoyance (VAS-A), irritability, awareness and intrusiveness. The VAS consists of a horizontal or vertical line anchored at both ends by a verbal descriptor referring to the tinnitus characteristics. The tinnitus characteristic is scored from 0 (not at all) to 10 or to 100 (extremely). A single question asks the patient to tick the line on the point that best matches to his or her tinnitus characteristic.

In the case of self-reported testimony, total tinnitus suppression is defined as suppression of the tinnitus percept as long as the electrical stimulation is applied.

Electrical stimulation parameters

We assessed the stimulation parameters used for intra- or extracochlear stimulation. We extracted four main parameters characterizing stimulation patterns : electrode location (E), current level (C), pulse rate (PR) and polarity (P) (Table 5). Intracochlear stimulation was always provided through a CI. Extracochlear stimulation was grouped into three different sites in the inner ear : promontory, oval window or round window. By convention, intracochlear electrical stimulation is characterized by an alternating current with charge-balanced biphasic pulse trains. Extracochlear stimulation can be delivered through direct (DC) or alternating current (AC) depending on the device used. For both modes, the current level, measured in amperes (A), and polarity, anodic or cathodic, can be adjusted to provide specific stimulation patterns and were reported. The pulse rate, measured in Hertz (Hz) or pulse per second (pps), is only relevant in AC mode. Occasionally, amplitude modulation can be performed, using a carrier wave to obtain specific patterns. The carrier wave and its specificity were reported, if applicable.

Results

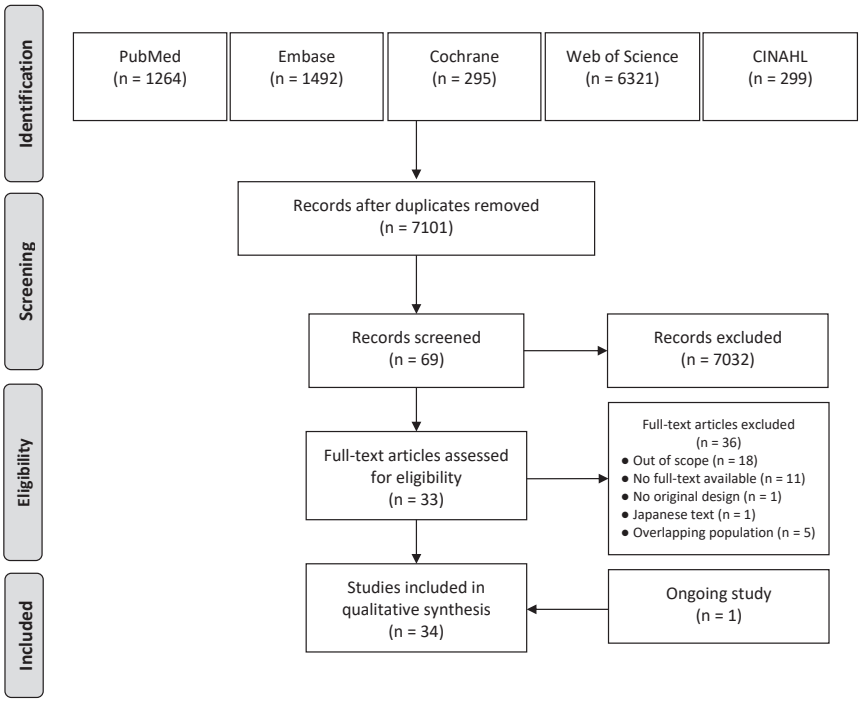
SEARCH STRATEGY AND STUDY SELECTION

The selection process is summarized in the PRISMA flowchart in Figure 1. The search resulted in 7101 articles after removal of duplicates. After title and abstract screening, 69 articles remained for full text screening.

After full-text screening, 36 articles were excluded. Fifteen studies did not report on intra- or extracochlear electrical stimulation for tinnitus[19–32]. Three studies reported only on standard CI stimulation patterns to rehabilitate hearing loss[33–35]. Due to lack of response from the corresponding authors contacted, full text was not available for 11 studies[36–46]. One study did not have an original design[47]. One publication was only available in Japanese, and the two screeners were not able to have it translated[48]. We found overlapping populations in five studies. Four studies reported tinnitus outcomes of the same population[49–52]. We included the publication with the most complete data[51]. This also applies for the overlapping studies by Matsushima et al. ; therefore, we excluded two studies[53,54].

Finally, 33 studies were selected for further analysis and data extraction[51,55–87]. Of these, 26 were prospective cohort studies. There were four case series[54,59,61,72], two case reports[62,63], and one pilot study[56]. Additionally, one ongoing study at the Mayo clinic, investigating the effect of promontory electrical stimulation, was included in our selection[78].

Figure 1. PRISMA flowchart of the literature search and study selection.



Last date of search : 7 August 2021.

QUALITY OF THE INCLUDED STUDIES

We assessed the quality of the included studies, using the NOS tool. The results of our critical appraisal can be found in Table 3. There were nine (29%) studies that had a low risk of bias[51,57,64,66,75,76,82,85,86]. All these studies selected homogeneous populations, using inclusion criteria based on tinnitus severity and hearing loss, which led to higher quality. Studies with the highest score had a non-exposed group to compare outcomes with the intervention group[51,57,66,83,85,86]. Eleven (35.5%) studies had a moderate risk of bias, in which neither tinnitus outcomes nor self-report tinnitus experience were available before stimulation[55,59,61,69,72,77,79,80,83,84,87]. The overall risk of bias was considered high in 11 (35.5%) studies[56,58,60,65,67,68,70,71,73,74,81]. This was due to lack of a non-exposed group and poor representativeness of the exposed group. A poor representativeness corresponded to a selection of individuals or to a lack of de-scription of the study population. These 11 studies did not report on pre-stimulation tinnitus outcome, nor on self-report tinnitus experience.

Table 3. Quality assessment of the included studies based on the NOS.

Study (Author, Year)	Study design	NOS Tool								Total	Risk of bias
		Selection				Comparability	Outcome				
		1)	2)	3)	4)	1)	1)	2)	3)		
Aran et al., 1981 [70]	Cohort	☆	NA	☆	☆	☆★	☆	★	☆	2	●
Arts et al., 2015 [75]	Cohort	★	NA	☆	★	★★	★	★	★	7	○
Arts et al., 2016 [51]	Cohort	★	★	☆	★	★★	★	★	★	8	○
Cazals et al., 1978 [68]	Cohort	☆	NA	☆	☆	☆★	☆	★	★	3	●
Cazals et al., 1984 [71]	Cohort	☆	NA	☆	☆	☆★	☆	★	★	3	●
Chang et al., 2012 [76]	Cohort	★	NA	☆	★	★★	★	★	★	7	○
Daneshi et al., 2005 [66]	Cohort	★	★	☆	★	★★	★	★	★	8	○
Dauman et al., 1993 [77]	Cohort	☆	NA	☆	★	★★	★	★	★	6	◐
Di Nardo et al., 2009 [82]	Cohort	★	NA	☆	★	★★	★	★	★	7	○
Graham et al., 1977 [67]	Cohort	☆	NA	☆	☆	☆☆	☆	★	☆	1	●
Hazell et al., 1993 [69]	Cohort	★	NA	☆	☆	★★	☆	★	★	5	◐
House et al., 1984 [65]	Cohort	☆	NA	☆	☆	★☆	☆	★	☆	2	●
Ito et al., 1994 [81]	Cohort	☆	NA	☆	☆	☆☆	☆	★	★	2	●
Kloostra et al., 2020 [64]	Cohort	★	NA	☆	★	★★	★	★	★	7	○
Konopka et al., 2001 [84]	Cohort	★	☆	☆	☆	★★	★	★	★	6	◐
Konopka et al., 2008 [83]	Cohort	★	★	☆	☆	☆★	☆	★	★	5	◐
Mahmoudian et al., 2013 [86]	Cohort	★	★	☆	★	★★	★	★	★	8	○
Mahmoudian et al., 2015 [85]	Cohort	★	★	☆	★	★★	★	★	★	8	○
Matsushima et al., 1994 [79]	Cohort	★	NA	☆	☆	★☆	☆	★	★	4	◐
Matsushima et al., 1996a [87]	Cohort	☆	NA	☆	☆	★★	☆	★	★	4	◐
Matsushima et al., 1996b [55]	Cohort	★	NA	☆	☆	★☆	☆	★	★	4	◐
Okusa et al., 1993 [80]	Cohort	★	NA	☆	☆	☆☆	★	★	★	4	◐
Olze et al., 2018 [56]	Cohort	☆	NA	☆	☆	☆☆	★	★	★	3	●
Péan et al., 2010 [72]	Cohort	★	NA	☆	☆	★★	★	★	★	6	◐
Portmann et al., 1979 [73]	Cohort	★	NA	☆	☆	☆☆	☆	★	★	3	●
Portmann et al., 1983 [74]	Cohort	☆	NA	☆	☆	☆☆	☆	★	★	2	●
Punte et al., 2013 [57]	Cohort	★	★	☆	★	★★	★	★	★	8	○

★ 1 point; ☆ 0 point; ● High risk of bias (0–3); ◐ Medium risk of bias (4–6); ○ Low risk of bias (7–9); NA : not applicable.

Rothera et al., 1986 [58]	Cohort	☆	NA	☆	☆	☆☆	☆	★	★	2	•
Rubinstein et al., 2003 [59]	Cohort	★	☆	☆	☆	★★	★	★	★	6	◐
Watanabe et al., 1997 [60]	Cohort	★	NA	☆	☆	☆☆	☆	★	★	3	•
Wenzel et al., 2015 [61]	Cohort	★	NA	☆	☆	★★	★	★	★	6	◐
Rothholtz et al., 2009 [63]	Case report	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Zeng et al., 2011 [62]	Case report	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Carlson et al., 2020 [78]	Cohort	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

★ 1 point; 0 point; • High risk of bias (0–3); ◐ Medium risk of bias (4–6);
○ Low risk of bias (7–9); NA : not applicable.

DATA EXTRACTION OF STUDY CHARACTERISTICS

We contacted eight authors for additional data[57,59,61,64,75–77], of which six responded to our request[59,61,64,75–77].

Study population

The characteristics of studies investigating the effect of intracochlear electrical stimulation on tinnitus, and studies assessing extracochlear electrical stimulation are presented in Table 4. In total, 89 tinnitus patients were treated with intracochlear electrical stimulation, and 1109 with extracochlear stimulation. The sample sizes varied between different study designs, from 1 individual in a case report[62,63] to 168 patients in a parallel group design[83]. Tinnitus severity was not used as a selection criterion in all studies. Among the studies assessing intracochlear stimulation, all patients were implanted for sensorineural hearing loss, except for the study by Olze et al. in which this information was not available[56]. In studies using extracochlear stimulation, the hearing profiles were more diverse, ranging from normal hearing[60,80,85,86] to profound sensorineural hearing loss [61,67,68,70,71,81,82].

Intervention

Nine studies (26%) investigated the effect of intracochlear electrical stimulation on tinnitus[51,56,57,62–64,75–77]. One study (3%) evaluated both types of stimulation : intracochlear stimulation in 3 patients and extracochlear stimulation in 11 patients[59]. Lastly, twenty-four (71%) studies assessed extracochlear electrical stimulation and its effect on tinnitus burden. Fifteen studies performed

promontory stimulation[46,55,58,60,65,66,78,80–87], three studies used round window stimulation[61,69,71] and one tested oval window stimulation[72]. Five studies reported the outcomes of promontory and round window stimulation[65,68,70,73,74].

Among the studies assessing intracochlear electrical stimulation, eight performed acute stimulation[56,59,62–64,75–77], ranging between 500 milliseconds to 15 min, and two performed chronic stimulation[51,57]. Seven studies assessing extracochlear stimulation performed chronic stimulation[61,65,69,71,72,78,87]. The follow-up with outcome assessment varied between a few minutes after stimulation for punctual stimulation at the clinic to 3.5 years after placement and activation of a round window implant[61].

Table 4. Study characteristics of the included studies. a) Studies reporting on intracochlear electrical stimulation ; b) Studies reporting on extracochlear electrical stimulation.

a) Studies reporting on intracochlear electrical stimulation

Authors, Year	Study design	N (Tinnitus patients)	Demographics		Study Population		Stimulation type	Outcomes		Harms reported
			Gender M (F)	Age (SD/Range)	Tinnitus criteria	Hearing loss		Follow-up (max)	Tinnitus question/ questionnaire	
Arts et al., 2015 [75]	PCS	11	6 (5)	60.1 (6.4)	VAS-L > 2, THI > 16	Severe to profound SNHL	CI	DS	THI, VAS-L	None
Arts et al., 2016 [51]	PCS	10	5 (5)	48.2 (12.5)	VAS-L > 7, THI > 38, TQ > 42	SSD	CI	3 months	THI, TQ, VAS-L	None
Chang et al., 2012 [76]	PCS	13	2 (11)	60.8 (13.6)	NI	Severe to profound SNHL	CI	DS	THI, TSI	NI
Dauman et al., 1993 [77]	PCS	2	NI	38–51 *	Bilateral	Profound SNHL	CI	DS	THQ, VAS-L	NI
Kloostra et al., 2020 [64]	PCS	19	12 (7)	60.6 (43–78)	Chronic, constant	Bilateral severe SNHL	CI	AS	THI, THQ, VAS-L	NI
Olze et al., 2018 [56]	Pilot	6 (4)	NI	NI	NI	NI	CI	AS	VAS-L	Yes
Punte et al., 2013 [57]	PCS	14	5 (9)	NI	VAS-L ≥ 6	Profound SNHL	CI	6 months	TQ, VAS-L	NI
Rothholtz et al., 2009 [63]	Case report	1	1 (0)	NI	Unilateral, debilitating	SSD	CI	AS	VAS-L	NI
Rubinstein et al., 2003 [59]	Case series	14	NI	NI	Bothersome	Severe to profound HF SNHL	CI (3), RW (11)	3 days	THQ, VAS-L, VAS-A	Yes
Zeng et al., 2011 [62]	Case report	1	1 (0)	46	NI	Profound SNHL	CI	AS	VAS-L	Yes

b) Studies reporting on extracochlear electrical stimulation

Authors, Year	Study design	N (Tinnitus patients)	Demographics		Study population		Outcomes			Harms reported
			Gender M (F)	Age (SD/Range)	Tinnitus criteria	Hearing loss	Stimulation type (OW, PM, RW)	Follow-up (Max)	Tinnitus question/ questionnaire	
Aran et al., 1981 [70]	PCS	106 (84)	NI	NI	NI	Profound SNHL	PM, RW	DS	Self-report	Yes
Cazals et al., 1978 [68]	PCS	16 (6)	11 (5)	NI	NI	Severe to profound HL	PM (3), RW (13)	AS	Self-report	Yes
Cazals et al., 1984 [71]	PCS	4 (1)	1	NI	NI	Totally deaf	RW	3 months	Self-report	Yes
Daneshi et al., 2005 [66]	PCS	52	32 (20)	42.2 (21–67) (PM)	Moderate to severe	Moderate to severe HL (PM)	CI (20), PM (32)	50 days	TQ, TSS	NI
Di Nardo et al., 2009 [82]	PCS	11	4 (7)	34–64	Severe	Profound SNHL	CI (control), PM	1 month	THI	NI
Graham et al., 1977 [67]	PCS	13 (9)	NI	NI	NI	Profound SNHL	PM	AS	Self-report	Yes
Hazell et al., 1993 [69]	PCS	9	NI	NI	Severe	Unilateral deafness	RW	NI	Self-report	NI
House et al., 1984 [65]	PCS	130 (125)	NI	NI	NI	HL in varying degrees	PM, RW	1 week	Self-report	NI
Ito et al., 1994 [81]	PCS	40 (30)	18 (12)	46.6 (18–63)	NI	Severe HL or totally deaf	PM	AS	Self-report	NI
Konopka et al., 2001 [84]	PCS	111	91 (20)	55.5 (15–67)	NI	NIHL and SNHL	PM	3 months	VAS-L	Yes
Konopka et al., 2008 [83]	PCS	248 (168)	NI	23–78	NI	NIHL and SNHL	PM	1 month	Assessment of subjective feelings	Yes
Mahmoudian et al., 2013 [86]	PCS	44	32 (12)	44.71 (18–65)	TQ > 44 VAS-L > 6	PTA(HF) < 60 dB	PM	1 week	VAS-L	NI
Mahmoudian et al., 2015 [85]	PCS	28	18 (10)	35.33 (22–45)	TQ > 44, THI > 39, VAS-L > 6	Normal hearing	PM	AS	TQ, VAS-L	NI
Matsushima et al., 1994 [79]	PCS	112	76 (36)	53 (19–73)	NI	NI	PM	1 month	Interview	NI
Matsushima et al., 1996a [87]	Case series	4	2 (2)	51.8 (44–57)	NI	HL in varying degrees	PM	3 months	Self-report	Yes
Matsushima et al., 1996b [55]	PCS	47	24 (23)	60.4 (42–75)	NI	HL in varying degrees	PM	DS	Self-report	NI
Okusa et al., 1993 [80]	PCS	65	NI	47 (17–72)	NI	Normal to profound SNHL	PM	>3 days	VAS-L	Yes
Péan et al., 2010 [72]	Case series	4	NI	NI	Severe	Unilateral deafness	OW	121 days	DET	NI
Portmann et al., 1979 [73]	PCS	28 (15)	NI	NI	NI	NI	PM (7), RW (11)	DS	Self-report	NI
Portmann et al., 1983 [74]	PCS	120 (72)	NI	NI	NI	NI	PM, RW	few days	Self-report	NI
Rothera et al., 1986 [58]	PCS	20 (16 ears)	NI	NI	NI	NI	PM	AS	Self-report	NI
Rubinstein et al., 2003 [59]	Case series	14	NI	NI	Bothersome	Mild to moderate SNHL	CI (3), RW (11)	3 days	THQ, VAS-L, VAS-A	Yes
Watanabe et al., 1997 [60]	PCS	56	35 (21)	49.4 (21–71)	NI	With and without HL	PM	1 month	Self-report	Yes
Wenzel et al., 2015 [61]	Case series	3	2 (1)	43.3 (38–50)	Unilateral, resistant to pharmacologic al treatment	Unilateral severe to profound SNHL	RW	3.5 years	THI, VAS-L, VAS-A	Yes
Carlson et al., 2020 [78]	on going	21	NI	NI	TFI > 52, THI > 56, VAS-L > 5	Normal to moderate SNHL	PM	1 week	THI, TFI, VAS-P	NI

↙ AS : after stimulation ; CI : cochlear implant ; DET : distress evaluation tinnitus ; DS : during stimulation ; HL : hearing loss ; HF : high frequencies ; LF : low frequency ; N : number of patients ; NI : no information ; OW : oval window ; PCS : prospective cohort study ; PM : promontory ; PTA : pure tone average ; RW : round window ; SNHL : sensorineural hearing loss ; SD : standard deviation ; SSD : single-sided deafness ; THI : tinnitus handicap questionnaire ; TQ : tinnitus questionnaire ; TSS : tinnitus severity scale ; VAS-A : visual analogue scale annoyance ; VAS-L : visual analogue scale loudness.

*Extracted from a graph.

In the studies of Aran et al. (1981)[70] and Cazals et al. (1978)[68], tinnitus was assessed by asking patients to raise hand and describe the sensation when they experienced a change during stimulation. Other studies using self-report as a tinnitus outcome did not provide further details on the instructions given to patients.

Outcomes

Twelve studies reported on tinnitus distress or burden using multi-item questionnaires : one study used the TFI[78], seven studies the THI[51,61,64,75,76,78,82], three studies the THQ[59,64,77] and four studies the TQ[51,57,66,85]. The used single-item questionnaires assessed tinnitus loudness (VAS-L) in 14 studies[51,56,57,59,61–64,75,77,80,84–86], annoyance (VAS-A) in two studies[59,61] and pain (VAS-P) in one study[78]. Among the studies using tinnitus questionnaires, seven used only one specific tinnitus questionnaire[56,63,72,80,82,84,86], where others used two or more. Tinnitus matching was performed in 14 studies[51,57,59,60,66,67,72,75,80,82–86].

SYNTHESIS OF RESULTS

Outcomes

Of the 34 studies included, 10 reported scores from tinnitus questionnaires pre- and post-stimulation. Seven out of 10 studies performed statistical analyses. A summary of the effects is detailed in Table 5.

Table 5. Extracted data of tinnitus distress outcomes. a) Studies reporting on intracochlear electrical stimulation ; b) Studies reporting on extracochlear electrical stimulation.

a) Studies reporting on intracochlear electrical stimulation

Authors, Year	N	ES configuration	Outcomes						
			Questionnaire	Group (CI, Control)	BS	DS	AS	FU	*p*-value
Arts et al., 2015 [75]	11	C: -10%	% VAS-L reduction	CI	0	7 (-4.5–29) °	NI	DS	>0.05
		C: 10% DR	% VAS-L reduction		0	18 (-2.25–76) °	NI	DS	>0.05
		C: 50% DR	% VAS-L reduction		0	22.5 (9.5–87.75) °	NI	DS	**0.033**
		C: 80% DR	% VAS-L reduction		0	56.5 (-3.5–94) °	NI	DS	**0.014**
		E: basal (x1, x3)	% VAS-L reduction		0	15 (4.5–29.5) °	NI	DS	>0.05
		E: central (x1, x3)	% VAS-L reduction		0	25 (5–60) °	NI	DS	>0.05
		E: apical (x1, x3)	% VAS-L reduction		0	4.5 (-6.5–39.5) °	NI	DS	>0.05
		E: pitch-matched (x1, x3)	% VAS-L reduction		0	22.5 (2–28.5) °	NI	DS	>0.05
Arts et al., 2016 [51]	10	combinations of E, C, PR, P, A, pulse width	THI	CI	45 (40–53) °	40.00 (25.00–44.50)	NI	1 month	0.06¨
						40.00 (25.00–52.00)	NI	3 months	0.15¨
		standard		CI (control)	45 (40–53) °	38.00 (21.50–44.50)	NI	1 month	0.06¨
						31.00 (22.00–46.50)	NI	3 months	0.15¨
		combinations of E, C, PR, P, A, pulse width	VAS-L	CI	7.1 (6.4–7.7) °	3.35 (2.68–6.95)	NI	1 month	0.25¨
						3.40 (2.40–7.63)	NI	3 months	0.39¨
		standard		CI (control)	7.1 (6.4–7.7) °	3.15 (2.00–5.80)	NI	1 month	0.25¨
						3.50 (1.55–6.63)	NI	3 months	0.39¨
		combinations of E, C, PR, P, A, pulse width	TQ	CI	40 (33–51) °	30.00 (19.25–38.25)	NI	1 month	0.77¨
						30.00 (22.50–34.75)	NI	3 months	0.18¨
		standard		CI (control)	40 (33–51) °	27.00 (23.50–38.50)	NI	1 month	0.77¨
						23.50 (13.75–43.25)	NI	3 months	0.18¨
Chang et al., 2012 [76]	13	combinations of E, C, PR	THI	CI	26.8 (17.6)	NI	NI	DS	NI
Kloostra et al., 2020 [64]	19	combinations of E, C, PR	THI	CI	28.4 (22.9)	NI	NI	NA	NI
			THQ	CI	38.6 (27.2)	NI	NI	NA	NI
Punte et al., 2013 [57]	7 (7 control)	E: 1 most basal	VAS-L	CI	8.3 (1.1)	7.2 *	7.9 *	pre	
		E: 2 most basal				7.3 *	7.2 *	1 week	>0.05
		E: 3 most basal				7.0 *	7.1 *	1 week	>0.05
		E: 4 most basal				7.0 *	7.5 *	1 week	>0.05
		E: all				4.4 (1.3)	7.5 *	1 week	**0.027**
						3.5 (1.7)	8.1 *	6 months	**0.042**
				Control (no CI)	8.8 (1.0)	NI	8.7 (0.8)	6 months	>0.05
		E: all	TQ	CI	60 (15.6)	NI	39.4 (12.4)	6 months	**<0.05**

				Control (no CI)	58.9 (27.4)	NI	56.3 (25.4)	6 months	>0.05
Rothholtz et al., 2019 [63]	1	E: E2 C: 120 µA PR: 60 pps	VAS-L	CI	5	0	6	200 ms AS	NI
Zeng et al., 2011 [62]	1	E: apical, C: 100 mA, PR: 100 Hz, bi-phasic (107.8 ms/phase), loudness 6	VAS-L	CI	4 *	0 *	7 *	~100 ms AS	NI
		1: apical, 2: 100 mA, 3: 100 Hz, bi-phasic (107.8 ms/phase), loudness 3,			4 *	0 *	5.5 *	~100 ms AS	NI
		1: basal, 2: 100 mA, 3: 100-Hz, bi-phasic (107.8 ms/phase), loudness 6			4 *	5 *	6 *	~300 ms AS	NI
		1: basal, 2: 150 mA, 3: 5000 Hz, bi-phasic (32.3 ms/phase), loudness 5			4 *	5 *	5 *	~100 ms AS	NI

b) Studies reporting on extracochlear electrical stimulation

		ES Configurations			Outcomes				
Authors, Year	**N**	**AC/DC**	**Parameter (s) tested**	**Questionnaire**	**Group (CI, Control, PM, RW)**	**BS**	**DS**	**AS**	**FU**	***p*-value**
Daneshi et al., 2005 [66]	32	AC	C: 60–500 µA PR: 50–600Hz	TQ	PM	50.66 (19.34)	NI	39.03 (20.35)	50 days	**0.001** 0.49¨
	20	AC	standard		CI (control)	52.84 (14.52)	NI	38.45 (13.99)	50 days	**0.001** 0.49¨
Di Nardo et al., 2009 [82]	11	DC+	C: 0–500 µA PR: 50–1600 Hz	THI	PM	49.1(22.9)	NI	33.6 (26.0)	1 month	NI
Mahmoudian et al., 2013 [86]	44	AC	C: 60–500 µA	VAS-L	PM (RI)	6.83 (1.37)	NI	3.13 (1.65)	AS	**<0.05** **<0.05¨** (NRI) **<0.05¨** (placebo)
					PM (NRI)	6.90 (1.17)	NI	6.65 (1.04)	AS	>0.05 **<0.05¨** (RI) >0.05¨ (placebo)
					placebo (control)	6.86 (1.27)	NI	6.68 (1.25)	AS	>0.05 **<0.05¨** (RI) >0.05¨ (NRI)
Mahmoudian et al., 2015 [85]	28	AC	C: 50–500 µA	VAS-L	PM (RI)	6.38 (1.26)	NI	2.92 (1.75)	AS	**<0.05** **<0.05¨** (NRI) **<0.05¨** (placebo)
					PM (NRI)	7.00 (1.25)	NI	6.73 (1.03)	AS	>0.05 **<0.05¨** (RI) >0.05¨ (placebo)
					placebo (control)	7.00 (1.21)	NI	6.75 (1.23)	AS	>0.05 **<0.05¨** (RI) >0.05¨ (NRI)

Wenzel et al., 2015 [61]	3	AC	C, PR, pulse duration	THI	RW	NI	83.33 (11.85) *	78.33 (25.66) *	9 months	NI
				VAS-L	RW	NI	8.0 (2.65) *	6.33 (5.51) *	9 months	NI
				VAS-A	RW	NI	8.67 (1.53) *	6.33 (5.51) *	9 months	NI

A : amplitude modulation ; AS : after stimulation ; BS : before stimulation ; C : current level ; CI : cochlear implant ; DS : during stimulation ; E : electrode location ; FU : follow-up period ; NA : not applicable ; NI : no information ; NRI: non-residual inhibition group ; P: polarity ; PM: promontory ; PR: pulse rate ; RI: residual inhibition group ; RW : round window.

* Extracted from a graph ; ° extracted from raw data not available in the publication.
The p-value is the results of a comparison test between the two scores of the same line. It refers either to pre-, intra-, or post-stimulation scores, or to intra- and post-stimulation scores, except for p-value with ¨, which is the result from a comparison between the intervention group and the control group. Significant p-values are in bold.

In the study of Punte et al. (2013), no comparison between groups was performed[57]. In the study of Wenzel et al. (2005), the follow-up period was restricted to 6 months because one patient received a speech coding program at 6 months post-implantation, which is out of the scope of this review[61].

THI

Arts et al. (n = 10) found no statistically significant difference in THI between personalized stimulation through CI (a combination of stimulation parameters chosen for each patient) and standard stimulation through CI (stimulation dependent of the environmental sound defined by an audiologist for speech perception purposes) after one and three months of stimulation, respectively (THI after three months of standard stimulation : 31.0 (IQR : 22.0–46.5), THI after three months of personalized stimulation : 40.0 (IQR : 25.0–52.0), p = 0.15)[51].

Di Nardo et al. (n = 11) showed a decrease in THI after promontory stimulation compared to pre-stimulation but did not report a p-value (THI pre-stimulation : 49.1 (SD : 22.9) ; THI post-stimulation : 33.6 (SD : 26.0))[82]. The three case series of Wenzel et al. showed a decrease in THI from activation of the round window implant to nine months after implantation, but did not report the statistical significance of the outcome (THI activation : 83.33 (SD : 11.85), THI 9 months : 78.33 (SD : 25.66))[61].

TQ

Arts et al. (n = 10) found no statistically significant difference in TQ between personalized stimulation and standard stimulation after one and three months of stimulation through CI respectively (TQ after three months standard stimulation : 23.5 (IQR : 13.75– 43.25), TQ after three months of personalized stimulation : 30.0 (IQR : 22.5–34.75), p = 0.18)[51].

Daneshi et al. (n = 32) showed a statistically significant decrease in TQ between pre- and post-promontory stimulation (TQ pre-stimulation : 50.66 (SD : 19.34), TQ post-stimulation : 39.03 (SD : 20.35), p = 0.001)[66].

VAS-L

Arts et al. (n = 10) found no statistically significant difference in VAS-L between personalized stimulation and standard stimulation after one and three months of stimulation through CI respectively (VAS-L after 3 months standard stimulation : 3.5 (IQR : 1.55–6.63), VAS-L after three months of personalized stimulation : 3.4 (IQR : 2.4–7.63), p = 0.039)[51]. In another study, Arts et al. (n = 11) showed a statistically significant decrease in VAS-L measured before and during stimulation with suprathreshold stimulation (50% dynamic range : 22.5 (IQR : 9.5–87.75) % VAS-L reduction, p = 0.033 ; 80% dynamic range : 56.5 (IQR : -3.5–94.0) % VAS-L reduction, p = 0.014)[75]. In contrast, they found no significant changes in improvement between before and during stimulation with different electrode locations (basal : 15 (4.5–29.5) % VAS-L reduction, p > 0.05 ; central : 25 (5–60) % VAS-L reduction, p > 0.05 ; apical : 4.5 (-6.5–39.5) % VAS-L reduction, p > 0.05 ; pitch-matched : 22.5 (2–28.5) % VAS-L reduction, p > 0.05). Furthermore, another study from Punte et al. (n = 7) reported a significant decrease in tinnitus loudness (VAS-L) after one week of stimulation through CI when all electrodes were activated (pre-implantation : 8.3 (SD : 1.1) ; 1 week : 4.4 (SD : 1.3), p = 0.027 ; 6 months : 3.5 (SD : 1.7), p = 0.042)[57]. The same study measured tinnitus loudness without providing stimulation and found that tinnitus loudness relapsed to its initial level. Rothholtz et al. (n = 1) showed a decrease in VAS-L during stimulation, but this decrease was not statistically tested (pre-stimulation : 5 ; during stimulation : 0 ; after stimulation : 6)[63]. Tinnitus loudness always increased after less than one second post stimulation.

In two studies, Mahmoudian et al. assessed the effect of promontory stimulation and reported the VAS-L of three groups : patients experiencing residual inhibition, patients without residual inhibition, and the control group. They showed a statistically significant decrease in VAS-L in the residual inhibition group and no statistically significant decrease in the non-residual group and the control group (Table 5). A comparison between groups (n = 28) showed that the mean VAS-L of the residual inhibition group (n = 13) was significantly different from the non-residual inhibition (n = 15) and the control group (n = 28) (VAS-L residual inhibition group : 2.92 (SD : 1.75) ; a) compared to the VAS-L non-residual inhibition group : 6.73 (SD : 1.03), p < 0.05 ; b) compared to the VAS-L control group : 6.75 (SD : 1.23), p < 0.05)[86]. There were no statistically significant

differences between the non-residual inhibition group and the control group. In a second study (n = 44), they showed the same findings (VAS-L residual inhibition group (n = 24) : 3.13 (SD : 1.65) ; (a) compared to the VAS-L non-residual inhibition group (n = 20) : 6.65 (SD : 1.04), $p < 0.05$; (b) compared to the VAS-L control group : 6.68 (SD : 1.25), $p < 0.05$)[85]. Wenzel et al. (n = 3) showed a decrease in VAS-L between activation of the round window implant and nine months but did not report a p-value (VAS-L activation : 8.0 (SD : 2.65), VAS-L nine months : 6.33 (SD : 5.51))[61].

VAS-A

Wenzel et al. (n = 3) showed a decrease in VAS-A between activation of the round window implant and nine months but did not report a p-value (VAS-A activation : 8.67 (SD : 1.53), VAS-A 9 months : 6.33 (SD : 5.51))[61].

Parameters

The parameters tested can be found in Table 6. Due to the wide variety of devices, the stimulation patterns were not always described using the four operating parameters : electrode location, current level, pulse rate, polarity.

Table 6. Parameters assessed by the included studies. a) Studies reporting on intracochlear electrical stimulation. b) Studies reporting on extracochlear electrical stimulation.

a) Studies reporting on intracochlear electrical stimulation

Authors, Year	Stimulation type (CI)	AC / DC	Parameter(s) tested	Value tested	Parameter comparison in terms of tinnitus reduction	*p*-value
Arts et al., 2015 [75]	CI	AC	C	sham stimulation, -10, 20, 50, 80% DR	50% > sham stimulation	**0.033**
					80% > sham stimulation	**0.014**
			E	Basal (x1, x3), central (x1, x3), apical (x1, x3), pitch-matched (x1, x3)	Apical > pitch-matched	**0.042**
					Central > pitch-matched	**0.043**
Arts et al., 2016 [51]	CI	AC	A	Random, sine wave, fixed	No comparison performed	NA
			C	2.5–12.1 nC	Low > high	NI
			E	1–all	No comparison performed	NA
			P	(+), (−) first charge-balanced	No comparison performed	NA
			PR	200–5000 pps/channel	High > low	NI
			Pulse width	60–88 µs	No comparison performed	NA
			Dependency of environmental sounds	Independent, dependent	Not statistically different	>0.05
Chang et al., 2012 [76]	CI	AC	C	Soft, medium, loud	Loud > soft	**0.027**
					High rate: medium > soft	**0.043**
					High rate: medium > loud	**0.008**
			E	Apical, middle, basal	Not statistically different	NI
			PR	100–200, 5000 pps	Not statistically different	NI
Dauman et al., 1993 [77]	CI	AC	C	0.1–1.7 mA	No comparison performed	NA
			E	Apical, middle, basal	No comparison performed	NA
			PR	80, 125, 250 Hz	No comparison performed	NA
Kloostra et al., 2020 [64]	CI	AC	C	Near-threshold (T level), moderate (C level)	Moderate > near-threshold	**<0.001**
			E	Basal, apical	Not statistically different	0.712
				Single electrode, full array	Not statistically different	NI
			PR	720, 1200, 2400 Hz	Not statistically different	0.493
Olze et al., 2018 [56]	CI	AC	A	Square wave	No comparison performed	NA
			PR	62 Hz	No comparison performed	NA
Punte et al., 2013 [57]	CI	AC	E	1, 2, 3, 4 most basal electrodes, all	All > most basal electrodes	**0.042**
Rothholtz et al., 2019 [63]	CI	AC	C	0–120 µA	No comparison performed	NA
			E	E1–E16	60 pps at most apical, high rates close to tinnitus matched pitch	NST
			PR	40–10000 Hz		
Rubinstein et al., 2003 [59]	CI	AC	C	300 µA–1.5 mA	No comparison performed	NA
			PR	4800 pps	No comparison performed	NA
			Pulse duration	25, 50, 80 µs/phase	No comparison performed	NA
			E	tinnitus pitch-matched	Not comparison performed	NA

Zeng et al., 2011 [62]	CI	AC	C	subthreshold, 0–10 loudness scale	1–6 > 7–10	NST
			E	Apical, basal	4 most apical > 4 most basal	NST
			PR	20–100, 5000 Hz	20–100 Hz > 5000 Hz	NST

b) Studies reporting on extracochlear electrical stimulation

Authors, Year	Stimulation type (RW, PM, OW)	AC/DC	Parameter(s) tested	Value tested	Parameter comparison in terms of tinnitus reduction	*p*-value
Péan et al., 2010 [72]	OW	AC	C	NI	No comparison performed	NA
			P	(+), (−) first charge-balanced	(+) > (−)	NST
			PR	NI	No comparison performed	NA
			Pulse shape	Square pulse, capacitive discharge	Square pulse followed by a capacitive discharge	NST
Daneshi et al., 2005 [66]	PM	AC	C	60–500 µA	No comparison performed	NA
			PR	50–600 Hz	No comparison performed	NA
Di Nardo et al., 2009 [82]	PM	DC+	C	0–500 µA	No comparison performed	NA
			PR	50–1600 Hz	50, 100 Hz > 200–1600 Hz	NST
Graham et al., 1977 [67]	PM	AC	C	1–100 µA	No comparison performed	NA
			PR	1–10000 Hz	No comparison performed	NA
Ito et al., 1994 [81]	PM	NI	NI	NI	No comparison performed	NA
Konopka et al., 2001 [84]	PM	DC+	C	20–600 mA	No statistically different	NI
			PR	60–10000 Hz	No statistically different	NI
Konopka et al., 2008 [83]	PM	AC	C	0.15–1.15 mA	No comparison performed	NA
			PR	Tinnitus pitch-matched	No comparison performed	NA
Mahmoudian et al., 2013 [86]	PM	AC	C	60–500 µA	No statistical difference between RI and NRI	0.61
			PR	1 Hz	No comparison performed	NA
			Frequency modulation	50 Hz	No comparison performed	NA
Mahmoudian et al., 2015 [85]	PM	AC	C	50–500 µA	No statistical difference between RI and NRI	>0.05
			PR	1 Hz	No comparison performed	NA
			Frequency modulation	50 Hz	No comparison performed	NA
Matsushima et al., 1994 [79]	PM	AC	A	Sinusoidal, 1 kHz	No comparison performed	NA
			C	0–70 µA	No comparison performed	NA
			PR	10 kHz	No comparison performed	NA
Matsushima et al., 1996a [87]	PM	AC	A	Sinusoidal, 100 Hz	No comparison performed	NA
			C	0–300 µA	No comparison performed	NA
			PR	10 kHz	No comparison performed	NA
	PM	AC	A	Sinusoidal	No comparison performed	NA

Matsushima et al., 1996b [55]			C	200 μA	No comparison performed	NA
			PR	10 kHz	No comparison performed	NA
Okusa et al., 1993 [80]	PM	AC	C	0–100 μA	No comparison performed	NA
			PR	50, 100, 200, 400 Hz	50 > 100 >200 > 400 Hz	NST
Rothera et al., 1986 [58]	PM	AC, DC	C	0–100 μA	AC suprathreshold, DC (+) subthreshold	NST
		DC	P	(+)/(-)	(+) > (-)	NST
		AC	PR	30–3000 Hz	No comparison performed	NA
Watanabe et al., 1997 [60]	PM	AC	C	5–160 μA	No comparison performed	NA
			PR	400 Hz	No comparison performed	NA
Carlson et al., 2020 [78]	PM	AC	C E P PR	NI	NA	NA
Aran et al., 1981 [70]	RW, PM	AC, DC	Tinnitus side	Ipsilateral, contralateral	Ipsilateral > contralateral	NST
		AC, DC	E	RM, PM	RW > PM	NST
		AC	PR	Low (<100 Hz), high (>200 Hz)	High > low	NST
		AC	C	5–300 μA	No comparison performed	NA
	RW	AC, DC	P	(+)/(-)	(+) > (-)	NST
Cazals et al., 1978 [68]	RW, PM	AC, DC	C	20–300 μA	No comparison performed	NA
		AC, DC	E	RW, PM	RW > PM	NST
		AC, DC	P	(+)/(-)	(+) > (-)	NST
		AC	PR	>50–200 Hz	No comparison performed	NA
Cazals et al., 1984 [71]	RW	DC+	C	2, 5V	No comparison performed	NA
Hazell et al., 1993 [69]	RW	AC	A	Square, ramp, sinusoid	Sinusoid > (ramp, square)	NST
			C	0–300 μA	≥+6 μA for hearing threshold	NST
			PR	10–200 Hz	(20–50 Hz) < 100 Hz	NST
House et al., 1984 [65]	PM	AC	A	Carrier wave dependent of sound	No comparison performed	NA
	RW (control)	AC	PR	60, 1600 Hz	No comparison performed	NA
Portmann et al., 1979 [73]	RW, PM	AC, DC	C	0–500 μA	No comparison performed	NA
			E	RW, PM	RW > PM	NST
			P	(+)/(-)	(+) > (-)	NST
			PR	50–6400 Hz	No comparison performed	NA
Portmann et al., 1983 [74]	RW, PM	DC+	C	1–5V	No comparison performed	NA
			E	RW, PM	RW > PM	NST
Rubinstein et al., 2003 [59]	RW	AC	C	300 μA–1.5 mA	No comparison performed	NA
			PR	4800 pps	No comparison performed	NA
			Pulse duration	25, 50, 80 μs/phase	No comparison performed	NA

Wenzel et al., 2015 [61]	RW	AC	C	0–3 mA	No comparison performed	NA
			PR	0–100 Hz	No comparison performed	NA
			Pulse duration	50 µs–8 ms	No comparison performed	NA

A : amplitude modulation ; AC : alternative current ; C : current level ; CI : cochlear implant ; DC : direct current ; E : electrode location ; NA : not applicable ; NI : no information ; NRI : non-residual inhibition group ; NST : no statistical test performed ; OW : oval window ; P : polarity ; PM : promontory ; PR : pulse rate ; RI : residual inhibition group ; RW : round window.
The p-value is the result of a statistical comparison test between the tinnitus questionnaire scores used for specific parameter values. Significant p-values are in bold.

Electrode location

Twelve studies directly compared the effect of different stimulated electrode locations (apical, middle, basal, or pitch-matched) on the experienced tinnitus. Arts et al. individually matched electrodes to the patient's tinnitus pitch in 11 CI users[75]. They found that apical and central stimulation were more effective in terms of tinnitus loudness reduction, assessed by the VAS-L, than pitch-matched electrode stimulation (apical : 39% subjects with VAS-L reduction of 30% or more, pitch-matched : 22% subjects with VAS-L reduction of 30% or more (apical vs. pitch-matched : p = 0.042) ; central : 25 (IQR : 5–60) % VAS-L reduction, pitch-matched : 22.5 (IQR : 2–28.5) % VAS-L reduction (central vs. pitch-matched : p = 0.043)). Kloostra et al. (n = 19) reported that there was no statistically significant difference between single-electrode stimulation at apical electrodes, compared to basal electrodes for a reduction of at least one point in VAS-L (apical : 29%, basal : 19% stimulus conditions (p = 0.712))[64]. Zeng et al. observed in their case study (n = 1) that total tinnitus suppression was achieved by stimulation of the four most apical electrodes, one by one, which could not be reached through stimulation of the most basal electrodes of the CI[62].

Several researchers performed electrical stimulation by placing the electrode on the round window or on the promontory and reported outcomes without statistical testing. Of these studies, entailing in total 84 patients, Aran and Cazals found that promontory stimulation resulted in self-reported total tinnitus suppression in 25% of patients and round window stimulation resulted in the same effect in 60% of patients[70]. Cazals et al. found self-reported total tinnitus suppression in 1 out of 6 patients using promontory stimulation and in 4 out of 6 using round window stimulation[68]. Portmann et al. described self-reported tinnitus reduction in 2 out of 7 patients using promontory stimulation and self-reported total tinnitus suppression in 4 out of 7 patients using round window stimulation[73].

Number of activated electrodes

Two studies using CI tested the effect of the number of activated electrodes on tinnitus loudness. Punte et al. (n = 14) showed that a statistically significant tinnitus loudness reduction occurred when all electrodes were activated, whereas activation of four or fewer basal electrodes did not provide significant tinnitus loudness reduction (Table 5)[57]. Kloostra et al. (n = 19) concluded that the effect of single-electrode stimulation on tinnitus was relatively insignificant in comparison to full-array stimulation and did not report statistical outcomes[64].

Current level

Twenty-six studies assessed the effect of current level on tinnitus loudness. Kloostra et al. (n = 19) found statistically significantly greater tinnitus reduction, defined as a reduction of at least one point in VAS-L, using a moderate current level (C level) compared to near-threshold level (T level) (moderate current level : 30%, low current level : 18% stimulus conditions with a reduction of at least one point in VAS-L ($p < 0.01$))[64]. Arts et al. (n = 10) found statistically significant differences between medium to loud stimulation through CI and a sham stimulation with no current provided (sham stimulation : 11 (IQR : -9–29) % VAS-L reduction ; (a) compared to medium stimulation : 22.5 (IQR : 9.5–87.75) % VAS-L reduction ($p = 0.033$) ; b) compared to loud stimulation : 56.5 (IQR : -3.5–94) % VAS-L reduction ($p = 0.014$))[75]. Chang et al. (n = 13) demonstrated that a current level eliciting a loud perception was significantly more effective in terms of VAS-L reduction than current levels eliciting soft perception ($p = 0.027$) ; further data were not reported in the publication[76]. Zeng et al. (n = 1) reported total tinnitus suppression at soft and comfortable levels[62].

Subthreshold vs. suprathreshold Level

In the case study of Zeng et al. (n = 1), subthreshold stimulation through CI did not produce tinnitus suppression, whereas suprathreshold stimulation at low pulse rates did[62]. Hazell et al. (n = 9) found similar results using round window stimulation with AC and showed total suppression with a current level of about six dB more than the current level needed for hearing thresholds[69]. They did not perform statistical testing. In another study, Arts et al. (n = 11) found no statistically significant differences between subthreshold and suprathreshold electrical stimulation through CI (subthreshold : 7 (IQR : - 4.5–29) % VAS-L reduction, soft level : 18 (IQR : -2.25–76) % VAS-L reduction, medium level : 22.5 (IQR : 9.5–87.75) % VAS-L reduction, loud level : 56.5 (IQR : -3.5–94) % VAS-L reduction ($p > 0.05$))[75]. Additionally, Rothera et al. (16 ears) reported total

tinnitus suppression at subthreshold level with anodic DC stimulation at the promontory window[58]. No statistical testing was performed because tinnitus was not the primary outcome of the study. This suppressive effect was only achieved at suprathreshold levels using AC.

Pulse rate

Nineteen studies reported on the effect of stimulation with high or low pulse rates on tinnitus distress. Rubinstein et al. (n = 14) showed that high pulse rates (5000 pps) suppressed tinnitus in 45% (5/11) of patients with round window stimulation and in 33.3% (1/3) of patients with a CI[59] but did not perform statistical tests. Arts et al. (n = 10) did not find statistically significant differences between low (< 2000 pps) and high (> 2000 pps) rates (p = 0.81) ; no further data were provided[50,51]. Kloostra et al. (n = 19) found that tinnitus reduction was more often observed when stimulation through CI was at medium (26% of stimulus conditions) or high (29% of stimulus conditions) pulse rates, compared to stimulation at low (16% of stimulus conditions) pulse rates, but this effect was not significant (p = 0.493)[64]. Zeng et al. (n = 1) found that low rate (20–100 Hz) stimulation suppressed tinnitus through an apical electrode in a CI user[62].

Low pulse rates resulted in total tinnitus suppression in five studies investigating round window stimulation, of which three did not provide quantitative data (n = 32)[66], (n = 11)[82], (n = 9)[67]. Okusa et al. (n = 65) identified low pulse rates as the most effective in tinnitus suppression (50 Hz : 40/65 total tinnitus suppression, 100 Hz : 33/65 total tinnitus suppression, 200 Hz : 20/65 total tinnitus suppression, 400 Hz : 16/65 total tinnitus suppression)[80]. Konopka et al. (n = 111) reported that better tinnitus reduction, measured as a reduction in tinnitus frequency of at least 1 kHz or in tinnitus loudness of at least 15 dB, was obtained using pulse rates below 1 kHz ; however, this was not statistically significant[84].

Additionally, three studies reported on the importance of pulse rate in combination with other parameters. Chang et al. (n = 13) found a statistically significant interaction between pulse rate and current level (p = 0.03), in which the medium level was significantly more effective than soft (p = 0.043) or loud (p = 0.008) current levels, specifically at a high pulse rate (5000 pps) ; further data were not provided[76]. Similarly, Rothholtz et al. identified combinations of different pulse rates suppressing tinnitus in a single individual : a high rate (4638 pps) stimulus around the tinnitus pitch-matched electrode and a low rate (60 pps) stimulus at the most apical electrode of the CI[63].

According to Dauman et al. (n = 2), a low rate (125 Hz) enabled suppression of tinnitus at lower current levels compared with other rates (80, 250, 500 Hz) ; further data were not available[77].

Polarity

Six studies investigated the effect of polarity on tinnitus. Cazals et al. (n = 6) reported total tinnitus suppression in 5 out of 6 patients, only when the polarity of the direct current was anodic[68]. In another study, Aran and Cazals (n = 84) found that tinnitus improvement was achieved when an anodic direct current was applied[70]. Portmann et al. reported that changing the polarity from cathodic to anodic resulted in total tinnitus suppression in 14 out of 15 patients[73]. Rothera et al. showed self-reported tinnitus reduction in 1 out of 16 ears with anodic and cathodic current and in 5 out of 16 ears with the anodic direct current only[58]. Arts et al. (n = 10) tested anodic and cathodic first charged-balanced biphasic pulses, and 8 out 10 patients preferred the cathodic first charged-balanced stimulation as the most convenient configuration in terms of tinnitus loudness reduction[51]. In that study, anodic and cathodic pulses were tested but no significant difference in tinnitus reduction was found at the tinnitus pitch-matched electrode (p = 0.59), data were not available in the publication[50]. In the same manner, Péan et al. also asked four patients to choose between anodic or cathodic first charged-balanced oval window stimulation with regards to tinnitus severity ; each of them opted for an anodic first pulse followed by a capacitive discharge[72].

Harms

The status of harms reported can be found in Table 4 and are listed in Table 7. In the study of Olze et al., one out of four patients experienced an increase in tinnitus loudness, not during, but after intracochlear electrical stimulation[56]. In a case study, Zeng et al. reported the same observation after stopping the stimulation at low rate (100 Hz) and medium current level[62]. This effect was avoided by lowering the current level or introducing a gradual offset ramp in the waveform. No other harms were reported for intracochlear stimulation.

Two studies delivering extra-cochlear stimulation with high intensities (< 300 µA) reported symptoms, such as dizziness and nausea, without providing the numbers of individuals affected[70], and an unpleasant effect in the head in one individual[71]. One study assessing promontory stimulation reported an increase in tinnitus severity in 12 out of 168 participants[83]. Among the 111 patients included in the study of Konopka et al., 4 patients experienced an increase in

tinnitus loudness, 2 reported an increase in tinnitus frequency, and 1 mentioned an increase in tinnitus loudness after promontory stimulation[84]. In 2 out of 14 patients, promontory stimulation above approximately 400 µA evoked pain[59]. Ear drum perforation was reported in one out of four patients after implantation of a ball electrode placed on the promontory[87]. Graham et al. reported somatic sensations in all nine patients tested, an increase in tinnitus loudness in one patient and vertigo in four patients[67]. In the study of Okusa et al., 17 out of 65 patients reported dizziness, 5 reported discomfort of the throat, 3 reported discomfort of the nose, 1 developed a facial nerve palsy, and 1 had numbness of the face[80]. Other discomforts were reported in the study of Watanabe et al. : discomfort of the throat (n = 3/56), discomfort of the nose (n = 1/56), discomfort inside the mouth (n = 1/56) and discomfort of the lips and inside the mouth (n = 1/56)[60]. Wenzel et al. reported an increase in tinnitus loudness in the contralateral ear side of one out three patients, due to Meniere's disease[61].

Table 7. Harms reported in the included studies, with the number of participants in which harms were reported in brackets.

Author, Year	N	Configurations	Harms
Aran et al., 1981 [70]	84	PM, RW at current level <300 µA	dizziness, nausea
Cazals et al., 1978 [68]	6	PM	faint auditory sensations (2), tactile feelings (3)
Cazals et al., 1984 [71]	1	RW, (+), 5V	unpleasant effect in the head (1)
Graham et al., 1977 [67]	9	PM	increase in tinnitus loudness with a current level >5 mA at 100 Hz (1), somatic sensations (pain in the ear, numbness, vibration, tingling in the throat or cheek) (9), vertigo (4)
Konopka et al., 2001 [84]	111	PM	increase in tinnitus loudness (4), increase in tinnitus frequency (2), increase in tinnitus loudness after stimulation (1)
Konopka et al., 2008 [83]	168	PM	increase of tinnitus severity (12)
Matsushima et al., 1996a [87]	4	PM	ear drum perforation (1)
Olze et al., 2018 [56]	4	CI	increase in tinnitus loudness after stimulation (1)
Okusa et al., 1993 [80]	65	PM	dizziness (17), discomfort of the throat (5), discomfort of the nose (3), facial nerve palsy (1), numbness on the face (1)
Rubinstein et al., 2003 [59]	14	PM at 400 µA	pain (2)
Watanabe et al., 1997 [60]	56	PM	discomfort of the throat (3) discomfort of the nose (1), pain inside the mouth (1), cough (1), discomfort of the lips and inside the mouth (1)
Wenzel et al., 2015 [61]	3	RW	increase in tinnitus loudness in the contralateral side due to Meniere's disease (1)
Zeng et al., 2011 [62]	1	CI at 100 Hz	increase in tinnitus loudness after stimulation (1)

A : amperes ; CI : cochlear implant ; N : numbers of patients reporting harms ; PM : promontory stimulation ; RW : round window stimulation ; V : volts ; (+) : anodic polarity.

The numbers in brackets correspond to the number of patients who reported the harm.

Discussion

So far, there are no therapies to directly counteract the origins of tinnitus, only tinnitus management therapies that reduce the burden. Since 1886[88], attempts have been made to develop electrical stimulation patterns to suppress tinnitus. Tinnitus reduction has been reported as a positive effect of intracochlear electrical stimulation in studies on cochlear implantation in hearing-impaired people[89,90]. Some of these studies demonstrated therapeutic suppression of tinnitus symptoms, but there is no consensus on the most effective type of stimulus[7,8]. In this systematic review, we aimed to provide a comprehensible overview of the electrical intra- and extracochlear stimulation patterns studied and their effect on tinnitus.

The current study systematically reviewed the effect of intracochlear and extracochlear electrical stimulation for patients with tinnitus. A total of 89 patients out of 10 studies on intracochlear stimulation and 1109 patients out of 25 studies on extracochlear stimulation were included in this review. The included studies are heterogeneous in their methods, inclusion of participants, interventions and assessment of outcomes. There was a high to medium risk of bias in 22 out of 34 studies, especially due to lack of a non-exposed group and poor selection of the exposed group. All included studies showed subjective tinnitus improvement during or after electrical stimulation, using different stimulation patterns. Harms, including an increase in tinnitus loudness, were reported by 2 out of 89 patients tested with intracochlear stimulation and by 77 out of 1109 patients receiving extracochlear stimulation.

The evaluation of the effect of electrical stimulation was challenged by the heterogeneous patient selection in included studies. Study populations were highly heterogeneous in etiology of tinnitus, laterality of symptoms, duration of tinnitus and hearing profile, ranging from normal hearing to profound hearing loss. Tinnitus severity was not used as a selection criterion in all studies. A total of 19 out of 34 studies did not state their inclusion criteria based on tinnitus characteristics. Moderate or more severe tinnitus was an inclusion criterion in 13 studies. Inclusion based on tinnitus severity holds particular importance, as studies were designed specifically to measure treatment-related changes in tinnitus. However, given the data available, most patients presented at least moderate tinnitus distress before stimulation.

Self-reported tinnitus improvement was observed during or after electrical stimulation in each study. In studies that controlled for placebo effect, significant tinnitus reduction was reported only when electrical stimulation was

applied[51,57,85,86]. This observation outlines the well-founded effect of electrical stimulation on tinnitus. However, the effect observed depends on the electrical patterns used and seems to be patient specific[75].

In a few cases, increase in tinnitus loudness, frequency and severity was reported during or after promontory stimulation[67,83,84] or stimulation through CI[56,62]. Other harms, such as vertigo, dizziness, and somatic sensations, were reported in few instances in studies investigating extracochlear stimulation[59,60,67,70,71,81]. These observations could be explained by the spread of electrical stimulation in the middle ear. The risk of developing harms related to electrical stimulation appears to be low. However, 19 out of 34 studies did not report harms in their methods or in the results. Therefore, the reporting of harms needs to be objectified in future studies.

To date, two reviews focused on electrical stimulation for tinnitus[8,29]. Zeng et al. identified opportunities and knowledge gaps in the use of electrical stimulation of the auditory nerve and the inner ear[8]. In this review, authors mentioned three different points of engagement : direct current stimulation, inner ear stimulation and auditory nerve stimulation. Zeng et al. suggested that the effectiveness of the different stimulation types depends on the etiology, the location and the type of tinnitus[8]. According to them, extracochlear stimulation is appropriate for patients with high-frequency tinnitus and normal audiograms. Another review focused solely on the effect of CI-programmed parameters for tinnitus[29]. Both reviews highlighted the differences between optimal stimulation parameters for speech perception and tinnitus suppression. Our study is the first to systematically review the effect of electrical stimulation of the inner ear for tinnitus relief, including intra- and extracochlear electrical stimulation.

We identified four main parameters characterizing stimulation patterns and having a potential influence on tinnitus : electrode location, current level, pulse rate and polarity. Some studies assessed a combination of parameters, whereas others aimed to evaluate the effect of a single parameter on tinnitus burden (Table A2). Most studies identified a combination of parameters effective in tinnitus suppression but were not able to isolate the effect of a single parameter on tinnitus. Moreover, the time of outcome assessment varied, ranging from during stimulation to days after stimulation. Given the aforementioned limitations, no comparison could be derived between the effect of intra- and extracochlear electrical stimulation. This heterogeneity in study design raises the question of what the best approach is to assess the effect of electrical patterns and, more specifically, the influence of each specific parameter. There is need for

the establishment of a methodology to assess the effect of electrical stimulation patterns for tinnitus relief. In this context, a placebo condition or sham stimulation is essential in evaluating the effectiveness of electrical stimulation.

Apart from the consideration regarding methodology, authors assessing the effect of electrical stimulation should take special care to assess tinnitus changes in both ears. Notably, most studies included in this review reported tinnitus suppression in individuals but did not distinguish between the ipsilateral or contralateral ear. Among the ones who did observe this distinction, Portmann, Cazals, and Aran et al. reported that promontory or round window stimulation suppressed tinnitus only in the tested ear and had no effect on contralateral tinnitus or on tinnitus localized centrally[70,73,74]. However, other included studies showed that unilateral stimulation could improve tinnitus in the contralateral ear[39,46,69,81]. Thus, matching the tinnitus side and electrical stimulation location in the case of unilateral tinnitus as well as assessing tinnitus changes in both ears should also be considered in order to assess the effect of different stimulation strategies.

The underlying mechanisms of tinnitus and effect of electrical stimulation are not fully understood. Two main mechanisms might be involved in tinnitus suppression by electrical stimulation : a masking effect and a reduction effect[91]. The masking effect can be achieved using acoustic and electrical stimulation. The sound induced by electrical stimulation of the auditory nerve can reduce the contrast between the tinnitus signal and silence, which led to a decrease in tinnitus perception[92]. Nevertheless, researchers showed that inaudible stimulation can also suppress tinnitus in some patients[39,58,75,80]. This finding highlights another stimulation-based mechanism involved : the reduction mechanism, which modulates activity of the auditory cortex and suspends tinnitus generation. Aran and Cazals emphasized the dependence between the reduction effect and tinnitus origins[70]. They suggested location-specific management for tinnitus suppression. Based on their results, they hypothesized that electrical stimulation may only be effective if tinnitus originates at the periphery of the auditory pathway, whereas tinnitus of a more central origin cannot be improved by electrical stimulation. Some authors linked mechanisms underlying tinnitus to the effects of specific electrical patterns. For instance, Rubinstein et al. supported a theory of the deafferentation and alteration of normal spontaneous activity as the principal causes of tinnitus. Therefore, high pulse rate stimulation might produce spontaneous-like patterns, restoring abnormal activity and suppressing tinnitus percepts[59]. Rubinstein et al. only investigated high pulse

rates and did not report comparison to other rates[59]. On the other hand, Zeng et al. used a case study to suggest that a low pulse rate might induce more robust and central activity, which would interfere with tinnitus-induced abnormal central activity[62]. Several questions remain regarding the extent to which a masking or reduction effect contributes to tinnitus suppression during and after electrical stimulation. Mallen et al. proposed a new audiological sequence (TILT) to isolate the masking and reduction effects of electrical stimulation[35]. Recent studies performed electrophysiological measurements, such as electrocochleography (ECochG) or auditory evoked potentials (AEPs), to further investigate the changes in neural activity induced by electrical stimulation (Table A3)[62,85,86]. Using objective measures, such as neuroimaging or electrophysiology, might be of additional value to better understand and optimize the effect of electrical stimulation on tinnitus.

The difference in reporting outcome can be of importance to the effect of electrical stimulation. The oldest studies did not have access to tinnitus questionnaires and assessed tinnitus changes based on self-reports[55,58,60,65,67–71,73,74,79,81,87]. More recent studies measured tinnitus severity using single-item questionnaires, multi-item questionnaires, or both. Among the 34 studies included, 10 studies monitored tinnitus changes, using tinnitus validated questionnaires. The change in tinnitus distress, burden or severity was often reported without introducing the notion of clinically relevant change. Self-reported tinnitus changes were available in almost every study included. However, the subjective changes reported do not belong to the same definitions and therefore, cannot be compared between studies. In the same way, comparing stimulation type is difficult as, for instance, DC stimulation cannot be translated to AC stimulation[57]. Considering the aforementioned limitations, no strong conclusion could be drawn from these data on differences between electrical stimulation patterns. This stresses the need for studies with adequate study designs and consistent selection of patients to provide homogeneity in outcomes.

Electrical stimulation has the potential to reduce tinnitus symptoms and has drawn attention in research for many years. Intracochlear stimulation through a CI is already highly developed for speech recognition in deafened patients. This technology could combine electrical stimulation to optimize both speech recognition and tinnitus suppression[7,8]. Nevertheless, due to its invasive approach, cochlear implantation can induce residual hearing deterioration in the ear implanted. Extracochlear stimulation for tinnitus can be provided using a

basic pattern generator and has been extensively investigated, due to its minimal invasiveness. Whether this can be a perspective of tinnitus treatment in normal hearing patients remains to be seen. Moreover, little is known about the long-term effects of extracochlear electrical stimulation on tinnitus. Finally, significant challenges still need to be addressed on how to optimize electrical stimulation for maximum efficacy and whether tinnitus relief can be achieved without an auditory percept.

Conclusion

From the data included in this review, we concluded that electrical stimulation of the auditory nerve has potential for tinnitus suppression. Due to methodological limitations and the low reporting quality of the included studies, the potential of intra- and extracochlear stimulation has not been fully explored. To draw conclusions on which stimulation patterns should be optimized for tinnitus relief, a deeper understanding of the mechanisms involved in tinnitus suppression is needed, and new study designs should be considered. Further research is needed to determine the optimal electrical stimulation patterns to suppress tinnitus.

Author contributions

Conceptualization : K.K.S.A., I.S., A.L.S. ; methodology : K.K.S.A., I.S., A.L.S. ; data curation : K.K.S.A., M.J.D. ; formal analysis : K.K.S.A., M.J.D. ; investigation : K.K.S.A, M.J.D. ; project administration : K.K.S.A., I.S., A.L.S. ; resources : R.J.S. ; supervision : B.v.D., R.J.S., I.S., A.L.S. ; validation : K.K.S.A., M.J.D., I.S., A.L.S. ; writing—original draft : K.K.S.A. ; writing—review and editing : K.K.S.A., M.J.D., R.J.S., B.v.D., I.S., A.L.S. All authors have read and agreed to the published version of the manuscript.

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Conflicts of interest

B.v.D. and K.K.S.A. are employed at the Cochlear Technology Centre, Mechelen, Belgium. No further conflict of interest is reported by the authors.

Appendix

Table A1. NOS checklist.

1) Representativeness of the exposed cohort

(★)-moderate-to-severe tinnitus

(★)-tinnitus patients

(☆)-selection of individuals

(☆)-no description

2) Selection of the non-exposed cohort

(★)-same as exposed cohort

(☆)-other source

(☆)-no description

3) Ascertainment of exposure

(★)-objective measure

(☆)-questionnaire

(☆)-no description

4) Demonstration that outcome of interest was not present at start of study

(★)-pre-stimulation tinnitus outcome available

(☆)-pre-stimulation tinnitus outcome not available

1) Comparability of cohorts on the basis of the design or analysis

(★)-inclusion based on tinnitus severity

(☆)-no inclusion based on tinnitus severity

(★)-inclusion based on HL

(☆)-no inclusion based on HL

1) Assessment of outcome

(★)-questionnaire

(☆)-self report

(☆)-no description

(☆)-other

2) Was follow-up long enough for outcomes to occur

(★)-at least during stimulation

(☆)-no data

3) Adequacy of follow up of cohorts

(★)-no missing data

(★)-<10% missing data

(☆)→10% missing data

(☆)-no description

★ 1 point ; ☆ 0 point ;

Table A2. Parameters assessed by the included studies. a) Studies reporting on intracochlear electrical stimulation ; b) Studies reporting on extracochlear electrical stimulation.

a) Studies reporting on intracochlear electrical stimulation

Authors, Year	Stimulation Type	Other Outcomes
Arts et al., 2015 [75]	CI	TLM, TPM
Arts et al., 2016 [51]	CI	TLM, BDI, HUI-III
Chang et al., 2012 [76]	CI	BDI, BAI
Dauman et al., 1993 [77]	CI	
Kloostra et al., 2020 [64]	CI	
Olze et al., 2018 [56]	CI	
Punte et al., 2013 [57]	CI	TLM, TPM
Rothholtz et al., 2009 [63]	CI	
Rubinstein et al., 2003 [59]	CI (3), RW (11)	TLM, TPM
Zeng et al., 2011 [62]	CI	AEPs

b) Stimulation reporting on extracochlear stimulation

Authors, Year	Stimulation Type (OW, PM, RW)	Other Outcomes
Aran et al., 1981 [70]	RW, PM	ECochG
Cazals et al., 1978 [68]	RW (13), PM (3)	
Cazals et al., 1984 [71]	RW	prosody test, SRT
Daneshi et al., 2005 [66]	PM (32), CI (20)	TLM, TPM
Di Nardo et al., 2009 [82]	PM, CI (control)	TLM, TPM, MML
Graham et al., 1977 [67]	PM	TLM
Hazell et al., 1993 [69]	RW	
House et al., 1984 [65]	PM, RW	
Ito et al., 1994 [81]	PM	
Konopka et al., 2001 [84]	PM	TLM, TPM, USGDoppler
Konopka et al., 2008 [83]	PM	TLM, TPM, MML
Mahmoudian et al., 2013 [86]	PM	TLM, TPM, RI, ECochG, ABR, BTT
Mahmoudian et al., 2015 [85]	PM	MMN, TLM, TPM, MML, RI
Matsushima et al., 1994 [79]	PM	PTA
Matsushima et al., 1996a [87]	PM	audiogram
Matsushima et al., 1996b [55]	PM	SRT
Okusa et al., 1993 [80]	PM	TLM, TPM
Péan et al., 2010 [72]	OW	TPM
Portmann et al., 1979 [73]	RW (11), PM (7)	ECochG
Portmann et al., 1983 [74]	RW, PM	
Rothera et al., 1986 [58]	PM	ECochG, ABR
Rubinstein et al., 2003 [59]	CI (3), RW (11)	TLM, TPM
Watanabe et al., 1997 [60]	PM	TLM, TPM, ECochG
Wenzel et al., 2015 [61]	RW	VAS-M

AC : alternative current ; CI : cochlear implant ; DC : direct current ; DC+ : anodic direct current ; OW : oval window ; PM : promontory ; RW : round window.

Table A3. Other outcomes assessed by the included studies. a) Studies reporting on intracochlear electrical stimulation ; b) Studies reporting on extracochlear electrical stimulation.

a) Studies reporting on intracochlear electrical stimulation

Authors, Year	Stimulation type (CI, RW)	AC/DC	1. Electrode location	2. Current level	3. Pulse rate	4. Polarity	5. Amplitude modulation
Arts et al., 2015 [75]	CI	AC	●	●			
Arts et al., 2016 [51]	CI	AC	●	●	●	●	●
Chang et al., 2012 [76]	CI	AC	●	●	●		
Dauman et al., 1993 [77]	CI	AC	●	●	●		
Kloostra et al., 2020 [64]	CI	AC	●	●	●		
Olze et al., 2018 [56]	CI	AC			●		●
Punte et al., 2013 [57]	CI	AC	●				
Rothholtz et al., 2019 [63]	CI	AC	●	●	●		
Rubinstein et al., 2003 [59]	CI (3), RW (11)	AC	●	●	●		
Zeng et al., 2011 [62]	CI	AC	●	●	●		

b) Stimulation reporting on extracochlear stimulation

Authors, Year	Stimulation type (OW, PM, RW, CI)	AC/DC	1. Electrode location	2. Current level	3. Pulse rate	4. Polarity	5. Amplitude modulation
Aran et al., 1981 [70]	RW, PM	AC, DC	●	●	●	●	
Cazals et al., 1978 [68]	RW (13), PM (3)	AC, DC	●	●	●	●	
Cazals et al., 1984 [71]	RW	DC+		●			
Daneshi et al., 2005 [66]	PM, CI (control)	AC		●	●		
Di Nardo et al., 2009 [82]	PM	DC+		●	●		
Graham et al., 1977 [67]	PM	AC		●	●		
Hazell et al., 1993 [69]	RW	AC		●	●		●
House et al., 1984 [65]	PM	AC			●		●
Ito et al., 1994 [81]	PM	NI					
Konopka et al., 2001 [84]	PM	AC		●	●		
Konopka et al., 2008 [83]	PM	DC+		●			
Mahmoudian et al., 2013 [86]	PM	AC		●	●		
Mahmoudian et al., 2015 [85]	PM	AC		●	●		
Matsushima et al., 1994 [79]	PM	AC		●			
Matsushima et al., 1996a [87]	PM	AC		●			
Matsushima et al., 1996b [55]	PM	AC					
Okusa et al., 1993 [80]	PM	AC			●		
Péan et al., 2010 [72]	OW	AC		●	●	●	
Portmann et al., 1979 [73]	RW (11), PM (7)	AC, DC	●	●	●	●	
Portmann et al., 1983 [74]	RW, PM	DC+		●			
Rothera et al., 1986 [58]	PM	AC, DC		●	●	●	
Rubinstein et al., 2003 [59]	CI (3), RW (11)	AC	●	●	●		
Watanabe et al., 1997 [60]	PM	AC		●			
Wenzel et al., 2015 [61]	RW	AC		●	●		
Carlson et al., 2020 [78]	PM	AC	●	●	●	●	

ABR : auditory brainstem response; AEPs : auditory evoked potentials ; BAI : Beck anxiety inventory ; BDI : Beck depression inventory ; BTT : brainstem transmission time ; CI : cochlear implant ; ECochG : electrocochleography ; HUI-III : health utilities index III ; MML : minimal masking level ; MMN : mismatch negativity ; OW : oval window ; PCS : prospective cohort study ; PM : promontory ; PTA : pure tone average ; RI : residual inhibition ; RW : round window ; SRT : speech recognition test ; TLM : tinnitus loudness matching ; TPM : tinnitus pitch matching ; VAS-M : visual analogue scale mood ; VAS-P : visual analogue scale pain. The numbers in brackets correspond to the number of patients who tested the stimulation type.

References

1. Shore, S. E., Roberts, L. E. & Langguth, B. Maladaptive plasticity in tinnitus--triggers, mechanisms and treatment. Nat. Rev. Neurol. 12, 150–160 (2016).
2. Pierzycki, R. H., Corner, C., Fielden, C. A. & Kitterick, P. T. Effects of Tinnitus on Cochlear Implant Programming. Trends Hear. (2019).
3. Peter, N., Liyanage, N., Pfiffner, F., Huber, A. & Kleinjung, T. The Influence of Cochlear Implantation on Tinnitus in Patients with Single-Sided Deafness: A Systematic Review. Otolaryngol. - Head Neck Surg. (2019) doi:10.1177/0194599819846084.
4. Ramakers, G. G. J., Van Zon, A., Stegeman, I. & Grolman, W. The effect of cochlear implantation on tinnitus in patients with bilateral hearing loss: A systematic review. Laryngoscope 125, 2584–2592 (2015).
5. Assouly, K. K. S., van Heteren, J. A. A., Stokroos, R. J., Stegeman, I. & Smit, A. L. Cochlear implantation for patients with tinnitus - A systematic review. Prog. Brain Res. 260, 27–50 (2021).
6. Yuen, E., Ma, C., Nguyen, S., Meyer, T. & Lambert, P. The Effect of Cochlear Implantation on Tinnitus and Quality of Life: A Systematic Review and Meta-analysis. Otol. Neurotol. (2021) doi:10.1097/MAO.0000000000003172.
7. Zeng, F.-G., Richardson, M., Tran, P., Lin, H. & Djalilian, H. Tinnitus Treatment Using Noninvasive and Minimally Invasive Electric Stimulation: Experimental Design and Feasibility. Trends Hear. 23, 1–12 (2019).
8. Zeng, F.-G., Djalilian, H. & Lin, H. Tinnitus treatment with precise and optimal electric stimulation. Curr. Opin. Otolaryngol. Head Neck Surg. 23, 382–387 (2015).
9. Moher, D. et al. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. PLoS Med. 6, (2009).
10. Schardt, C., Adams, M. B., Owens, T., Keitz, S. & Fontelo, P. Utilization of the PICO framework to improve searching PubMed for clinical questions. BMC Med. Inform. Decis. Mak. 7, 1–6 (2007).
11. Ouzzani, M., Hammady, H., Fedorowicz, Z. & Elmagarmid, A. Rayyan-a web and mobile app for systematic reviews. Syst. Rev. 5, 1–10 (2016).
12. Wells, G., Shea, B., O'Connell, D. & Peterson, J. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Ottawa, ON: Ottawa Hospital Research Institute (2000).
13. Meikle, M. B. et al. The tinnitus functional index: Development of a new clinical measure for chronic, intrusive tinnitus. Ear Hear. (2012) doi:10.1097/AUD.0b013e31822f67c0.
14. Newman, C. W., Sandridge, S. A. & Jacobson, G. P. Psychometric adequacy of the Tinnitus Handicap Inventory (THI) for evaluating treatment outcome. J. Am. Acad. Audiol. 9, 153–60 (1998).
15. Zeman, F. & Koller, M. Tinnitus Handicap Inventory for Evaluating Treatment Effects : Which -- Head and Neck Surgery Tinnitus Handicap Inventory for Evaluating Treatment Effects : Which Changes Are Clinically. (2011) doi:10.1177/0194599811403882.

16. Kuk, F. K., Tyler, R. S., Russell, D. & Jordan, H. The psychometric properties of a tinnitus handicap questionnaire. Ear Hear. (1990) doi:10.1097/00003446-199012000-00005.

17. Goebel, G. & Hiller, W. [The tinnitus questionnaire. A standard instrument for grading the degree of tinnitus. Results of a multicenter study with the tinnitus questionnaire]. HNO 42, 166–172 (1994).

18. Hall, D. A., Mehta, R. L. & Argstatter, H. Interpreting the Tinnitus Questionnaire (German version): what individual differences are clinically important? Int. J. Audiol. 57, 553–557 (2018).

19. Kuk, F. K., Tyler, R. S., Rustad, N., Harker, L. A. & Tye-Murray, N. Alternating Current at the Eardrum for Tinnitus Reduction. J. Speech, Lang. Hear. Res. 32, 393–400 (1989).

20. Mielczarek, M. & Olszewski, J. Direct current stimulation of the ear in tinnitus treatment: A double-blind placebo-controlled study. Eur. Arch. Oto-Rhino-Laryngology 271, 1815–1822 (2014).

21. Bartels, H., Staal, M. J., Holm, A. F., Mooij, J. J. A. & Albers, F. W. J. Long-term evaluation of treatment of chronic, therapeutically refractory tinnitus by neurostimulation. Stereotactic and functional neurosurgery vol. 85 150–157 (2007).

22. Holm, A. F., Staal, M. J., Mooij, J. J. A. & Albers, F. W. J. Neurostimulation as a new treatment for severe tinnitus: a pilot study. Otol. Neurotol. 26, 425–8; discussion 428 (2005).

23. Hasegawa, J. I. Clinical investigation of tinnitus therapy in our department. Pract. Otol. Suppl. (1999) doi:10.5631/jibirinsuppl1986.1999.supplement102_61

24. Matsushima, J. . et al. Surgical Method for Implanted Tinnitus Suppressor. Int. Tinnitus J. 2, 21–25 (1996).

25. Matsushima, J. I. et al. A tinnitus case with an implanted electrical tinnitus suppressor. Nihon Jibiinkoka Gakkai kaiho vol. 97 661–667 (1994)..

26. Mielczarek, M., Konopka, W. & Olszewski, J. Tinnitus treatment by using electrical stimulation. Otolaryngol. Pol. = Polish Otolaryngol. 61, 902–904 (2007).

27. Matsushima, J. I., Sakai, N., Uemi, N., Miyoshi, S. & Ifukube, T. Functional Electrical Stimulation of Tinnitus Patients in the Auditory Nervous System. Japanese J. Med. Electron. Biol. Eng. 33, 242–247 (1995).

28. Matsushima, J. I., Kumagai, M., Takahashi, K., Miyoshi, S. & Ifukube, T. Electroconduction system for implantable tinnitus suppressor. Nihon Jibiinkoka Gakkai Kaiho 97, 654–660 (1994).

29. Perreau, A., Tyler, R. & Mancini, P. C. Programming a Cochlear Implant for Tinnitus Suppression. J. Am. Acad. Audiol. (2020) doi:10.3766/jaaa.18086.

30. Mielczarek, M., Norena, A., Schlee, W. & Olszewski, J. Excitation of the Auditory System as a Result of Non-invasive Extra-Cochlear Stimulation in Normal Subjects and Tinnitus Patients. Front. Neurosci. 12, 146 (2018).

31. Mielczarek, M., Michalska, J., Polatyńska, K. & Olszewski, J. An Increase in Alpha Band Frequency in Resting State EEG after Electrical Stimulation of the Ear in Tinnitus Patients-A Pilot Study. Front. Neurosci. 10, 453 (2016).

32. van den Berge, M. J. C. et al. Cluster analysis to identify possible subgroups in tinnitus patients. Front. Neurol. 8, 1–7 (2017).

33. Ito, J. & Sakakihara, J. Suppression of tinnitus by cochlear implantation. Am. J. Otolaryngol. 15, 145–148 (1994).

34. Mertens, G., Van Rompaey, V. & Van de Heyning, P. Electric-acoustic stimulation suppresses tinnitus in a subject with high-frequency single-sided deafness. Cochlear Implants Int. (2018) doi:10.1080/14670100.2018.1473940.

35. Mallen, J. R. et al. Quantifying tinnitus suppression in cochlear implantation using tinnitus interval-limited tracking. Laryngoscope 1–6 (2019) doi:10.1002/lary.28414.

36. Aran, J. M. Electrical stimulation of the auditory system and tinnitus control. J. Laryngol. Otol. Suppl. 153–161 (1981).

37. Latkowski, B. et al. Treatment of persistent tinnitus with electric stimulation of the ear. Polski tygodnik lekarski (Warsaw, Poland : 1960) vol. 38 893–896 (1983).

38. Von Wedel, H., Strahlmann, U. & Zorowka, P. A longitudinal study on the benefits of different therapeutic methods in tinnitus. Laryngorhinootologie. (1989) doi:10.1055/s-2007-998330.

39. Battmer, R. D., Heermann, R. & Laszig, R. Suppression of tinnitus by electric stimulation in cochlear implant patients. HNO 37, 148–152 (1989).

40. Harada, C. Electrical tinnitus suppression--a comparative study of clinical trials and animal experiments. Hokkaido J. Med. Sci. 67, 785–800 (1992).

41. Bazarov, V. G., Karamzina, L. A. & Loza, T. P. Tinnitus: The effects of acoustic and electric stimulation. Zh. Ushn. Nos. Gorl. Bolezn. 42–49 (1998).

42. Szymiec, E., Szyfter, W. & Karlik, M. The possibility of tinnitus suppression by electrical stimulation. Mozliwość leczenia uporczywych szumów usznych Metod. elektrostymulacji. 51, 487–491 (1997).

43. Gryczynski, M., Jozwiak, J. & Wisniewski, M. Tinnitus rehabilitation in sensorineural hearing loss. Based on 400 patients. OTORINOLARINGOLOGIA 44, 227–229 (1994).

44. Wang, Y., Li, M. & Zhang, J. [The research on electrical promontory stimulation in treating severe disabling tinnitus:12 case reports]. Lin chuang er bi yan hou tou jing wai ke za zhi = Journal of clinical otorhinolaryngology, head, and neck surgery vol. 26 1037–1039 (2012).

45. Mielczarek, M., Konopka, W. & Olszewski, J. The application of direct current electrical stimulation of the ear and cervical spine kinesitherapy in tinnitus treatment. Auris Nasus Larynx vol. 40 61–65 (2013).

46. Matsushima, J. I., Harada, C., Ifukube, T., Hirata, Y. & Sakajiri, M. A study of electrical stimulation of the cochlea in tinnitus patients. JPN. J. MED. ELECTRON. BIOL. ENG. 31, 31–36 (1993).

47. Tyler, R. S. et al. Electrical stimulation of the cochlea to reduce tinnitus. Semin. Hear. 29, 326 (2008).

48. Ohkawara, D. & Watanabe, K. Effects of electrical promontory stimulation and band-noise masker in the suppression of tinnitus. Nihon Jibiinkoka Gakkai kaiho vol. 98 1303–1309 (1995).

49. Arts, R. A. G. J. et al. The effect of tinnitus specific intracochlear stimulation on speech perception in patients with unilateral or asymmetric hearing loss accompanied with tinnitus and the effect of formal auditory training. Int. J. Audiol. 57, 426–439 (2018).

50. Arts, R. A. G. J., George, E. L. J., Griessner, A., Zierhofer, C. & Stokroos, R. J. Tinnitus suppression by intracochlear electrical stimulation in single-sided deafness: A prospective clinical trial - Part i. Audiol. Neurotol. 20, 294–313 (2015).

51. Arts, R. A. G. J. et al. Tinnitus Suppression by Intracochlear Electrical Stimulation in Single Sided Deafness – A Prospective Clinical Trial: Follow-Up. PLoS One 11, e0153131 (2016).

52. Arts, R. A. G. J., George, E. L., Griessner, A., Zierhofer, C. & Stokroos, R. J. Long-term effects of intracochlear electrical stimulation with looped patterns on tinnitus: A case study. Ear, Nose Throat J. 95, E9–E9 (2016).

53. Matsushima, J. I., Harada, C., Miyoshi, S., Ifukube, T. & Sakajiri, M. Development of Implanted Electrical Tinnitus Suppressor. Japanese J. Med. Electron. Biol. Eng. 32, 21–27 (1994).

54. Matsushima, J. . et al. Preliminary study of improved perception of words with the same sound but different intonation in tinnitus patients following electrical stimulation of the ear. Acta Otolaryngol. Suppl. 532, 112–114 (1997).

55. Matsushima, J. I. et al. Improved Selective Attention and Word Perception in Tinnitus Patients Treated with Electrical Stimulation. Int. Tinnitus J. 2, 115–122 (1996).

56. Olze, H., Szczepek, A. J., Reich, U., Gräbel, S. & Uecker, F. Tinnitus suppression using electrical stimulation. Curr. Dir. Biomed. Eng. 4, 5–8 (2018).

57. Kleine Punte, A., De Ridder, D. & Van De Heyning, P. On the necessity of full length electrical cochlear stimulation to suppress severe tinnitus in single-sided deafness. Hear. Res. 295, 24–29 (2013)..

58. Rothera, M., Conway, M., Brightwell, A. & Graham, J. Evaluation of patients for cochlear implant by promontory stimulation. Psychophysical responses and electrically evoked brainstem potentials. Br. J. Audiol. 20, 25–28 (1986).

59. Rubinstein, J. T., Tyler, R. S., Johnson, A. & Brown, C. J. Electrical suppression of tinnitus with high-rate pulse trains. Otol. Neurotol. 24, 478–485 (2003).

60. Watanabe, K. I., Okawara, D., Baba, S. & Yagi, T. Electrocochleographic analysis of the suppression of tinnitus by electrical promontory stimulation. Int. J. Audiol. 36, 147–154 (1997).

61. Wenzel, G. I. et al. Non-penetrating round window electrode stimulation for tinnitus therapy followed by cochlear implantation. Eur. Arch. Oto-Rhino-Laryngology 272, 3283–3293 (2015).

62. Zeng, F. G. et al. Tinnitus suppression by low-rate electric stimulation and its electrophysiological mechanisms. Hear. Res. 277, 61–66 (2011).

63. Rothholtz, V. S. et al. Exploring the parametric space of tinnitus suppression in a patient with a cochlear implant. Laryngoscope 119, S177 (2009).

64. Kloostra, F. J. J., De Kleine, E., Free, R. H., Hofman, R. & Van Dijk, P. Changes in tinnitus by cochlear implantation: A parametric study of the effect of single-electrode stimulation. Audiol. Neurotol. 1–9 (2020) doi:10.1159/000509202.

65. House, J. W. Effects of electrical stimulation on tinnitus. J. Laryngol. Rhinol. Otol. 98, 139–140 (1984).

66. Daneshi, A., Mahmoudian, S., Farhadi, M., Hasanzadeh, S. & Ghalebaghi, B. Auditory electrical tinnitus suppression in patients with and without implants. Int. Tinnitus J. 11, 85–91 (2005).

67. Graham, J. M. & Hazell, J. W. Electrical stimulation of the human cochlea using a transtympanic electrode. BR. J. AUDIOL. 11, 59–62 (1977).

68. Cazals, Y., Negrevergne, M. & Aran, J. M. Electrical stimulation of the cochlea in man: hearing induction and tinnitus suppression. J. Am. Audiol. Soc. 3, 209–213 (1978).

69. Hazell, J. W. P., Jastreboff, P. J., Meerton, L. E. & Conway, M. J. Electrical tinnitus suppression: Frequency dependence of effects. Int. J. Audiol. (1993) doi:10.3109/00206099309072929.

70. Aran, J. M. & Cazals, Y. Electrical suppression of tinnitus. Ciba Found. Symp. 85, 217–231 (1981).

71. Cazals, Y., Rouanet, J. F., Negrevergne, M. & Lagourgue, P. First results of chronic electrical stimulation with a round-window electrode in totally deaf patients. Arch. Otorhinolaryngol. 239, 191–196 (1984).

72. Péan, V., Cazals, Y., Rosanis, G. & Frachet, B. Étude de divers aspects de la prise en charge des acouphènes pour un sourd unilatéral avec le stimulateur électrique implantable extracochléaire Tinnelec RW®. Irbm 31, 115–121 (2010).

73. Portmann, M., Cazals, Y., Negrevergne, M. & Aran, J. M. Temporary tinnitus suppression in man through electrical stimulation of the cochlea. Acta Otolaryngol. 87, 294–299 (1979).

74. Portmann, M., Aran, J. M., Nègrevergne, M. & Cazals, Y. Electrical stimulation of the ear: Clinical applications. Ann. Otol. Rhinol. Laryngol. 92, 621–622 (1983).

75. Arts, R. A. G. J., George, E. L. J., Chenault, M. N. & Stokroos, R. J. Optimizing intracochlear electrical stimulation to suppress tinnitus. Ear Hear. 36, 125–135 (2015).

76. Chang, J. E. & Zeng, F. G. Tinnitus suppression by electric stimulation of the auditory nerve. Front. Syst. Neurosci. 6, 1–11 (2012).

77. Dauman, R., Tyler, R. S. & Aran, J. M. Intracochlear electrical tinnitus reduction. Acta Otolaryngol. 113, 291–295 (1993).

78. Carlson. ClinicalTrials.gov [Internet]. Carlson (MD): National Library of Medicine (US). 2000 Feb 29- . Identifier NCT03759834, Cochlear Promontory Stimulation for Treatment of Tinnitus; 2018 Nov 30. https://clinicaltrials.gov/ct2/show/study/NCT03988699#contacts.

79. Matsushima, J. I. et al. A Study of Electrical Promontory Stimulation in Tinnitus Patients. Auris Nasus Larynx 21, 17–24 (1994).

80. Okusa, M., Shiraishi, T., Kubo, T. & Matsunaga, T. Tinnitus suppression by electrical promontory stimulation in sensorineural deaf patients. Acta Otolaryngol. Suppl. 501, 54–58 (1993).

81. Ito, J. & Sakakihara, J. Tinnitus suppression by electrical stimulation of the cochlear wall and by cochlear implantation. Laryngoscope 104, 752–754 (1994).

82. Di Nardo, W. et al. Transtympanic electrical stimulation for immediate and long-term tinnitus suppression. Int. Tinnitus J. 15, 100–106 (2009).

83. Konopka, W., Mielczarek, M. & Olszewski, J. Electrical stimulation as an alternative method of tinnitus treatment. Otolaryngol. Pol. 62, 601–605 (2008).

84. Konopka, W., Zalewski, P., Olszewski, J., Olszewska-Ziaber, A. & Pietkiewicz, P. Tinnitus suppression by electrical promontory stimulation (EPS) in patients with sensorineural hearing loss. Auris Nasus Larynx 28, 35–40 (2001).

85. Mahmoudian, S. et al. Alterations in auditory change detection associated with tinnitus residual inhibition induced by auditory electrical stimulation. J. Am. Acad. Audiol. 26, 408–422 (2015).

86. Mahmoudian, S. et al. Alterations in early auditory evoked potentials and brainstem transmission time associated with tinnitus residual inhibition induced by auditory electrical stimulation. Int. Tinnitus J. 18, 63–74 (2013).

87. Matsushima, J. I. et al. An experience of the usage of electrical tinnitus suppressor. Artif. Organs 20, 955–958 (1996).

88. Althaus, J. ON TINNITUS AURIUM AND ITS TREATMENT BY ELECTRICITY. Lancet (1886) doi:10.1016/S0140-6736(00)49789-8.

89. Van De Heyning, P. et al. Incapacitating unilateral tinnitus in single-sided deafness treated by cochlear implantation. Ann. Otol. Rhinol. Laryngol. 117, 645–652 (2008).

90. Ramos Macías, A. et al. One-Year Results for Patients with Unilateral Hearing Loss and Accompanying Severe Tinnitus and Hyperacusis Treated with a Cochlear Implant. Audiol. Neurotol. 23, 8–19 (2018).

91. Knipper, M. et al. The neural bases of tinnitus: lessons from deafness and cochlear implants. Journal of Neuroscience vol. 40 7190–7202 (2020).

92. Vernon, J. Attemps to relieve tinnitus. J. Am. Audiol. Soc. 2, 124–131 (1977).

PART 03

impact of tinnitus

Impact of tinnitus on cochlear implant recipients

PART 03

Influence of tinnitus annoyance on hearing-related quality of life in cochlear implant recipients

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Abstract

Tinnitus is a common symptom in cochlear implant (CI) recipients. There is no clear evidence of the influence of tinnitus on hearing-related quality of life (QoL) in this population. The aim of this study was to assess the relationship between hearing-related QoL measured by the Speech, Spatial and Qualities of Hearing scale (SSQ12) and tinnitus annoyance or perceived change in tinnitus annoyance after cochlear implantation. The study sample consisted of 2322 implanted adults across France, Germany, Ireland, Italy, the Netherlands, Sweden and the United Kingdom. Information relating to QoL measured using the SSQ12 and tinnitus annoyance and change in tinnitus annoyance, assessed using single-item questions, were collected one or more years post-implantation. The relationship between SSQ12 score and tinnitus annoyance or change in tinnitus annoyance was analysed using linear models adjusted for age and unilateral versus bilateral implants. Tukey pairwise tests were used to compare mean SSQ12 scores across levels of tinnitus annoyance and changes. Tinnitus prevalence was 33.9% post-implantation. Recipients with tinnitus had a significantly lower SSQ12 score than recipients without tinnitus. SSQ scores varied significantly with tinnitus annoyance, age and unilateral versus bilateral implants. Overall, CI recipients who experienced less bothersome tinnitus reported better hearing-related QoL. Healthcare professionals should be aware of the influence of tinnitus on CI recipients' hearing to manage patient expectations.

Introduction

Tinnitus is the perception of sound in the ears or in the head without an external stimulus[1]. It is reported in 10 to 15% of the general adult population, and the prevalence increases with age[2–4]. Tinnitus does not only vary in terms of sound perception and location but also in terms of distress. Some people are not bothered by tinnitus at all, whereas others experience it as bothersome and debilitating. Up to 3% of the general population experience severe and bothersome tinnitus resulting in a substantial reduction in their quality of life[2,5].

Hearing impairment is the most common risk factor associated with tinnitus[6,7] People with severe to profound hearing loss can get hearing benefit from a cochlear implant (CI) when hearing aids no longer provide a sufficient level of speech understanding in everyday situations. Amongst CI candidates, pre-implant tinnitus prevalence ranges from 52% to 86%[8–10]. The cochlear implant primarily aims to partially restore hearing by providing electrical stimulation to the auditory nerve. Tinnitus reduction can be experienced as a beneficial secondary effect of cochlear implantation[8,9,11–13]. While some studies showed that tinnitus loudness, distress or annoyance can be reduced or suppressed after cochlear implantation, others reported that tinnitus can also be worsened in up to 10% of CI recipients, or induced in up to 4% of patients receiving a CI[9,10.] As the prevalence of tinnitus is relatively high in CI candidates and the effect of cochlear implantation on tinnitus distress seems to vary widely between patients, it is of clinical importance to further investigate the impact of tinnitus on CI recipients and how it might influence hearing performance with a CI.

There is no consensus about the influence of tinnitus on hearing performance. Some previous studies showed that tinnitus may interfere with speech perception and reduce hearing performance. Huang et al. compared speech perception between subjects with normal hearing and tinnitus and a control with normal hearing and no tinnitus[14]. The subjects with tinnitus performed significantly worse than subjects without tinnitus. Mertens et al. found that unilateral tinnitus in a single-sided deaf ear reduced speech reception in the non-tinnitus ear[15]. In contrast, Zeng et al. concluded from their data that tinnitus does not interfere with speech perception and perception of external sounds[16]. Therefore, some uncertainties remain about the relationship between tinnitus and hearing performances.

Hearing-related quality of life (QoL) has become a standard outcome measure to quantify the hearing impairment and its associated deficits. Using patient-reported outcome measures (PROMs), several studies found a negative

correlation between tinnitus distress and hearing-related QoL in adult CI recipients, meaning that an increase in perceived tinnitus distress correlated with a decrease in hearing-related QoL[10,17–19]. Two studies showed that pre-operative tinnitus was associated with poorer hearing-related QoL outcomes post-implantation[20,21]. In a cohort of 210 adult CI recipients, Opperman et al. showed that both pre- and post-implantation tinnitus were predictive of poorer hearing-related QoL[19].

Although hearing-related QoL seems related to tinnitus presence and distress, literature does not provide clear evidence for this association. Studies assessing this association used small sizes, which lead large margins of error. Furthermore, previous studies have used different PROMs to assess hearing-related QoL and the impact of tinnitus. Therefore, attempts to merge independent studies into a meta-analysis can hardly be performed to provide an objective appraisal of the evidence. Given this limitation, the association should be validated in a large-scale study. A large-scale study has the advantage of estimating the association with high precision, high statistical power and representativeness of the results.

The availability of hearing-related QoL in a large cohort of CI recipients, as in this report, presents an opportunity to investigate this association. In addition, identifying the relationship between tinnitus and hearing-related QoL might be clinically useful to understand the heterogeneity in hearing outcomes in CI recipients and better manage patient's expectations. In this cross-sectional study, we aimed to assess the relationship between hearing-related QoL measured by the 12-item Speech, Spatial and Qualities (SSQ12) questionnaire, the level of tinnitus annoyance measured with a multiple choice question, and the perceived change in the level of tinnitus annoyance produced by cochlear implantation.

Methods

STUDY POPULATION

Data from subjects implanted with a Nucleus® CI512, CI522 and CI532 cochlear implants (Cochlear Limited, Macquarie University, NSW, Australia) were extracted from a post-market patient survey. This survey was designed to capture data on self-reported hearing performance and potential side-effects in cochlear implant users. Subjects were adults aged ≥ 18 years old at time of implantation with at least 1 year of experience using the device. Subjects were grouped by whole years of follow-up.

DATA COLLECTION

The survey was provided digitally through a web-based survey platform, designed by Cochlear Ltd. Registered users of the Nucleus devices who subscribed to a mailing list were invited by email to participate in the voluntary survey between December 2019 and January 2020. Data were collected across seven European countries: France, Germany, Ireland, Italy, the Netherlands, Sweden and the United Kingdom. All materials were translated using a certified translation process[22,23], verified for cultural appropriateness by a native speaker and thereafter provided in the local language of the participant. All participants consented to share their data with Cochlear, and to complete the survey. The data were extracted from the web-based survey platform and anonymized.

SURVEY

The Speech, Spatial, and Qualities of Hearing scale (SSQ) measures hearing-related QoL[24]. For the purposes of the survey, the short form of the SSQ, the SSQ12, was used[25]. It consists of twelve items that cover speech understanding, spatial hearing, and other qualities of sound. Each item is scored using a visual analogue scale ranging from 0 (not at all) to 10 (excellent). The item scores are then averaged to yield an SSQ12 "total" score. Validated versions of the SSQ were used if available in any particular language[26–28].

Next in the survey, tinnitus presence, defined as ringing in the ear, was assessed using a single-item question. Subjects were first asked to report, at the time of the assessment, if they had tinnitus when the CI was active. If they reported tinnitus, they were asked to complete two single-item questions about how bothersome the tinnitus was perceived and how tinnitus changed since implantation. Possible self-reported tinnitus annoyance levels were not at all bothersome; slightly bothersome; quite a bit bothersome; moderately bothersome or extremely bothersome. For those reporting tinnitus, changes in tinnitus annoyance since implantation were assessed using seven different categories: much less bothersome; a little less bothersome; no change; a little more bothersome; much more bothersome; "I don't recall the condition before surgery" and "I did not experience this condition before surgery".

Demographics such as age, gender, time period with implant and unilateral versus bilateral implantation were collected from device registration. There were additional questions in the survey about other potential side effects of cochlear implantation (e.g., dizziness) and magnetic resonance imaging (MRI).

ETHICAL CONSIDERATIONS

The ethics committee of Medizinische Hochschule Hannover (MHH) confirmed on May 2018 that the Medical Research Involving Human Subjects Act did not apply to the study and therefore an ethical waiver was obtained under the number 7896_MPG_23b_K_2018 and no official ethical approval was required. This study was performed according to the declaration of Helsinki. The subjects provided their informed consent to participate in the survey and to use their data after anonymization, which complies with the General Data Protection Regulation (GDPR).

STATISTICAL ANALYSIS

Data analysis was performed using R version 4.1.2 and R Studio version 1.3.1073 (®R Studio). Any normally distributed data were presented as mean and standard deviation (SD). Where data were not normally distributed, data were reported as median and interquartile range (IQR). The distribution of variables was assessed using normal quantile plots.

Fisher's exact or chi-squared tests were used to determine whether the tinnitus prevalence, differed between time with implant (1 year, 2 years and 3 years or more), age groups and between unilateral and bilateral implantation. Jonckheere-Terpstra tests (nonparametric one-way analysis of variance [ANOVA] for ordered alternatives) were used to determine whether the SSQ12 scores increased or decreased significantly between the ordinal tinnitus annoyance categories and change categories.

Linear regression models were developed to assess the association between tinnitus characteristics (self-reported tinnitus absence or presence, self-reported tinnitus annoyance, self-reported tinnitus annoyance change) and the SSQ12 scores. The usual regression assumptions were checked using a normal quantile plot of the residuals and plots of the residuals versus fitted values. Models were constructed with and without an interaction for time with implant and adjusted for age and unilateral versus bilateral implants as covariate factors. ANOVA tests were used to compare nested regression models to determine the significance of adding predictors. Relative importance of predictors was assessed using the Lindeman, Merenda and Gold's (LMG) method available in the relaimpo R package[29]. Tukey pairwise tests were used to determine which pairs of tinnitus characteristics differed in SSQ12 scores. A p-value lower than 0.05 was considered statistically significant.

Results

STUDY POPULATION CHARACTERISTICS

A total of 7387 CI recipients were invited to participate, of which 2322 consented. Table 1 summarizes the study population characteristics. The mean age of the cohort was 57.9 ± 15.7 years, with range 18–95 years. Fifty percent were female and 69.4% were unilaterally implanted.

Table 1. Characteristics of study population.

Characteristics	
Age	
Mean (SD)	57.9 (15.7)
Range	18-95
Gender, n (%)	
Male	1151 (49.6%)
Female	1161 (50.0%)
Missing	10 (0.4%)
Implantation, n (%)	
Unilateral	1612 (69.4%)
Left	484 (20.8%)
Right	498 (21.5%)
Unknown side	630 (27.1%)
Bilateral	695 (30.0%)
Missing	15 (0.6%)
Time with implant, n (%)	
1 year	429 (18.5%)
2 years	522 (22.5%)
3 years or more	1371 (59.0%)

TINNITUS ANNOYANCE PROFILE

Table 2 summarizes tinnitus characteristics. The presence of tinnitus was reported by 33.9% (787/2322) of responders and proportions were similar by time with implant (chi-squared test, p = 0.434, Table 3). A larger proportion of unilateral experienced tinnitus versus bilateral implants (35.5% vs 30.5%, p = 0.023, chi-squared test, Table 2) and the proportion of those with tinnitus differed between age groups (chi-squared test, p = 0.034, Table 4). Of those reporting tinnitus postoperatively, 11.1% (87/787) rated their tinnitus as not at all

bothersome, 59.7% (470/787) considered it slightly or quite a bit bothersome, and 29.2% (230/787) qualified it as moderate to extremely bothersome (Table 2). Among those reporting tinnitus change postoperatively, 44.0% (346/787) of subjects reported a decrease in bothersome tinnitus since implantation and 18.0% (142/787) indicated that tinnitus had become a little or much more bothersome since implantation. No change in tinnitus annoyance since implantation was reported by 25.9% (204/787, Table 2) and 12.0% could not recall experiencing or having tinnitus before implantation.

Figure 1 shows the percentage of each tinnitus annoyance level within perceived change in tinnitus annoyance. A higher proportion of participants with much more post-implantation tinnitus also have more bothersome tinnitus compared to those with less post-implantation tinnitus (Fisher's exact test, $p < 0.001$).

Table 2. Number (%) of subjects reporting tinnitus characteristics by unilateral versus bilateral implants.

	All (*n* = 2322)	**Unilateral (*n* = 1612)**	**Bilateral (*n* = 695)**	**Missing (*n* = 15)**	**p-value**
No tinnitus	1535 (66.1%)	1040 (64.5%)	483 (69.5%)	12 (80.0%)	**0.023**
Tinnitus	787 (33.9%)	572 (35.5%)	212 (30.5%)	3 (20.0%)	
Tinnitus annoyance (*n* = 787)					0.463
Not at all bothersome	87 (11.1%)	65 (11.4%)	22 (10.4%)	0 (0.0%)	
Slightly bothersome	241 (30.6%)	178 (31.1%)	62 (29.2%)	1 (6.6%)	
Quite a bit bothersome	229 (29.1%)	167 (29.2%)	62 (29.2%)	0 (0.0%)	
Moderately bothersome	167 (21.2%)	123 (21.5%)	43 (20.3%)	1 (6.6%)	
Extremely bothersome	63 (8.0%)	39 (6.8%)	23 (10.8%)	1 (6.6%)	
Tinnitus annoyance change (*n* = 787)					0.068
Much less bothersome	153 (19.4%)	110 (19.2%)	42 (19.8%)	1 (33.3%)	
A little less bothersome	193 (24.5%)	144 (25.2%)	48 (22.6%)	1 (33.3%)	
No change	204 (25.9%)	148 (25.9%)	56 (26.4%)	0 (0.0%)	
A little more bothersome	72 (9.2%)	60 (10.5%)	11 (5.2%)	1 (33.3%)	
Much more bothersome	71 (9.0%)	52 (9.1%)	19 (9.0%)	0 (0.0%)	
Don't recall the condition before surgery	33 (4.2%)	19 (3.3%)	14 (6.6%)	0 (0.0%)	
Did not experience this condition before surgery	61 (7.8%)	39 (6.8%)	22 (10.4%)	0 (0.0%)	

P-values are from chi-squared tests comparing unilateral and bilateral (i.e. missing category excluded). Bold indicates statistically significant $p < 0.05$.

Table 3. Number (%) of subjects reporting tinnitus relative to implant experience.

	1 year (*n* = 429)	2 years (*n* = 522)	3 or more years (*n* = 1371)	p-value
No tinnitus	295 (69%)	341 (65%)	899 (66%)	0.434
Tinnitus	134 (31%)	181 (35%)	472 (34%)	

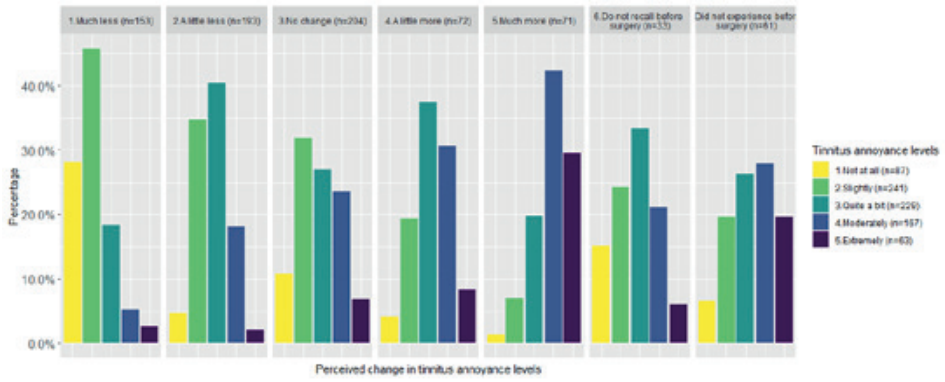
P-value is from a chi-squared test.

Table 4. Number (%) of subjects reporting tinnitus by age group.

	18-34 (*n* = 222)	35-44 (*n* = 214)	45-54 (*n* = 415)	55-64 (*n* = 596)	65-74 (*n* = 549)	75-95 (*n* = 324)	Missing (*n* = 2)	p-value
No tinnitus	162 (73.0%)	143 (66.8%)	273 (65.7%)	366 (61.4%)	367 (66.8%)	224 (69.1%)	0 (0%)	**0.034**
Tinnitus	60 (27.0%)	71 (33.2%)	142 (34.2%)	230 (38.6%)	182 (33.2%)	100 (30.9%)	2 (100%)	

P-value is from a chi-squared test excluding the missing category. Bold indicates statistically significant $p < 0.05$.

Figure 1. Percentage of recipients in each tinnitus annoyance level within perceived change in tinnitus annoyance groups.



The proportion of recipients in each self-reported tinnitus annoyance level differed between perceived change groups (Fisher's exact test, $p < 0.001$).

AGE AND UNILATERAL VERSUS BILATERAL IMPLANTS AS COVARIATES

There was no significant association between time with implant and SSQ12 scores (ANOVA test, F = 0.705, p = 0.49). Older age and unilateral (versus bilateral implants) were significantly associated with lower SSQ12 scores in all models (p < 0.001, Table 5).

Table 5. Multiple regression models of the SSQ12 scores.

Coefficient	Parameter estimate	Standard error	t value	p-value	R^2
Model 0: age and unilateral versus bilateral implants					3.4%
Intercept	5.60	0.18	31.14	**<0.001**	
Age (years)	-0.02	0.01	-5.40	**<0.001**	
Bilateral CI (versus unilateral CI)	0.56	0.10	5.77	**<0.001**	
Model 1: tinnitus presence					5.9%
Intercept	5.85	0.18	32.41	**<0.001**	
Age (years)	-0.02	0.01	-5.44	**<0.001**	
Bilateral CI (versus unilateral CI)	0.53	0.10	5.48	**<0.001**	
Tinnitus presence (versus tinnitus absence)	-0.71	0.09	-7.79	**<0.001**	
Model 2: tinnitus annoyance					8.4%
Intercept	5.84	0.18	32.78	**<0.001**	
Age (years)	-0.02	0.01	-5.51	**<0.001**	
Bilateral CI (versus unilateral CI)	0.55	0.10	5.77	**<0.001**	
Tinnitus level (versus tinnitus absence)					
Not at all bothersome	0.32	0.22	1.44	0.149	
Slightly bothersome	-0.35	0.14	-2.45	**0.015**	
Quite a bit bothersome	-0.90	0.14	-6.23	**<0.001**	
Moderately bothersome	-1.00	0.17	-5.99	**<0.001**	
Extremely bothersome	-2.04	0.26	-7.71	**<0.001**	

Model 3: tinnitus annoyance change					7.8%
Intercept	5.85	0.18	32.66	**<0.001**	
Age (years)	-0.02	0.01	-5.51	**<0.001**	
Bilateral CI (versus unilateral CI)	0.53	0.10	5.58	**<0.001**	
Tinnitus change (versus tinnitus absence)					
Much less bothersome	0.07	0.17	0.39	0.700	
A little less bothersome	-0.64	0.16	-4.10	**<0.001**	
No change	-0.62	0.15	-4.02	**<0.001**	
A little more bothersome	-1.08	0.25	-4.35	**<0.001**	
Much more bothersome	-1.55	0.25	-6.24	**<0.001**	
Don't recall it before surgery	-1.45	0.36	-4.02	**<0.001**	
Did not experience it before surgery	-1.32	0.27	-4.92	**<0.001**	

Bold indicates statistically significant $p < 0.05$.

ASSOCIATION BETWEEN HEARING-RELATED QOL AND TINNITUS STATUS

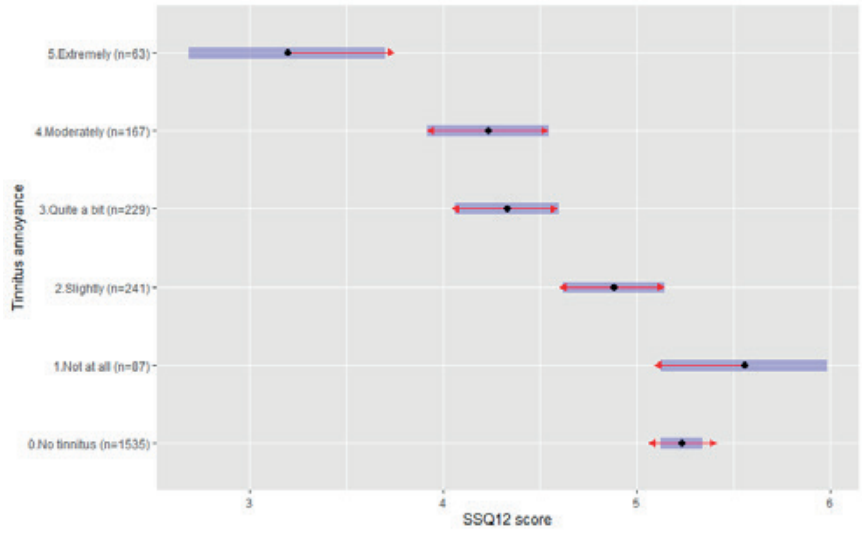
The association between SSQ12 scores and tinnitus presence is presented in Table 5 (Model 1). Recipients with tinnitus had significantly lower SSQ12 scores than recipients without tinnitus (mean difference -0.71 [SD: 0.09], F-test, $p < 0.001$, Figure A1) after adjusting for age and presence of unilateral/bilateral implants. Using tinnitus presence as a predictive factor, Model 1 explained significantly more of the variability in SSQ12 scores compared with the simplest Model 0, using only age and unilateral versus bilateral implants as predictors (Model 0 ($R^2 = 3.4\%$) vs Model 1 ($R^2 = 5.9\%$), ANOVA test, $p < 0.001$, Table 5).

ASSOCIATION BETWEEN HEARING-RELATED QOL AND SELF-REPORTED TINNITUS ANNOYANCE

The association between SSQ12 scores and tinnitus annoyance is presented in Table 5 (Model 2). SSQ12 scores significantly decreased with increased tinnitus annoyance (Jonckheere-Terpstra test, $p < 0.001$, Figure A2). Figure 2 shows Tukey pairwise comparisons of mean SSQ12 scores between annoyance level groups. The mean difference in SSQ12 scores between recipients without tinnitus and recipients rating their tinnitus as not at all bothersome was not significant at only -0.32 (SD: 0.22) (Tukey test, $p = 0.67$, Table A1). Recipients rating their tinnitus as not at all bothersome had significantly higher mean SSQ12 scores than recipients with higher tinnitus annoyance levels (quite a bit bothersome: mean difference 1.23 [SD: 0.26], Tukey test, $p < 0.001$; moderately bothersome:

mean difference 1.32 [SD: 0.27], Tukey test, p < 0.001; extremely bothersome: mean difference 2.36 [SD: 0.34], Tukey test, p < 0.001), except for tinnitus rated as slightly bothersome (Table A1). Mean SSQ12 scores were significantly lower for tinnitus rated as extremely bothersome than for all other tinnitus annoyance levels (Tukey test, p < 0.001, Table A1). Model 2, explained significantly more of the variability in SSQ12 scores compared to Model 0 (Model 0 R^2 = 3.4% vs Model 2 R^2 = 8.4%, ANOVA test, p < 0.001).

Figure 2. SSQ12 scores by tinnitus annoyance levels.



Blue bars are the 95% confidence intervals for the estimated marginal means, the red arrows are for the comparisons among them. If an arrow from one group overlaps with an arrow from another group, the difference is not statistically significant (Tukey tests, p > 0.05).

ASSOCIATION BETWEEN HEARING-RELATED QOL AND PERCEIVED CHANGES IN TINNITUS ANNOYANCE

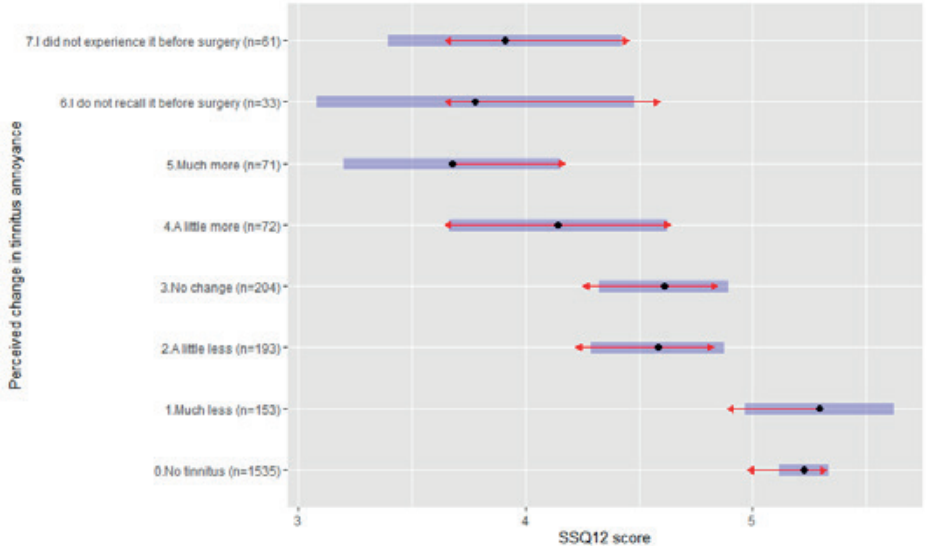
The association between SSQ12 scores and perceived changes in tinnitus annoyance since implantation is presented in Table 5 (Model 3) with Tukey pairwise comparisons shown in Figure 3. SSQ12 scores significantly decreased with increasing perceived changes in tinnitus annoyance (Jonckheere-Terpstra test, *p* < 0.001, Figure A3). Recipients rating their tinnitus as much more bothersome had significantly lower mean SSQ12 scores compared with those

rating their tinnitus as much less bothersome (mean difference -1.62 [SD: 0.29], Tukey test, $p < 0.001$, Table A1). Recipients reporting no change in tinnitus annoyance had significantly higher mean SSQ12 scores than the ones with much more bothersome tinnitus (mean difference 0.93 [SD: 0.28], Tukey test, p = 0.02, Table A1) and significantly lower mean SSQ12 scores than those reporting much less bothersome tinnitus (mean difference -0.68 [SD: 0.22], Tukey test, $p = 0.03$, Table A1). Recipients with post-operative tinnitus who answered "I did not experience it before surgery" had significantly lower mean SSQ12 scores than recipients without post-operative tinnitus (mean difference -1.45 [SD: 0.36], Tukey test, $p = 0.001$, Table A1) and recipients with much less bothersome tinnitus (mean difference -1.38 [SD: 0.32], Tukey test, $p < 0.001$, Table A1). Model 3, using perceived change in tinnitus annoyance as a predictor, explained significantly more of the variance in SSQ12 scores compared with Model 0 (*Model 0* R^2 = 3.4% vs *Model 3* R^2 = 7.8%, ANOVA test, $p < 0.001$).

RELATIVE IMPORTANCE OF PREDICTORS

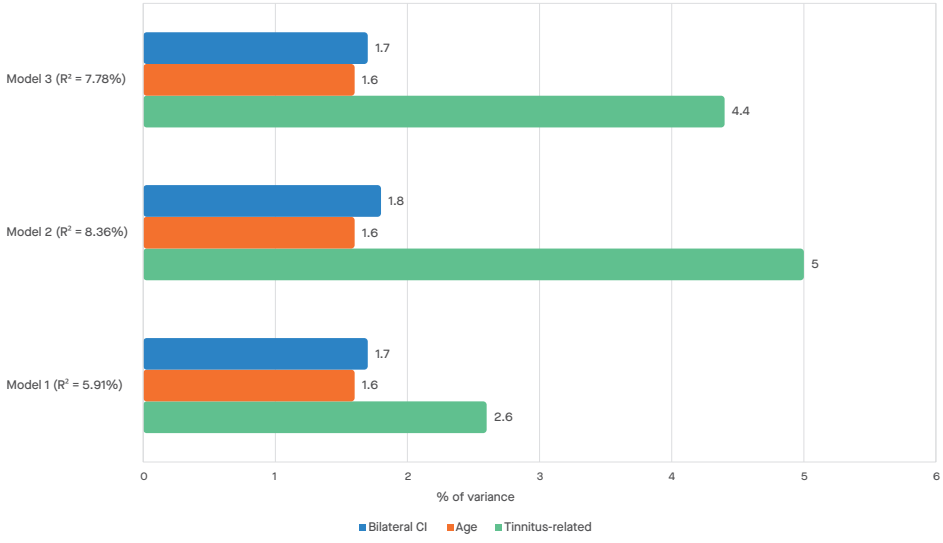
Figure 4 summarizes the relative importance of predictive factors in each model. In the three linear models, the predictor related to tinnitus was always most important: tinnitus presence (2.6% in *Model 1*, LMG method), tinnitus annoyance level (5.0% in *Model 2*, LMG method) or change in tinnitus annoyance (4.4% in *Model 3*, LMG method). Age contributed the least to each model (1.6% in *Model 1, 2* and *3*, LMG method).

Figure 3. SSQ12 scores by perceived changes in tinnitus annoyance.



Blue bars are the 95% confidence intervals for the estimated marginal means, the red arrows are for the comparisons among them. If an arrow from one group overlaps with an arrow from another group, the difference is not statistically significant (Tukey tests, $p > 0.05$).

Figure 4. Relative importance of predictors (% of variance) in Model 1, Model 2, Model 3.



The method used for relative importance is the Lindeman, Merenda and Gold's (LMG) method. R^2 corresponds to the determination coefficient of each model.

Discussion

Our data-driven approach assessed the relationship between the hearing-related QoL, the level of tinnitus annoyance, and also the perceived change in the level of tinnitus annoyance since cochlear implantation in 2322 adult CI recipients. The analysis demonstrated a statistically significant association between hearing-related QoL assessed by the SSQ12 and both tinnitus annoyance and perceived change in tinnitus annoyance at least one year after implantation. Overall, results suggested that CI recipients who experienced bothersome tinnitus showed worse subjective hearing-related QoL; whereas, CI recipients reporting less bothersome tinnitus since implantation had better hearing-related QoL. The SSQ12 scores were also statistically significantly associated with the age of a recipient and presence of unilateral versus bilateral implants (Table 5). Coefficients of determination (R^2) showed that only 8.4% of the variance in SSQ12 scores was explained by age, unilateral versus bilateral implantation and tinnitus annoyance levels combined. Therefore, it is highly likely that other important factors might contribute to the variations in SSQ12 scores.

Tinnitus prevalence was 33.9% in our cohort population, which is lower than the expected 40-54% prevalence found in previous studies on adult CI users[10,19,30]. The variability in tinnitus prevalence in CI users can be explained by a non-response bias in previous studies and variations in tinnitus definition and heterogeneous assessment methods to identify the presence of tinnitus[2,31]. For instance, in our study, the presence of tinnitus was estimated on the basis of a self-report when the CI was active, which may differ from the situation when the CI is off. Indeed, tinnitus presence can vary among CI recipients depending on the CI active status (CI on or CI off)[32–34].

This prevalence significantly varies with age (Table 4), as reported by other authors[2,35–37]. Based on the age group classification used in this study, there was a trend for tinnitus prevalence to increase with age up to 65 years, with 38.6% for the recipients aged between 54 and 65 years, and thereafter reduce for older subject. The same trend was reported by previous studies using different cut offs and age groupings[2,35]. This suggests that tinnitus might not be related to an aging process[38]. However, given the slight differences in proportion of age groups, it is difficult to conclude whether this trend is a true pattern of tinnitus prevalence.

Unilateral CI recipients reported significantly more tinnitus than bilateral CI recipients (Table 2). However, differences in proportion between the two groups is relatively small and questions the relevance of this finding. Moreover,

the distribution of age groups varied significantly between unilateral and bilateral CI recipients (chi-squared test, $p < 0.001$, Table A2). Therefore, age could play a role as a confounding factor. Levels of tinnitus annoyance and change in tinnitus annoyance do not significantly differ between unilateral and bilateral implants. This might suggest that two implants do not bring significant benefit in terms of tinnitus annoyance compared to a single implant. These findings, however, remain hard to interpret without detailed information about the tinnitus percept (e.g. location), pre-implantation tinnitus outcomes and complementary information on recipients' hearing loss profiles.

In our study, we used a validated multi-item questionnaire, the SSQ12, to measure hearing-related QoL[25]. The SSQ12 has no question related to tinnitus. The total score ranges from 0 to 10, with 10 indicating a perfect hearing-related QoL. We found that SSQ12 scores significantly decreased with increasing tinnitus annoyance. A mean difference of 2.36 points in SSQ12 scores was found between CI recipients reporting their tinnitus as not at all bothersome and recipients with extremely bothersome tinnitus, which is more than double the clinically significant change of 1.0 SSQ points suggested by the SSQ developers [24]. A mean difference in SSQ12 scores of the same range (2.55 SSQ12 points) was reported in a study investigating the difference between normal-hearing and hearing-loss groups[39]. Likewise, Wyss et al. showed a statistically significant improvement of 2.2 SSQ12 points at one-year post-implant in 1013 auditory implant recipients[40]. Hence, the difference observed between the two extreme levels in tinnitus annoyance post-implantation showed the same magnitude of difference reported between pre-implantation and one-year post-implantation. The high mean differences found between different levels of tinnitus annoyance raises questions about the importance and the impact of tinnitus on hearing-related QoL in CI recipients, which may need further focus in clinics and exploration in future studies.

This study suggested a negative association between tinnitus and hearing-related QoL. When controlling for age and unilateral versus bilateral implants, mean SSQ12 scores were significantly lower in adult CI recipients with tinnitus than in CI recipients without tinnitus. Furthermore, tinnitus annoyance was also negatively associated with hearing-related QoL. The demonstrated association corresponds with the findings of previous studies investigating perceived tinnitus distress in CI recipients[10,17–19]. In a study from Opperman et al., an increase in perceived tinnitus distress was correlated with a decrease in hearing-related QoL based on the Abbreviated Profile of Hearing Aid Benefit (APHAB) scores[19]. This is in line with our findings on perceived changes in tinnitus annoyance

where CI recipients who experienced less bothersome tinnitus showed better subjective hearing-related QoL. This might be related to the impact of tinnitus on psychological distress such as stress, coping strategies and depressive and anxiety symptoms[41,42], but also its impact on speech perception[43]; that is, both psychological and perceptual factors can affect hearing-related QoL. Moreover, SSQ12 scores were not significantly different between adult CI recipients experiencing tinnitus as not at all bothersome and CI recipients without tinnitus, highlighting the importance of the degree of tinnitus-related distress over the presence of tinnitus. Further research is needed to fully understand the factors involved in this relation and its implications on CI outcomes.

SSQ12 scores significantly decreased with age (Table 5). The age effect on SSQ scores (including short forms) was already observed in other studies examining minimally hearing-impaired subjects[44] or CI recipients[10]. Also, SSQ12 scores were significantly higher for bilateral CI recipients compared to unilateral recipients (Table 5). This association should be further investigated to assess if it could be related to other factors such as the implant side[10,20] or patients' hearing loss characteristics[45].

Based on the linear models, 8.4 % of the variance in SSQ12 scores was explained by the combination of age, unilateral versus bilateral implants and the level of tinnitus annoyance, with the latter being the most important predictor. Tinnitus annoyance and other tinnitus related characteristics deserve further research to understand what the causal relationship of the association is. The other 92% of the variance in SSQ12 scores could be potentially explained by differences in hearing impairment[45,46], in speech perception performance[47], in implant characteristics such as implant side[20] and in cognitive and linguistic factors[10]. The influence of non-auditory aspects, such as education level[45], socioeconomic level or additional comorbidities, should also be considered in explaining the variance in SSQ12 scores. Investigating the above characteristics and then adding the tinnitus variable would be a valuable approach to confirm or temper our findings.

The study cohort is derived from a multi-country database collected in a web-based survey platform. This unique database gathers tinnitus and individual characteristics from a large sample of 2322 Nucleus cochlear implant users. Therefore, the findings of the study are expected to be generalizable to the European adult cochlear implant population.

Some methodological issues in this study are worth considering. The first limitation is that the observational study design was not primarily aimed to study

the effects of tinnitus. Due to limitations in the number of questions and length of the survey, only three questions were used to assess tinnitus characteristics. From the three tinnitus-related questions used, only one sub-domain of the impact of tinnitus was measured, tinnitus annoyance. Indeed, the impact of tinnitus is complex, often associated with comorbidities such as concentration, sleep or mental health problems and impaired quality of life[48]. Since many different domains can be affected by tinnitus, tinnitus validated questionnaires are often multi-item questionnaires containing sub-scales to assess the different domains of the overall impact of tinnitus[49–52]. In this study, only tinnitus annoyance was assessed, and results cannot be generalized to the overall impact of tinnitus nor the effect of cochlear implantation on tinnitus. Further research is needed to investigate the influence of the overall impact of tinnitus on hearing-related QoL using validated multi-item tinnitus questionnaires. Furthermore, the question related to change in tinnitus annoyance addressed past experience, which could present a potential recall bias. In fact, CI recipients were asked to report the perceived change in tinnitus annoyance since implantation, which corresponded to a time interval of 3 years or more for 472 recipients, potentially increasing recall bias even further. Collecting prospective tinnitus outcomes pre-implantation and post-implantation would provide better insights in order to assess the change in tinnitus annoyance since implantation. In fact, the lack of longitudinal data limits the scope of our study to post-implantation tinnitus experience and prevents us from definitively estimating the effect of cochlear implant on tinnitus annoyance between pre- and post-implantation. Nevertheless, the retrospective design ensures that no adaptation process has taken place between the pre- and post-implantation periods by assessing changes at a given point in time and, thus, controlling for response shift[53]. Finally, we did not fully define tinnitus and other terms in the questions and answers[31]. For instance, the options related to the perceived change in tinnitus annoyance "*I did not experience it before surgery*" and "*I don't recall it before surgery*" could both be interpreted as reporting tinnitus newly after implantation. Therefore, these deliberations should be taken with caution since we did not have access to the pre-implantation tinnitus report to validate this interpretation.

Considering the clear association between hearing-related QoL and level of tinnitus annoyance, the identification of accompanying tinnitus should be a requirement in the standard CI candidacy evaluation. Clinicians and CI manufacturers should address tinnitus as an important factor to better manage patients' expectation. This study highlights a need for individualized tinnitus management therapies to be made available within CI counselling

and rehabilitation. Further research is needed to determine the underlying mechanisms and relationships. Another aspect that will require further investigation is whether tinnitus annoyance has a direct impact on CI performance such as speech recognition.

Conclusion

Tinnitus prevalence was 33.9% post-implantation. This prevalence varied with age, with the highest prevalence in middle age. CI recipients with tinnitus had a significantly lower SSQ score than recipients without tinnitus. SSQ scores decreased significantly with increasing level of tinnitus annoyance and age. Overall, CI recipients who experienced less bothersome tinnitus showed better subjective hearing-related QoL. The association of better subjective hearing performance with a positive change in tinnitus annoyance after cochlear implantation should be further explored using a prospective study design and complementary associated factors. Furthermore, healthcare professionals may be well advised to give tinnitus management a higher priority for CI recipients in order for them to maximize their hearing experience.

Data availability

The data that support the findings of this study will be available from the corresponding author, KKSA, upon reasonable request.

Acknowledgements

We would like to thank CI recipients for agreeing to have their data collected for this study. We would also like to thank the Cochlear EMEA clinical team for managing the data capture and compliance.

Author contributions

K.K.S.A., R.A.G.J.A. and C.J. were part of the design of the manuscript. K.K.S.A., P.L.G. and C.J. were part of the design of the statistical analysis. K.K.S.A performed the analysis. K.K.S.A. drafted the manuscript. R.A.G.J.A., P.L.G., B.D. and C.J. substantively revised the work. All authors read and approved the submitted version.

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Competing interests

K.K.S.A. received funding from the European Union's Horizon 2020 research and innovation program under the Marie Sklodowska-Curie grant (agreement number 764604). K.K.S.A. and B.D. are employed at Cochlear Technology Centre Belgium, Mechelen, Belgium. R.A.G.J.A. is employed at Cochlear Benelux NV, Mechelen, Belgium. C.J. is employed at Cochlear France SAS, Toulouse, France. P.L.G. is a paid consultant for Cochlear Europe. No further conflict of interest is reported by the authors.

Appendix

Figure A1. SSQ12 scores by tinnitus status.

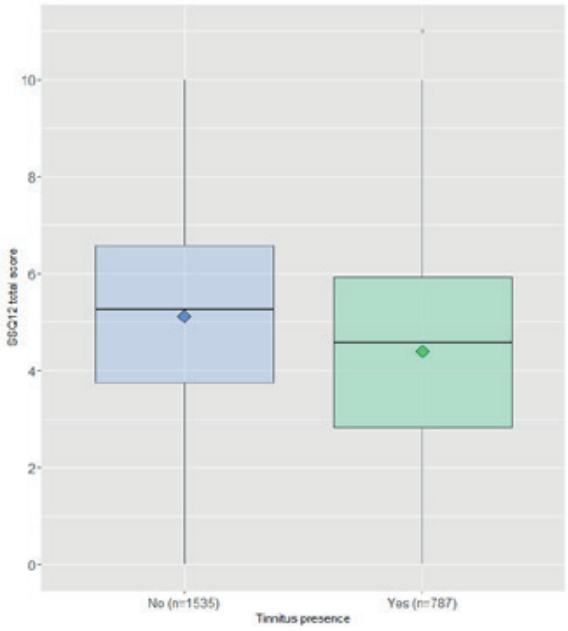

Figure A2. SSQ12 scores by tinnitus annoyance levels.

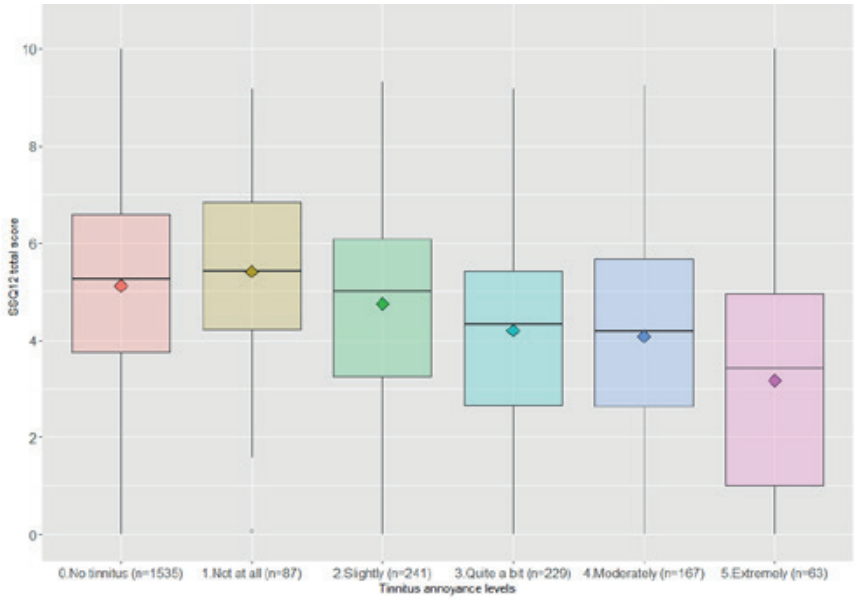

Figure A3. SSQ12 scores by perceived changes in tinnitus annoyance.

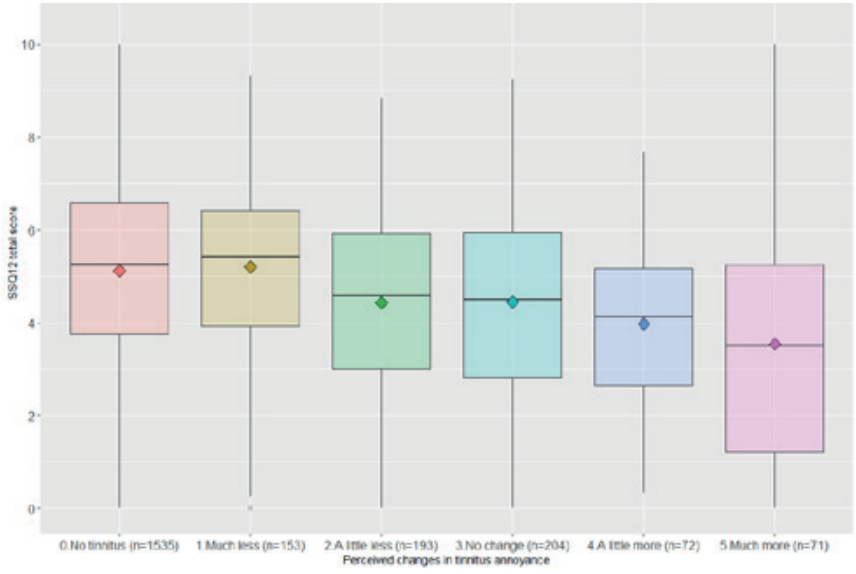

Table A1. Pairwise comparison tests of SSQ total scores between tinnitus annoyance levels and perceived changes in tinnitus annoyance.

Pairwise comparison	Difference estimate	Standard error	t value	p-value
Tinnitus annoyance levels				
No tinnitus – Not at all bothersome	-0.32	0.22	-1.45	0.673
No tinnitus – Slightly bothersome	0.35	0.14	2.45	0.127
No tinnitus – Quite a bit bothersome	0.90	0.14	6.23	**<0.001**
No tinnitus – Moderately bothersome	0.99	0.17	5.99	**<0.001**
No tinnitus – Extremely bothersome	2.04	0.26	7.71	**<0.001**
Not at all bothersome – Slightly bothersome	0.67	0.26	2.63	0.080
Not at all bothersome – Quite a bit bothersome	1.23	0.26	4.77	**<0.001**
Not at all bothersome – Moderately bothersome	1.32	0.27	4.90	**<0.001**
Not at all bothersome – Extremely bothersome	2.36	0.34	6.97	**<0.001**
Slightly bothersome – Quite a bit bothersome	0.55	0.19	2.93	**0.035**
Slightly bothersome – Moderately bothersome	0.65	0.21	3.15	**0.018**
Slightly bothersome – Extremely bothersome	1.69	0.29	5.81	**<0.001**
Quite a bit bothersome – Moderately bothersome	0.10	0.21	0.47	1.00
Quite a bit bothersome – Extremely bothersome	1.13	0.29	3.89	**0.001**
Moderately bothersome – Extremely bothersome	1.04	0.30	3.42	**0.007**

Tinnitus annoyance change				
No tinnitus – Much less bothersome	-0.07	0.17	-0.39	1.00
No tinnitus – A little less bothersome	0.64	0.16	4.10	**<0.001**
No tinnitus – No change	0.61	0.15	4.02	**0.001**
No tinnitus – A little more bothersome	1.08	0.25	4.35	**<0.001**
No tinnitus – Much more bothersome	1.55	0.25	6.24	**<0.001**
No tinnitus – Don't experience it before surgery	1.45	0.36	4.02	**0.001**
No tinnitus – Did not recall it before surgery	1.32	0.27	4.92	**<0.001**
Much less bothersome – A little less bothersome	0.71	0.22	3.20	**0.026**
Much less bothersome – No change	0.68	0.22	3.11	**0.035**
Much less bothersome – A little more bothersome	1.15	0.29	3.91	**0.002**
Much less bothersome – Much more bothersome	1.62	0.29	5.50	**<0.001**
Much less bothersome – Don't experience it before surgery	1.51	0.39	3.85	**0.003**
Much less bothersome – Did not recall it before surgery	1.38	0.31	4.46	**<0.001**
A little less bothersome – No change	-0.03	0.21	-0.13	1.00
A little less bothersome – A little more bothersome	0.44	0.28	1.55	0.752
A little less bothersome – Much more bothersome	0.91	0.28	3.19	**0.027**
A little less bothersome – Don't experience it before surgery	0.80	0.39	2.08	0.390
A little less bothersome – Did not recall it before surgery	0.67	0.30	2.24	0.300
No change – A little more bothersome	0.47	0.28	1.65	0.683
No change– Much more bothersome	0.93	0.28	3.31	**0.018**
No change – Don't experience it before surgery	0.83	0.38	2.16	0.341
No change – Did not recall it before surgery	0.70	0.30	2.34	0.243
A little more bothersome – Much more bothersome	0.47	0.34	1.36	0.854
A little more bothersome – Don't experience it before surgery	0.36	0.43	0.84	0.988
A little more bothersome – Did not recall it before surgery	0.23	0.36	0.65	1.00
Much more bothersome – Don't experience it before surgery	-0.10	0.43	-0.24	1.00
Much more bothersome – Did not recall it before surgery	-0.23	0.36	-0.66	1.00
Don't experience it before surgery – Did not recall it before surgery	-0.13	0.44	-0.30	1.00

P-value is from a Tukey pairwise test. Bold indicates statistically significant $p < 0.05$.

Table A2. Number (%) of unilateral and bilateral CI subjects by age group.

	18-34 (*n* = 222)	**35-44 (*n* = 213)**	**45-54 (*n* = 410)**	**55-64 (*n* = 594)**	**65-74 (*n* = 546)**	**75-95 (*n* = 320)**	**Missing (*n* = 2)**	**p-value**
Unilateral	104 (46.8%)	130 (61.0%)	259 (63.2%)	422 (71.0%)	422 (77.3%)	273 (85.3%)	2 (100%)	**<0.001**
Bilateral	118 (53.1%)	83 (39.0%)	151 (36.8%)	172 (29.0%)	124 (22.7%)	47 (14.7%)	0 (0%)	

P-value is from a chi-squared test excluding the missing category. Bold indicates statistically significant $p < 0.05$.

References

1. Baguley, D. M., McFerran, D. & Hall, D. Tinnitus. in The Lancet (2013). doi:10.1016/S0140-6736(13)60142-7.
2. McCormack, A., Edmondson-Jones, M., Somerset, S. & Hall, D. A systematic review of the reporting of tinnitus prevalence and severity. Hearing Research (2016) doi:10.1016/j.heares.2016.05.009.
3. Kochkin, S., Tyler, R. & Born, J. MarkeTrak VIII: The Prevalence of Tinnitus in the United States and the Self-reported Efficacy of Various Treatments. Hear. Rev. 18, 10–27 (2011).
4. Jarach, C. M. et al. Global Prevalence and Incidence of Tinnitus: A Systematic Review and Meta-analysis. JAMA Neurol. (2022) doi:10.1001/jamaneurol.2022.2189.
5. Stegeman, I. et al. Tinnitus and its associations with general health and hearing loss. Prog. Brain Res. Press. (2021).
6. Nondahl, D. M. et al. Tinnitus and its risk factors in the Beaver Dam Offspring Study. Int. J. Audiol. (2011) doi:10.3109/14992027.2010.551220.
7. Eggermont, J. J. & Roberts, L. E. Tinnitus: animal models and findings in humans. Cell Tissue Res. 361, 311–336 (2015).
8. Baguley, D. M. & Atlas, M. D. Cochlear implants and tinnitus. in Tinnitus: Pathophysiology and Treatment (eds. Langguth, B., Hajak, G., Kleinjung, T., Cacace, A. & Møller, A. R. B. T.-P. in B. R.) vol. 166 347–355 (Elsevier, 2007).
9. Quaranta, N., Wagstaff, S. & Baguley, D. M. Tinnitus and cochlear implantation. International Journal of Audiology vol. 43 245–251 (2004).
10. James, C. J. et al. The Listening Network and Cochlear Implant Benefits in Hearing-Impaired Adults. Front. Aging Neurosci. 13, 1–13 (2021).
11. Assouly, K. K. S., van Heteren, J. A. A., Stokroos, R. J., Stegeman, I. & Smit, A. L. Cochlear implantation for patients with tinnitus - A systematic review. Prog. Brain Res. 260, 27–50 (2021).
12. Peter, N., Liyanage, N., Pfiffner, F., Huber, A. & Kleinjung, T. The Influence of Cochlear Implantation on Tinnitus in Patients with Single-Sided Deafness: A Systematic Review. Otolaryngol. - Head Neck Surg. (2019) doi:10.1177/0194599819846084.
13. Ramakers, G. G. J., Van Zon, A., Stegeman, I. & Grolman, W. The effect of cochlear implantation on tinnitus in patients with bilateral hearing loss: A systematic review. Laryngoscope 125, 2584–2592 (2015).
14. Huang, C. Y. et al. Relationships among speech perception, self-rated tinnitus loudness and disability in tinnitus patients with normal pure-tone thresholds of hearing. ORL (2006) doi:10.1159/000096713.
15. Mertens, G., Kleine Punte, A., De Ridder, D. & Van de Heyning, P. Tinnitus in a single-sided deaf ear reduces speech reception in the nontinnitus ear. Otol. Neurotol. 34, 662–666 (2013).

16. Zeng, F. G., Richardson, M. & Turner, K. Tinnitus does not interfere with auditory and speech perception. J. Neurosci. (2020) doi:10.1523/JNEUROSCI.0396-20.2020.

17. Olze, H. et al. The Impact of Cochlear Implantation on Tinnitus, Stress and Quality of Life in Postlingually Deafened Patients. Audiol. Neurotol. 17, 2–11 (2012).

18. Knopke, S. et al. Cochlear Implantation of Bilaterally Deafened Patients with Tinnitus Induces Sustained Decrease of Tinnitus-Related Distress. Front. Neurol. 8, 1–11 (2017).

19. Opperman, E., le Roux, T., Masenge, A. & Eikelboom, R. H. The effect of tinnitus on hearing-related quality of life outcomes in adult cochlear implant recipients. Int. J. Audiol. 0, 1–9 (2020).

20. Lenarz, T. & Czerniejewska-wolska, H. Patient-Related Benefits for Adults with Cochlear Implantation : A Multicultural Longitudinal Observational Study. Audiol. Neurotol. 22, 61–73 (2017).

21. Le Roux, T. et al. Predictors of health-related quality of life in adult cochlear implant recipients in South Africa Predictors of health-related quality of life in adult cochlear implant recipients in South Africa. Int. J. Audiol. 56, 16–23 (2017).

22. International Organization for Standardization. Quality Management Systems - Requirements (ISO standard no. 9001:2015). https://www.iso.org/obp/ui/#iso:std:iso:9001:ed-5:v1:en (2015).

23. International Organization for Standardization. Quality Management Systems - Requirements (ISO standard no. 17100:2015). https://www.iso.org/fr/standard/59149.html (2015).

24. Gatehouse, S. & Noble, I. The Speech, Spatial and Qualities of Hearing Scale (SSQ). Int. J. Audiol. (2004) doi:10.1080/14992020400050014.

25. Noble, W. et al. A short form of the Speech , Spatial and Qualities of Hearing scale suitable for clinical use: The SSQ12. 52, (2013).

26. Moulin, A., Pauzie, A. & Richard, C. Validation of a French translation of the speech, spatial, and qualities of hearing scale (SSQ) and comparison with other language versions. Int. J. Audiol. 54, 889–898 (2015).

27. Kießling, J., Grugel, L., Meister, H. & Meis, M. Transmission of the questionnaires SADL, ECHO and SSQ into German and their evaluation. Zeitschrift für Audiol. 50, 6–16 (2011).

28. Hua, H., Johansson, B., Jönsson, R. & Magnusson, L. Cochlear implant combined with a linear frequency transposing hearing aid. J. Am. Acad. Audiol. 23, 722–732 (2012).

29. Grömping, U. Relative importance for linear regression in R: The package relaimpo. J. Stat. Softw. 17, 1–27 (2006).

30. Pierzycki, R. H. et al. Tinnitus and Sleep Difficulties after Cochlear Implantation. Ear Hear. (2016) doi:10.1097/AUD.0000000000000341.

31. De Ridder, D. et al. Tinnitus and tinnitus disorder: Theoretical and operational definitions (an international multidisciplinary proposal). in Progress in Brain Research vol. 260 1–25 (Elsevier B.V., 2021).

32. Ahmed, M. F. & Khater, A. Tinnitus suppression after cochlear implantation in patients with single-sided deafness. Egypt. J. Otolaryngol. 33, 61–66 (2017).

33. Ramos Macías, A. et al. Cochlear Implant in Patients With Sudden Unilateral Sensorineural Hearing Loss and Associated Tinnitus. Acta Otorrinolaringol. (English Ed. 63, 15–20 (2012).

34. Mertens, G., De Bodt, M. & Van de Heyning, P. Cochlear implantation as a long-term treatment for ipsilateral incapacitating tinnitus in subjects with unilateral hearing loss up to 10 years. Hear. Res. 331, 1–6 (2016).

35. Al-Swiahb, J. & Park, S. N. Characterization of tinnitus in different age groups: A retrospective review. Noise Health 18, 214–219 (2016).

36. Sharma, A., Sood, N., Munjal, S. & Panda, N. Perception of Tinnitus Handicap And Stress Across Age Groups in Normal Hearing. Int. Tinnitus J. 25, 13–17 (2021).

37. Kim, D. K. et al. Tinnitus in patients with profound hearing loss and the effect of cochlear implantation. Eur. Arch. Oto-Rhino-Laryngology 270, 1803–1808 (2013).

38. Oosterloo, B. C., Croll, P. H., de Jong, R. J. B., Ikram, M. K. & Goedegebure, A. Prevalence of Tinnitus in an Aging Population and Its Relation to Age and Hearing Loss. Otolaryngol. - Head Neck Surg. (United States) 164, 859–868 (2021).

39. Miranda-Gonsalez, E. C. de & Almeida, K. de. Incapacidade auditiva medida por meio do questionário Speech, Spatial and Qualities of Hearing Scale (SSQ): estudo piloto da versão reduzida em Português Brasileiro. Audiol. - Commun. Res. 22, (2017).

40. Wyss, J., Mecklenburg, D. J. & Graham, P. L. Self-assessment of daily hearing function for implant recipients: A comparison of mean total scores for the Speech Spatial Qualities of Hearing Scale (SSQ49) with the SSQ12. Cochlear Implants Int. 21, 167–178 (2020).

41. Andersson, G., Freijd, A., Baguley, D. M. & Idrizbegovic, E. Tinnitus distress, anxiety, depression, and hearing problems among cochlear implant patients with tinnitus. J. Am. Acad. Audiol. (2009) doi:10.3766/jaaa.20.5.5.

42. Brüggemann, P. et al. In Patients Undergoing Cochlear Implantation, Psychological Burden Affects Tinnitus and the Overall Outcome of Auditory Rehabilitation. Front. Hum. Neurosci. 11, 226 (2017).

43. Jagoda, L. et al. Speech perception in tinnitus is related to individual distress level - A neurophysiological study. Hear. Res. 367, 48–58 (2018).

44. Banh, J., Singh, G. & Pichora-Fuller, M. K. Age affects responses on the Speech, Spatial, and Qualities of Hearing Scale (SSQ) by adults with minimal audiometric loss. J. Am. Acad. Audiol. 23, 40–81 (2012).

45. Moulin, A. & Richard, C. Sources of variability of speech, spatial, and qualities of hearing scale (SSQ) scores in normal-hearing and hearing-impaired populations. Int. J. Audiol. 55, 101–109 (2016).

46. Akeroyd, M. A., Guy, F. H., Harrison, D. L. & Suller, S. L. A factor analysis of the SSQ (Speech, spatial, and qualities of hearing scale). Int. J. Audiol. (2014) doi: 10.3109/14992027.2013.824115.

47. Dingemanse, G. & Goedegebure, A. The relation of hearing-specific patient-reported outcome measures with speech perception measures and acceptable noise levels in cochlear implant users. Int. J. Audiol. (2020) doi: 10.1080/14992027.2020.1727033.

48. Tyler, R., Perreauf, A., Mohr, A.-M., Ji, H. & Mancini, P. C. An Exploratory Step Toward Measuring the 'Meaning of Life' in Patients with Tinnitus and in Cochlear Implant Users. J. Am. Acad. Audiol. 31, 277–285 (2020).

49. Meikle, M. B. et al. The tinnitus functional index: Development of a new clinical measure for chronic, intrusive tinnitus. Ear Hear. (2012) doi:10.1097/AUD.0b013e31822f67c0.

50. Newman, C. W., Sandridge, S. A. & Jacobson, G. P. Psychometric adequacy of the Tinnitus Handicap Inventory (THI) for evaluating treatment outcome. J. Am. Acad. Audiol. 9, 153–60 (1998).

51. Wilson, P. H., Henry, J., Bowen, M. & Haralambous, G. Tinnitus reaction questionnaire: psychometric properties of a measure of distress associated with tinnitus. J. Speech Hear. Res. 34, 197–201 (1991).

52. Tyler, R. et al. Development and validation of the tinnitus primary function questionnaire. Am. J. Audiol. 23, 260–272 (2014).

53. Kloostra, F. J. J., Arnold, R., Hofman, R. & Van Dijk, P. Changes in tinnitus after cochlear implantation and its relation with psychological functioning. Audiol. Neurootol. 20, 81–89 (2015).

The impact of tinnitus on adult cochlear implant recipients : *a mixed-method approach*

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Abstract

Background

Tinnitus is a common problem in patients with a cochlear implant (CI). Between 4% and 25% of CI recipients experience a moderate to severe tinnitus handicap. However, apart from handicap scores, little is known about the real-life impact tinnitus has on those with CIs. We aimed to explore the impact of tinnitus on adult CI recipients, situations impacting tinnitus, tinnitus-related difficulties and their management strategies, using a mixed-method approach.

Methods

A 2-week web-based forum was conducted using Cochlear Ltd.'s online platform, Cochlear Conversation. A thematic analysis was conducted on the data from the forum discussion to develop key themes and sub-themes. To quantify themes and sub-themes identified, a survey was developed in English and validated using cognitive interviews, then translated into French, German and Dutch and disseminated on the Cochlear Conversation platform, in six countries (Australia, France, Germany, New Zealand, the Netherlands and United Kingdom). Participants were adult CI recipients experiencing tinnitus who received a Cochlear Ltd. CI after 18 years of age.

Results

Four key themes were identified using thematic analysis of the discussion forum: tinnitus experience, situations impacting tinnitus, difficulties associated with tinnitus and tinnitus management. Among the 414 participants of the developed survey, tinnitus burden on average was a moderate problem without their sound processor and not a problem with the sound processor on. Fatigue, stress, concentration, group conversation and hearing difficulties were the most frequently reported difficulties and was reported to intensify when not wearing the sound processor. For most CI recipients, tinnitus seemed to increase when performing a hearing test, during a CI programming session, or when tired, stressed, or sick. To manage their tinnitus, participants reported turning on their sound processor and avoiding noisy environments.

Conclusion

The qualitative analysis showed that tinnitus can affect everyday life of CI recipients in various ways and highlighted the heterogeneity in their tinnitus experiences. The survey findings extended this to show that tinnitus impact, related difficulties, and management strategies often depend on sound processor use. This exploratory sequential mixed-method study provided a better understanding of the potential benefits of sound processor use, and thus of intracochlear electrical stimulation, on the impact of tinnitus.

Introduction

Tinnitus is the perception of sound in the ears or in the head without an external stimulus, often described as ringing or buzzing in the ears[1]. It can vary in sound perception and location and can also impact people differently. Some experience tinnitus as not bothersome at all, while others experience it as bothersome and debilitating, resulting in a substantial reduction in quality of life[2]. The prevalence of chronic tinnitus ranges between 10 and 15% in the general adult population and is higher among hearing impaired patients[3–5], with up to 80% of tinnitus prevalence in cochlear implant candidates[6].

For those severely affected by hearing loss, a cochlear implant (CI) could be considered, to restore speech perception function. The CI primarily aims to restore hearing by providing electrical stimulation to the auditory nerve. While the primary purpose of cochlear implantation is to restore hearing, systematic reviews showed that tinnitus reduction can be a secondary beneficial effect[7–9]. However, the effect of implantation seems to vary widely between patients, ranging from total tinnitus suppression to tinnitus induction in up to 9% of CI users[6,10]. Recent studies compared tinnitus presence pre- and post-implantation in patients receiving a cochlear implant for severe to profound hearing and showed that tinnitus prevalence decreased post-implantation[10–13]. In these studies, between 34% and 53% of cochlear implant (CI) users still experienced tinnitus after implantation[10–13] and only a small proportion, between 4% and 25%, experienced it as a moderate to severe handicap[14–16].

There is a gap in the literature regarding the impact of tinnitus on CI users' everyday life. In the general population experiencing tinnitus, tinnitus can result in substantial reduction in quality of life and associated emotional and functional difficulties[2]. In CI users, tinnitus could be influenced by the intracochlear electrical stimulation provided by the sound processor, which has shown potential to reduce tinnitus[17]. As shown in studies assessing the effect of CI on tinnitus, the presence and impact of tinnitus seems to differ significantly when wearing the processor or not wearing the processor in CI users experiencing tinnitus[9,18,19]. Several tinnitus questionnaires have been developed and validated to assess different aspects of tinnitus impact in the general population experiencing tinnitus. However, these questionnaires do not address the complexity of tinnitus for CI users.

To better understand how tinnitus impacts CI users in their everyday life, we adopted a mixed-method approach[20]. Using a qualitative phenomenological approach, we aimed to explore the impact of tinnitus on CI users, the difficulties

associated with tinnitus, the situations impacting tinnitus and the tinnitus management strategies. We then developed a survey to quantify how tinnitus impacts CI users, what difficulties are associated with tinnitus, what situations impact tinnitus, and how they manage it. To investigate the influence of the sound processor on tinnitus, a secondary aim was to assess the presence of tinnitus with regards to the sound processor status in this cohort of cochlear implant users.

Methods

STUDY DESIGN

This observational study is based on a mixed-method approach consisting of two parts: (1) an exploratory sequential design involving collecting qualitative exploratory data using a phenomenological approach and (2) using the findings to develop a survey for CI users to quantitatively measure the impact of tinnitus in CI users.

For the purpose of this study, a web-based approach was used to collect qualitatively rich data for a large and diverse pool of CI users[21]. Cochlear Conversation is a web-based platform designed by Cochlear Ltd., offering several discussion forums and surveys on topics related to their CI or bone conduction devices. Members of the platform are Cochlear™ Nucleus®, BAHA® and OSIA® system users who have agreed to the terms and conditions of Cochlear Conversation.

Although a theoretical framework was not explicitly defined a priori, the authors considered the ESIT Framework of variables defining and characterizing tinnitus sub-phenotypes particularly relevant to the current work as it describes the high dimensionality of tinnitus heterogeneity[22]. We followed the Mixed Methods Article Reporting Standards (MMARS) for reporting this study[23].

ETHICAL CONSIDERATIONS

The Central Committee on Research Involving Human Subjects in the Netherlands (CCMO) confirmed that the Medical Research Involving Human Subjects Act did not apply to the study. Therefore, an ethical waiver was obtained. This study was performed according to the declaration of Helsinki. The participants provided informed consent to participate in the forum discussion and the survey and to use their data after anonymization, in compliance with the General Data Protection Regulation (GDPR).

PART 1: FORUM STUDY

Forum design

The forum study relied on prospectively gathered data from the Cochlear Conversation web-based platform. The discussion forum was launched on the Cochlear Conversation platform in four European countries: France, Germany, United Kingdom, and the Netherlands. Registered users of the Cochlear Nucleus implant were invited by email to participate in the discussion forum. The invitation and reminder emails contained a link to the discussion forum website. Participation was on a voluntary basis and all posts were submitted anonymously. The forum discussion was a moderator-led online forum discussion where a moderator encouraged the discussion and participants discussed specific topics through posting a series of messages and commented on each other's post[24]. Every 2 days, the forum opened the discussion, per country, on pre-defined topics: impact of tinnitus on everyday life ('How much are you affected by your tinnitus?',' In what situations does tinnitus most impact your everyday life?'), impact of CI on tinnitus ('How did receiving your cochlear implant affect your tinnitus experience?') and management strategies used to manage tinnitus ('What do you do to manage your tinnitus?') (Figure 1). Each forum per country was moderated by an independent moderator using a flexible moderation style. All moderators were trained by the researcher KKSA about the phenomenological approach and research objectives. Depending on the content of their post, the moderator encouraged participants to elaborate their responses by referring to a pre-defined script, containing a series of questions. Pseudonyms rather than names were used to distinguish individuals, preserving their anonymity.

Forum participants

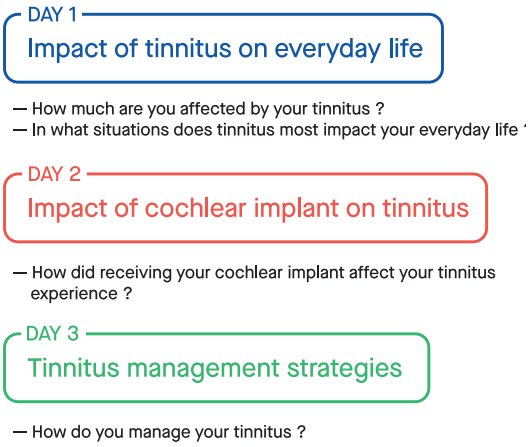
→ Recruitment

Participants were adult CI recipients who received a Cochlear Nucleus implant (Cochlear Ltd., Macquarie University, NSW, Australia) and were registered on the Cochlear Conversation platform. They were invited via email to voluntarily participate in the discussion forum, with the single criterion that they had tinnitus. The level of tinnitus burden patients experience was not used as an inclusion criterion. Before receiving access to the discussion forum, participants provided digital informed consent, agreeing that their data would be anonymized and used for research purposes.

→ Sample size and participant characteristics

Of the 222 participants who consented to participate in this forum study, 136 submitted one or more posts on the discussion forum (55 from France, 33 from Germany, 14 from the Netherlands and 34 from the United Kingdom). The remaining 86 participants joined the forum but did not post in the discussion. To preserve anonymity, we did not collect further demographic information on the participants.

Figure 1. Design of the web-based discussion forum.



The forum opened the discussion on a new topic every two days. Each topic was open for discussion until the forum closed, six days after it opened.

QUALITATIVE ANALYSIS

A qualitative analysis was performed based on the responses from the forum. Responses were clustered into categories using the inductive thematic analysis method described by Braun and Clarke[22]. Authors KKSA and MS familiarized themselves with the messages on the forum by reading and re-reading the data. Codes were then individually created by highlighting manually and making notes on key findings for each of the discussion topic questions. Codes were then refined, by a process of merging and adding to the initial codes. Finally, the codes were discussed between KKSA and MS and any discrepancies were resolved to improve the descriptions of the codes. This was followed by grouping codes with related topic together into categories, developing sub-themes, and finally, into themes using mind maps to illustrate the relationship between the different

themes. The themes were discussed and a final version of the coding manual was agreed upon by the two coders to reflect the tinnitus experiences of the CI users from the data set.

PART 2: SURVEY STUDY

Survey development

A survey in English was developed to quantify the themes: tinnitus impact in adult CI recipients, situations impacting tinnitus, tinnitus related difficulties, and management strategies. The first step of the survey development was the creation of the list of sub-themes emerging from the qualitative analysis of the forum discussion. The number of questions in the survey was determined based on the number of sub-themes derived from descriptive quantitative analysis. To build the survey content, tinnitus validated questionnaires (Tinnitus Functional Index[26], the Tinnitus Handicap Questionnaire[27], Self-Efficacy for Tinnitus Management Questionnaire[28], Sound Sensitive Tinnitus Index[29], Tinnitus Cognitions Questionnaire[30], Tinnitus Reaction Questionnaire[31], Tinnitus Handicap Inventory[32], Tinnitus Questionnaire[33], Tinnitus Primary Function Questionnaire[34], Tinnitus Magnitude Index[35], International Tinnitus Inventory[36], Tinnitus Coping Style Questionnaire[37], Fear of Tinnitus Questionnaire[38], Chronic Tinnitus Acceptance Questionnaire[39], Subjective Tinnitus Severity Scale[40], Tinnitus Acceptance Questionnaire[41], Tinnitus Fear Avoidance Scale[42]) were reviewed to extract already existing questions which were judged to be related to the identified sub-themes. After reviewing the lists of existing questions by sub-themes, two authors (KKSA and MS) chose which question to use for each sub-theme based on their own judgement. Where no question was available to assess a sub-theme, a question was developed.

KKSA and MS refined the survey to harmonize the structure and order of the questions and response options. KKSA and MS also added additional response options to existing questions: “other, please give details”, “don’t know” and “none” in case none of the existing response options were judged to be relevant for the participants. The final version of the survey was presented to the rest of the research team and the content and structure was discussed and further refined based on their input. Any changes required were made after a consensus with all authors. This was done iteratively until a final version was approved.

Survey validity

As the survey contained novel questions and response options, face validity needed to be confirmed. This was done using cognitive interviews. A cognitive

interview is a one-on-one interview, exploring how respondents process information as they complete a questionnaire, detecting problems that respondents may have in understanding survey instructions and in providing responses[43]. For this, CI users registered as volunteers of Cochlear Benelux were invited by email to participate in the cognitive interviews. Participation was on a voluntary basis and the only condition to participate was to experience tinnitus. Before the interview, a list of probing questions was prepared by KKSA. The interview probe is available in the publicly available dataset. During the interview, participants were invited to verbalize their mental process involved in providing responses to each question. The methodology used for the cognitive interviews followed the guidelines by ISPOR[44].

KKSA conducted two cognitive interviews with each of two volunteer CI users experiencing tinnitus. The interviewer, KKSA, had extensive experience of conducting interviews as part of her doctoral studies and had no prior relationship to the interviewees. She carried out the interviews and took notes during and after the interviews. The interviews were not recorded. No personal information was asked during the interviews. The interviews were conducted online with participant verbal consent and lasted between 30 to 60 minutes. The survey was modified based on the first cognitive interviews with each participant after which KKSA conducted a second round with the same participants to validate the changes made and agree on the new version of the survey. The validation of the new version and the absence of further comments from the two participants did not require another round. After validation, the survey was translated from English to French, German and Dutch by external translators, verified for cultural appropriateness by native speakers[45] and disseminated on the Cochlear Conversation platform.

Survey dissemination

Patients willing to participate were asked to complete the 15-minute survey containing questions about their current tinnitus experience, situations impacting tinnitus, difficulties associated with tinnitus, impact of CI on their tinnitus burden and their management strategies. Patient characteristics gender, age range, laterality of implantation, bimodal hearing, and type of hearing loss were collected. No personal identifiable information was collected from the survey. The survey was open from 8 November 2021 to 5 December 2021 and implemented on the Cochlear Conversation platform in the official language of the country in Australia, France, Germany, New Zealand, the Netherlands, and United Kingdom.

Survey participants

→ Recruitment

Participants were adult CI recipients who received a Cochlear™ Nucleus® implant (Cochlear Ltd., Macquarie University, NSW, Australia) and were registered on the Cochlear Conversation platform. They were invited via email to voluntarily participate in the online survey, with the criterion that they currently experience tinnitus. Participants who had already taken part in the discussion forum could also take part in the survey. Therefore, the survey population might, to some extent, overlap with the one of the discussion forum. Before participating, they digitally signed an informed consent agreeing that their data will be anonymized and used for research purposes. A reminder email was also sent 1 week after the first invitation to try maximizing participation.

→ Sample size and participant characteristics

Four-hundred and fourteen participants completed the survey across six countries, Australia: n = 104, France: n = 65, Germany: n = 167, New Zealand: n = 16, the Netherlands: n = 29, United Kingdom: n = 33. About eighty percent (n = 329) of the participants were aged between 65 and 84 years of age, and 54.8% (n = 227) of the participants were female (Table 1). Participants had different hearing profiles, with 87.9% reporting bilateral hearing loss (hearing loss in both ears equally: 43.0% (n = 178); hearing loss in both ears, but in one more than in other: 44.9% (n = 186)) and 12.1% (n = 50) reporting unilateral deafness (Table 1). Forty-four percent (n = 182) were bimodal users, using a CI on one side and a hearing aid on the other side, 26.8% (n = 111) were unilateral CI recipients and 29.2% (n = 121) were bilaterally implanted (Table 1). They reported wearing their sound processor on average 15.0 hours per day (IQR: 13-16, Table 1).

Table 1. Patient demographics.

Demographics	N (%)
Age	
19-24	4 (1.0)
25-49	62 (15.0)
50-64	146 (35.3)
65-84	183 (44.2)
85+	5 (1.2)
Missing	14 (3.4)
Gender	
Male	187 (45.2)
Female	227 (54.8)
Hearing loss type	
Hearing loss in one ear, good hearing in the other ear	50 (12.1)
Hearing loss in both ears equally	178 (43.0)
Hearing loss in both ears, but in one more than in other	186 (44.9)
Device usage	
Unilateral CI stimulation	111 (26.8)
Bilateral CI stimulation	121 (29.2)
Bimodal stimulation	182 (44.0)
Hours wearing the SP per day	
Median (IQR)	15.0 (13.0-16.0)
Range	0-24

IQR: interquartile; N: number of CI recipients; SP: sound processor

Data analysis

Descriptive statistics were performed on the dataset. Proportion were used for categorical or binary variables and median and interquartile (IQR) were used for continuous variables. The main study parameters were the survey outcomes on the following items: tinnitus presence, tinnitus impact, tinnitus related difficulties, situations impacting tinnitus and management strategies use.

Tinnitus presence was measured by a multiple choice question (Q1, Table A1). The effect of CI on tinnitus was measured by two multiple choice questions (Q6-7, Table A1). Tinnitus awareness and annoyance were rated on a numerical scale ranging between 0 "none of the time" to 100 "all of the time" (Q9-10, Table A1).

Tinnitus impact was measured by three multiple choice questions assessing different conditions: in general, when wearing the sound processor, and when not wearing the sound processor. Each question was rated using five impact levels ranging between "not a problem" to "a very big problem" (Q11-13, Table A1).

Difficulties were assessed by 13 questions using visual analogue scales (Q14-26, Table A1). Participants were asked to focus on the difficulties caused by tinnitus, independent of difficulties caused by hearing loss. Each difficulty was rated in two conditions: when wearing the sound processor and when not wearing the sound processor. The rating scale ranged from 0 for "never" to 10 for "always".

Situations impacting tinnitus were assessed by three multiple choice questions using visual analogue scales (Q27-29, Table A1). The first question (Q27, Table A1) assessed 10 situations rated on a numerical scale between 0 "increase tinnitus" and 10 "reduce tinnitus", with 5 corresponding to "no change". The ratings were then grouped into three categories: *increase tinnitus* for all the ratings between 0 and 4, *decrease tinnitus* for all the ratings between 6 and 10 and *no change* for all the ratings of 5. Other situations were depicted by recipients using open field texts (Q28-29, Table A1) and were then grouped into similar themes.

Management strategies use and effect were measured by four multiple choice questions (Q30-33, Table A1). Participants were asked how easy it is to manage tinnitus in general on a numerical scale between 0 "very easy" and 10 "impossible" (Q33, Table A1). Responses provided in the open field text were grouped into similar themes.

The secondary outcome measure was the presence of tinnitus depending on the use of the sound processor, which relied on a multiple-choice question (Q1, Table A1). Fisher tests were performed to assess the difference in the occurrence of difficulties between the two conditions: when wearing the sound processor and when not wearing it. All analyses were performed in R Studio 1.3.1073 (®R Studio). A p-value lower than 0.05 indicated a statistically significant result.

Results

PART 1: FORUM STUDY

Themes derived from forum data

Four key themes were identified from the thematic analysis of the forum: (1) *tinnitus experience,* (2) *situations impacting tinnitus,* (3) *difficulties associated with tinnitus* and (4) *tinnitus management strategies*. The sub-themes and codes emerging from the discussion thread under each main theme are presented in Figure 2 and summarized in S3 Table.

Theme 1: Tinnitus experience

Different degrees of tinnitus awareness and annoyance were reported by the participants (Figure 2). Some participants described the tinnitus as "*a friend*" or "*a music in the head*" which they are aware of without any associated burden. Whereas others characterized their tinnitus as "*uncomfortable*", "*unbearable*" or "*a problem*". Participants reported that tinnitus awareness and annoyance can depend on the sound processor use (*always aware, only bothered when not wearing the sound processor and only aware when not wearing the sound processor*, Figure 2): "*No tinnitus when I have my implant, they are present just after I have unhinged when I go to bed*". According to the participants, tinnitus awareness can also depend on which side was implanted with the CI. Some participants reported tinnitus only on the non-implanted side (*aware in the non-implanted ear*, Figure 2): "*Since implantation on the left ear, almost more tinnitus on the right*".

Theme 2: Situations impacting tinnitus

Overall, six sub-themes related to the key theme *situations impacting tinnitus* emerged from the thematic analysis: *bedtime, environmental change, mental state, physical state, sound environment and sound processor status* (Figure 2). At *bedtime*, CI users felt an increase in tinnitus (*when going to sleep, when sleeping or when waking up*, Figure 2): *"I feel a lot of tinnitus especially before going to bed and getting up in the morning"*. Participants mentioned that changes in their environment affected their tinnitus (*extreme change in weather or change in atmospheric pressure*, Figure 2): *"Stress, noise and, suddenly, extreme changes in weather make tinnitus worse"*.

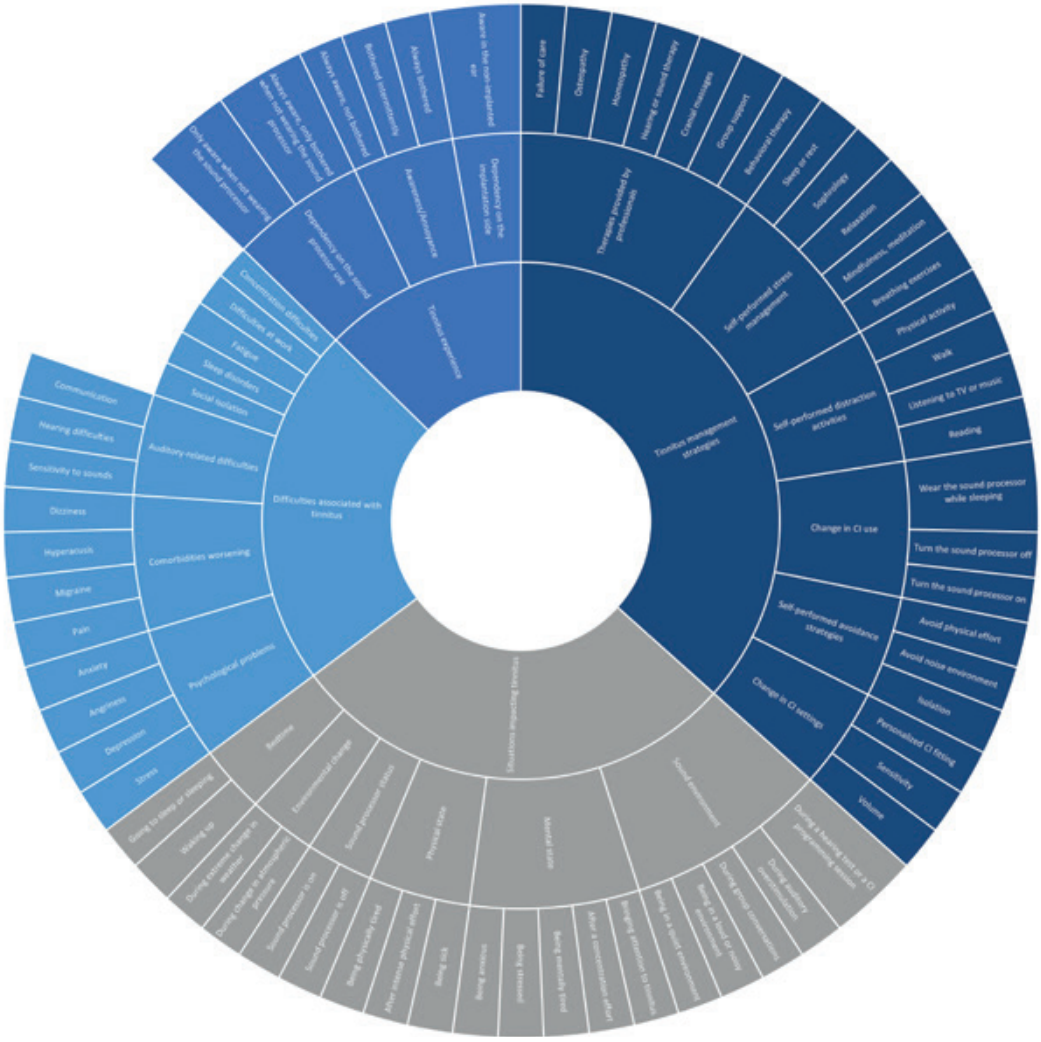
Mental states relating to some form of emotional distress such as *being anxious, stressed, mentally tired* or *after a concentration effort* were answered to have an impact on their tinnitus: *"tinnitus occurs when fatigue occurs"*. For

some participants, focusing on their tinnitus experience made their tinnitus worse (*when bringing attention to tinnitus*, Figure 2): *"The more focused you are on your tinnitus the louder the sound gets"*. Physical states related to *intense physical effort, being physically tired* or *sick* were also listed as situations having an impact on their tinnitus: *"When I jog, I remove my processors and the intense effort created tinnitus"*.

Participants said that tinnitus impact can vary depending on the sound environment. Depending on the individual, tinnitus impact was reported to be worse in presence of sounds (*in loud or noisy environment, during group conversations* or during *auditory overstimulation*, Figure 2): *"tinnitus has developed mainly in a noisy atmosphere"* or in absence of sounds (*in quiet environment*, Figure 2): *"In situations of silence, my tinnitus reappears despite the activated processors".* CI users experiencing tinnitus also mentioned *hearing test* or *CI programming session* as situations that could affect tinnitus impact: *"I have to say that it is enormously strong every time I do hearing tests, specifically the one with the beep. Afterwards my head is buzzing and I can almost only hear noises."*.

CI users reported tinnitus being more present or bothersome when they were not wearing their sound processor (*when the sound processor is off*, Figure 2) and therefore noticed a change in tinnitus impact when they were wearing their sound processor (*when the sound processor is on*, Figure 2): *"Decrease sharply when my implant is activated, always present when I remove my external processor"*.

Figure 2. Themes, sub-themes and codes from the thematic analysis.



Theme 3: Difficulties associated with tinnitus

Participants noted that tinnitus can, to various degrees, cause difficulties in different aspects of their daily life (Figure 2). In addition to hearing loss, *auditory-related problems* appeared to be associated with tinnitus (*hearing difficulties, communication difficulties, sensitivity to sounds*, Figure 2): "tinnitus bothers me to hear and listen to ambient sounds". Other comorbidities such as *dizziness, hyperacusis, migraine* and *pain* were described as created or exacerbated by tinnitus: *"I had to take off the CI as soon as I noticed that the tinnitus was getting stronger. If I didn't do that, dizziness and pain followed, and hearing was especially painful in the high notes."*.

Participants described *concentration difficulties* resulting in fatigue: *"This comes with a lot of fatigue in my daily life."* as well as *difficulties at work: "In online meetings the concentration is lost if tinnitus dominates too much they happen to me to refuse encounters that would put me in difficulty because too embarrassed"*. Participants also mentioned *fatigue* and *sleep disorders* related to their tinnitus: *"At night it just wakes me up and makes sleep difficult again."* Psychological problems such as *anxiety, anger, depression* and *stress* developed or were aggravated by tinnitus: *"I am continually anxious and stressed by this tinnitus."*. Participants who reported situations that could make their tinnitus worse, described *social isolation* due to avoiding such situations: *"Sometimes I isolate myself so that I can be operational again."*.

Theme 4: Tinnitus management strategies

Participants discussed their ways of managing tinnitus, which included strategies varying between self-administrated practices, such as *stress management* or *distraction activities*, to *therapies provided by professionals* (Figure 2).

As CI users, participants reported *turning on* or *off their sound processor* and *changing their CI settings* (*changing volume*, *changing sensitivity*, *having personalized CI fitting*, Figure 2) to manage their tinnitus depending on the situation: "*I mostly unplug my implant and prosthesis when I'm overworked by tinnitus*", "*I had to take my remote control and lower the sensitivity or volume to support*". Discussion on tinnitus management revealed that different strategies were used depending on the time of the day, during the day or at night, and whether they were wearing their sound processor: "*During the day I can largely ignore the tinnitus - it's always there in the background but I am now used to the continual sound, although I would prefer not to have it.*

Initially at night the tinnitus prevented me from sleeping but I began streaming sounds through my processor using the GN Resound App.".

Recipients were able to ignore their tinnitus, although aware of it under certain conditions: "*Mostly I am able to ignore it.*". Most participants said that CI provided sufficient improvement to their tinnitus and don't need further strategies: "*Since having the implant I have simply found that wearing it helps dull the tinnitus and make it more bearable.".* Some participants explained that they tried to avoid situations or environments where tinnitus can get worse (*isolation*, *avoid noisy environment*, *avoid physical effort*, Figure 2): "*I try to be careful to avoid all that is acoustic disturbances that can amplify tinnitus in the left ear*". Other participants mentioned managing their tinnitus by performing activities to distract themselves or manage their stress: "*You have to be able to live with them, to forget them. Daily physical activity (to aerate the brain, to cause physical fatigue that helps you fall asleep). Have a playful intellectual activity that occupies the brain.".*

Some participants reported attending *therapies provided by professionals*, whereas others said they never tried tinnitus therapies: *"I'm afraid I haven't managed to find any other remedies for my tinnitus. I have never been offered any tinnitus therapy*". Some participants reported following *behavioral therapy* or *group support* to learn to deal with their tinnitus: "*I made an initial appointment with a behavior therapist in my area. […] During the therapy I found out together with the therapist what stresses me and how I can deal with it better. […] Over a longer period of time, I have learned to recognize stressful situations early on and to deal with them better. […] In the event of setbacks, the therapist supported me wonderfully and helped me to keep going.*". Participants mentioned the effect of *cranial massages* in reducing tinnitus related distress "*I had a session of cranial massages which was very relaxing and learnt to where to run my fingers to replicate a near massage. It did relax as I mentioned and sleep was easier, although the Tinnitus remained.*". *Hearing or sound therapy* were reported by participants: "*Initially at night the tinnitus prevented me from sleeping but I began streaming sounds through my processor using the GN Resound App*".

Alternatives therapies such as *homeopathy* or *osteopathy* were also mentioned by participants: *"it's osteopathy that's helping me most right now by discouraging my necks and jaws, which are very tense."*. *Failure of care* was also mentioned by participants in the forum: *"I've tried all the usual recommendations such as listening to music & other recorded sounds, meditation, mindfulness, exercise. None really help."*.

PART 2: SURVEY STUDY

TINNITUS CHARACTERISTICS

Table 2 summarizes tinnitus characteristics of the study participants. The presence of tinnitus did not depend on the sound processor use for 68.4% (*n* = 283) of the participants. Among those reporting tinnitus depending on the sound processor use, 29.7% (*n* = 123) had tinnitus only when they were not wearing their sound processor and 1.9% (*n* = 8) had it only when wearing the sound processor. Tinnitus was described as constant by 54.8% (*n* = 227) of participants and intermittent by the other 45.2% (*n* = 187). Tinnitus was unilateral for 24.7% (*n* = 102) of participants (*right ear*: 10.2% (*n* = 42); *left ear*: 14.0% (*n* = 58); *sometimes on the left, sometimes on the right*: 0.5% (*n* = 2)), bilateral for 45.2% (*n* = 166) of participants (*both ears but worse in the right*: 17.4% (*n* = 72); *both ears but worse in the left*: 22.7% (*n* = 94); *both ears equally*: 5.1% (*n* = 21)) and inside the head for 28.0% (*n* = 116) of them (*inside the head*: 25.8% (*n* = 107); *both ears and inside the head*: 1.2% (*n* = 5); *somewhere specific in the head*: 1.0% (*n* = 4)). Participants were aware of their tinnitus 30% (IQR: 10-70) of their time awake and were annoyed on average 20.0% (IQR: 10.0-50.0) of their time awake.

Fourteen percent (*n* = 58) of recipients reported not experiencing tinnitus prior to implantation, 82.4% (*n* = 341) reported having tinnitus pre-implantation and 3.6% (*n* = 15) did not know. No change in tinnitus was noticed between pre and post implantation for 29.5% (*n* = 122) of the recipients and 7.0% (*n* = 29) did not recall change. The other 63.5% (*n* = 263) of recipients reported tinnitus changes post-implantation. Positive changes described by recipients could depend on the sound processor use (*tinnitus got better while wearing the sound processor*: 37.2% (*n* = 154); *tinnitus got better while not wearing the sound processor*: 1.5% (*n* = 6)) or not (*no longer have tinnitus*: 2.4% (*n* = 10); *tinnitus got better*: 2.4% (*n* = 10)). Recipients also accounted for negative changes post-implantation (*tinnitus got worse while wearing the sound processor*: 4.8% (*n* = 20); *tinnitus got worse while not wearing*

the sound processor: 8.7% (*n* = 87); *got tinnitus after implantation*: 10.4% (*n* = 43); *tinnitus got worse*: 2.4% (*n* = 10)). Changes in tinnitus sounds (2.7%, *n* = 11), changes in tinnitus side (0.7%, *n* = 3) or fluctuating changes (*tinnitus got worse after implantation and then got better*: 1.0% (*n* = 4); *better in one side and worse in the other side*: 0.7% (*n* = 3); *sometimes better, sometimes worse*: 0.7% (*n* = 3)) were also described by participants.

Table 2. Tinnitus characteristics.

Tinnitus characteristics	**N (%)**
Tinnitus presence	
It does not depend on my SP use	283 (68.4)
Only when I am wearing my SP	8 (1.9)
Only when I am not wearing my SP	123 (29.7)
Tinnitus type	
Constant: I can always or usually hear it	227 (54.8)
Intermittent: "comes and goes"	187 (45.2)
Tinnitus side	
Right ear	42 (10.2)
Left ear	58 (14.0)
Both ears but worse in the right	72 (17.4)
Both ears but worse in the left	94 (22.7)
Inside the head	107 (25.8)
Somewhere else	33 (8.0)
*Both ears equally **	21 (5.1)
*Both ears and inside the head **	5 (1.2)
*Sometimes on the left, sometimes on the right **	2 (0.5)
*Surrounding me **	1 (0.2)
*Somewhere specific in the head **	4 (1.0)
Don't know	8 (1.9)

Tinnitus awareness	
Median (IQR)	30.0 (10.0-7
Range	0-100
Tinnitus annoyance	
Median (IQR)	20.0 (10.0-5
Range	0-100
Tinnitus pre-implantation	
Yes	341 (82.4)
No	58 (14.0)
Don't know	15 (3.6)
Tinnitus changes post-implantation	
Yes, my tinnitus got better while wearing my SP	154 (37.2)
Yes, my tinnitus got better while not wearing my SP	6 (1.5)
Yes, my tinnitus got worse while wearing my SP	20 (4.8)
Yes, my tinnitus got worse while not wearing my SP	36 (8.7)
Yes, I got tinnitus after my implantation	43 (10.4)
Yes, I no longer have tinnitus	10 (2.4)
Yes, other change	51 (12.3)
*Tinnitus sounds changed **	11 (2.7)
*Tinnitus got better **	10 (2.4)
*Tinnitus got worse **	10 (2.4)
*Tinnitus got worse after implantation and then got better **	4 (1.0)
*Better in one side and worse in the other side **	3 (0.7)
*Tinnitus side changed **	3 (0.7)
*Sometimes better, sometimes worse **	3 (0.7)
*Other **	7 (1.7)
No	122 (29.5)
Don't know	29 (7.0)

IQR: interquartile; N: number of CI recipients; SP: sound processor. Options marked with an asterisk (*) are extracted from an open field question and grouped into similar themes.

TINNITUS IMPACT

Outcomes of pre-implantation tinnitus impact and post-implantation tinnitus impact evaluated when wearing the sound processor, when not wearing the sound processor and in general are shown in Table 3.

Most CI recipients (63.9%, *n* = 218) described their pre-implantation tinnitus as a moderate or a big problem (*moderate problem*: 39.6% (*n* = 135); *a big problem*: 24.3% (*n* = 83)) and 15.8% (*n* = 54) described their tinnitus as a very big problem. In general, post-implantation, a small problem (25.4%, *n* = 105) and a moderate problem (36.5%, *n* = 151) were reported, with 10.1% (*n* = 42) reporting their tinnitus as being not a problem and 7.5% (*n* = 31) reporting it as a very big problem.

When wearing the sound processor, most recipients rated their tinnitus as not a problem (31.9%, *n* = 132) or a small problem (30.9%, *n* = 128), and 10.2% rated it as a big to very big problem (*big problem*: 8.0% (*n* = 33); *very big problem*: 2.2%, *n* = 9). When not wearing the sound processor, most recipients reported having a moderate problem (35.0%, *n* = 145) or a big problem (23.4%, *n* = 97), and a minority qualified their tinnitus as not a problem (6.8%, *n* = 28). There was a statistically significant difference in tinnitus impact between wearing the sound processor and not wearing it (Chi square test, $X^2 = 202.75$, $p < 0.01$).

Table 3. Tinnitus impact.

Tinnitus impact **N (%)**	**Pre-implantation** **(*n* = 341)**	**Post-implantation *General*** **(*n* = 414)**	**Post-implantation *With SP*** **(*n* = 414)**	**Post-implantation *Without SP*** **(*n* = 414)**
Not a problem	10 (2.9)	42 (10.1)	132 (31.9)	28 (6.8)
A small problem	59 (17.3)	105 (25.4)	128 (30.9)	95 (23.0)
A moderate problem	135 (39.6)	151 (36.5)	112 (27.0)	145 (35.0)
A big problem	83 (24.3)	85 (20.5)	33 (8.0)	97 (23.4)
A very big problem	54 (15.8)	31 (7.5)	9 (2.2)	49 (11.8)

N: number of CI recipients; SP: sound processor.

SITUATIONS IMPACTING TINNITUS

Table 4 summarizes the occurrence and rating of situations identified as impacting tinnitus. The most frequently scored situations impacting tinnitus negatively were *when stressed* (90.3% (*n* = 374); described in open field text: 12.3% (*n* = 51)), *when tired* (90.8% (*n* = 376); described in open field text: 2.9% (*n* = 12)), *when sick* (92.5% (*n* = 383)) and *during a hearing test or CI programming session* (90.8% (*n* = 376)). Moreover, the situations *when waking up*, *when sick* and *during a hearing test or CI programming session* had the lowest ratings, with a median of 0.0 (IQR: 0.0-3.0)). With the exception of *when anxious,* which was categorized as not impacting tinnitus by 35.3% (*n* = 146) of participants, all situations were ranked as negatively impacting tinnitus by at least 84.5% participants. For less than a quarter of participants, the most common situations impacting tinnitus positively were *when being in a loud environment* (23.4% (*n* = 97)), *when being in a quiet environment* (12.3% (*n* = 51); described in open field text: 2.2% (*n* = 9)) and *when waking up* (15.6% (*n* = 64)).

Table 4. Situations impacting tinnitus.

Situations affecting tinnitus	N (%)	Median (IQR)
When you wake up		0.0 (0.0-3.0)
Increase tinnitus	350 (84.5)	0.0 (0.0-1.0)
Decrease tinnitus	64 (15.6)	9.0 (8.0-10.0)
No change	0 (0.0)	
When you are tired		1.0 (0.0-3.0)
Increase tinnitus	376 (90.8)	1.0 (0.0-3.0)
Decrease tinnitus	38 (9.2)	8.0 (7.0-9.0)
No change	0 (0.0)	
When you are going to sleep		1.0 (0.0-3.0)
Increase tinnitus	361 (87.2)	0.0 (0.0-2.0)
Decrease tinnitus	53 (12.8)	8.0 (7.0-9.0)
No change	0 (0.0)	
When you are in a quiet environment		1.0 (0.0-3.0)
Increase tinnitus	363 (87.7)	1.0 (0.0-2.5)
Decrease tinnitus	51 (12.3)	8.0 (7.5-10.0)
No change	0 (0.0)	

When you are in a loud environment		1.0 (0.0-4.0)
Increase tinnitus	317 (76.6)	0.0 (0.0-2.0)
Decrease tinnitus	97 (23.4)	8.0 (7.0-9.0)
No change	0 (0.0)	
When you are performing a hearing test or CI programming session		0.0 (0.0-3.0)
Increase tinnitus	376 (90.8)	0.0 (0.0-2.0)
Decrease tinnitus	38 (9.2)	8.0 (7.0-9.0)
No change	0 (0.0)	
After physical effort		1.0 (0.0-3.0)
Increase tinnitus	366 (88.4)	0.0 (0.0-2.0)
Decrease tinnitus	48 (11.6)	8.0 (7.0-9.0)
No change	0 (0.0)	
When you are sick		0.0 (0.0-3.0)
Increase tinnitus	383 (92.5)	0.0 (0.0-2.0)
Decrease tinnitus	31 (7.5)	8.0 (7.0-9.5)
No change	0 (0.0)	
When you are stressed		1.0 (0.0-3.0)
Increase tinnitus	374 (90.3)	0.0 (0.0-2.0)
Decrease tinnitus	40 (9.7)	7.0 (6.0-9.0)
No change	0 (0.0)	
When you are anxious		4.0 (1.0-5.0)
Increase tinnitus	230 (55.5)	2.0 (0.0-3.0)
Decrease tinnitus	38 (9.2)	8.0 (7.0-9.8)
No change	146 (35.3)	
Other situations where tinnitus gets better	148 (35.7)	
*When wearing the SP (and hearing aid) **	37 (8.9)	
*When listening music or other auditory input **	24 (5.8)	
*When being distracted **	21 (5.1)	
*When being relaxed, not stressed **	19 (4.6)	
*When being in a quiet environment **	9 (2.2)	
*When being at rest **	8 (1.9)	
*After physical exercises **	7 (1.7)	

*After physical exercises **	7 (1.7)
*Other situations **	19 (4.6)
Other situations where tinnitus gets worse	182 (44.0)
*When being stressed **	51 (12.3)
*When being in loud/noisy/crowed environment **	36 (8.7)
*When not wearing the SP **	22 (5.3)
*When being in a quiet environment **	15 (3.6)
*When being tired **	12 (2.9)
*When concentrated or doing a mental/listening effort **	11 (2.7)
*When being concerned **	10 (2.4)
*When drinking alcohol or coffee **	7 (1.7)
*After physical exercises **	6 (1.4)
*When falling asleep **	6 (1.4)
*Other situations **	46 (11.1)

IQR: interquartile; CI: cochlear implant; N: number of CI recipients; SP: sound processor.
Each situation was rated according to the scale:
0 Increases tinnitus – 1 – 2 – 3 – 4 –5 No change – 6 – 7 – 8 – 9 – 10 Reduces tinnitus.
The Increase tinnitus group consists of participants rated the situation between 0 and 4.
The Decrease tinnitus group consists of participants rated the situation between 6 and 10.
The No change group corresponds to participants rated the situation equal to 5.
Options marked with an asterisk (*) are extracted from an open field question and grouped into similar themes.

TINNITUS-RELATED DIFFICULTIES

Table 5 summarizes the ratings of participants on the occurrence of 12 tinnitus-related difficulties. Fatigue, group conversation and hearing difficulties were the most frequently reported difficulties when wearing the sound processor, with a median score of 2 out of 10 (*fatigue*: 2.0 (IQR: 0.0 – 4.0); *group conversation*: 2.0 (IQR: 0.0 - 5.0); *hearing difficulties*: 2.0 (IQR: 0.0 - 5.0)). Without sound processor, group conversation and hearing difficulties were the most frequently reported, with a median score of 4, followed by difficulties in listening to radio or TV, concentration difficulties and stress, with a median score of 3. All tinnitus-related difficulties were significantly more present when not wearing the sound processor (Fisher's exact test, p <0.001). Some tinnitus-related difficulties, such as sleep disorders, depressive feeling, anxiety, anger, and difficulties at work, were on average never present while wearing the sound processor

(*sleep disorders*: 0.0 (IQR: 0.0 – 3.0), depressive feeling: 0.0 (IQR: 0.0 – 2.0), anxiety: 0.0 (IQR: 0.0 – 2.0), anger: 0.0 (IQR: 0.0-2.8), difficulties at work: 0.0 (IQR: 0.0 – 3.0)) but appeared when not wearing it (*sleep disorders*: 2.0 (IQR: 0.0 – 6.0), depressive feeling: : 1.0 (IQR: 0.0 – 4.0), anxiety: 1.0 (IQR: 0.0 – 4.0), anger: 1.0 (IQR: 0.0 – 4.0), difficulties at work: 1.0 (IQR: 0.0 – 5.0)). For fatigue, the lowest difference in occurrence between the two conditions was shown, with and without sound processor.

Eighty out of 414 participants (19.3%) mentioned other health problems caused or aggravated by tinnitus (Q26, Table A1). These comorbidities were extracted from an open field question and grouped into similar themes (Table A2). Balance disorders (*n* = 12, 2.9%), depression (*n* = 10, 2.4%), migraine (*n* = 11, 2.7%), hypertension (*n* = 6, 1.4%) and neck pain (*n* = 6, 1.4%) were the most mentioned comorbidities. Although already rated in the previous questions, anxiety (*n* = 6, 1.4%), concentration difficulties (*n* = 3, 0.7%), hearing difficulties (*n* = 2, 0.5%), fatigue (*n* = 10, 2.4%), sleep disorders (*n* = 8, 1.9%) and stress (*n* = 11, 2.7) were also mentioned.

Table 5. Tinnitus-related difficulties with and without sound processor (SP) on.

Difficulties	Median (IQR)	p-value
Sleep disorders		**<0.001**
With SP	0.0 (0.0-3.0)	
Without SP	2.0 (0.0-6.0)	
Fatigue		**<0.001**
With SP	2.0 (0.0-4.0)	
Without SP	2.0 (0.0-7.0)	
Stress		**<0.001**
With SP	1.0 (0.0-4.8)	
Without SP	3.0 (1.0-7.0)	
Depressive feeling		**<0.001**
With SP	0.0 (0.0-2.0)	
Without SP	1.0 (0.0-4.0)	
Anxiety		**<0.001**
With SP	0.0 (0.0-2.0)	
Without SP	1.0 (0.0-4.0)	
Anger		**<0.001**
With SP	0.0 (0.0-2.8)	
Without SP	1.0 (0.0-4.0)	
Concentration		**<0.001**
With SP	1.0 (0.0-4.0)	
Without SP	3.0 (1.0-7.0)	
Work		**<0.001**
With SP	0.0 (0.0-3.0)	
Without SP	1.0 (0.0-5.0)	
Hearing		**<0.001**
With SP	2.0 (0.0-5.0)	
Without SP	4.0 (0.0-9.0)	
Listening radio/TV		**<0.001**
With SP	1.0 (0.0-5.0)	
Without SP	3.0 (0.0-8.0)	

Group conversation		**<0.001**
With SP	2.0 (0.0-5.0)	
Without SP	4.0 (0.0-10.00)	
Social life		**<0.001**
With SP	1.0 (0.0-4.0)	
Without SP	2.0 (0.0-8.0)	

IQR: interquartile; N: number of CI recipients; SP: sound processor; TV: television.
Each difficulty was rated according to the scale:
0 Never – 1 – 2 – 3 – 4 – 5 – 6 – 7 – 8 – 9 – 10 Always
P-values are from Fisher's exact tests between the two conditions: with SP and without SP. Bold indicates statistically significant p<0.05.

TINNITUS MANAGEMENT STRATEGIES

Tinnitus management strategies and techniques adopted by CI recipients are shown in Table 6. They described tinnitus being easier to manage when wearing the sound processor compared to when not wearing it (*with sound processor*: 2.0 (IQR: 0.0-4.0); *without sound processor*: 5.0 (IQR: 2.0-8.0)). Turning on their sound processor was the most successful and used tinnitus strategy during the day, as rated by 32.1% (*n* = 133). Additionally, 8.5% (n = 35) of recipients changed their CI settings. On the other hand, only 8.7% (*n* = 36) turned off their sound processor as a management strategy. To manage their tinnitus during the day, 26.8% (*n* = 111) avoided noisy situations and 20.4% (*n* = 84) avoided silent situations. Activities such physical exercises (25.3%, *n* = 105) and relaxing activities (24.2%, *n* = 101) were rated as improving tinnitus. Finally, 18.9% (*n* = 78) did not use any specific management strategy.

Many recipients did not use tinnitus management strategies at night (46.6% (*n* = 193); described in open field text: 4.3% (*n* = 18)). Among those who had used management strategies at night, 19.6% (*n* = 81) did relaxing activities and 16% (*n* = 66) listened to sound (with SP: 6.8% (*n* = 28); without SP: 7.7% (*n* = 32); described in open field text: 1.5% (*n* = 6)). Despite the manufacturer contra-indications, a few participants reported wearing their sound processor while sleeping and that this led to tinnitus improvement (2.9%, *n* = 12).

Less than a third of participants had tried a treatment provided by healthcare professionals (31.2%, *n* = 129). CI fitting session with an audiologist was the most frequently reported treatment (14.0% (*n* = 58)) and was also rated the most effective (7.0 (IQR: 5.0-9.0)). Additionally, 10.9% (*n* = 45) had drug-based

treatment (9.9% (*n* = 41); described in open field text: 1.0% (*n* = 4)), 7.7% (*n* = 32) had psychological treatment and 3.3% (*n* = 14) tried sound-based treatment (3.1% (*n* = 13); described in open field text: 0.2% (*n* = 1)). Alternative therapies such as homeopathy, supplements, acupuncture, osteopathy were on average reported as not effective, with a median of 5.

Table 6. Tinnitus management strategies and techniques.

Tinnitus management	N (%)	Median (IQR)
Tinnitus management level		
With SP	414 (100.0)	2.0 (0.0-4.0)
Without SP	414 (100.0)	5.0 (2.0-8.0)
Day management strategies/techniques		
Avoid noisy situations	111 (26.8)	7.0 (5.0-9.0)
Avoid silent situations	84 (20.4)	7.0 (6.0-9.0)
Physical exercises	105 (25.3)	7.0 (6.0-9.0)
Relaxing activities	101 (24.4)	8.0 (6.0-9.0)
Turn SP off	36 (8.7)	7.0 (5.0-10.0)
Turn SP on	133 (32.1)	9.0 (8.0-10.0)
Change SP setting	35 (8.5)	7.0 (6.0-9.5)
Change volume *	21 (5.1)	
Change program *	16 (3.9)	
Change microphone sensitivity *	4 (1.0)	
Activate Forward focus *	1 (0.2)	
Use Bluetooth devices *	1 (0.2)	
Other strategy/technique	96 (16.7)	7.0 (5.0-9.0)
Ignore tinnitus *	35 (8.5)	
Distractions *	16 (3.9)	
Listen or create sounds/music *	13 (3.1)	
Avoid and manage stress *	4 (1.0)	
Rest *	4 (1.0)	
Physical movement/position *	4 (1.0)	
Relaxation activities *	3 (0.7)	

*Always wear SP **	2 (0.5)	
Wait for it to go away	2 (0.5)	
*Turn tinnitus into music **	1 (0.2)	
*Avoid noisy situation **	1 (0.2)	
*Turn SP and hearing aid on **	1 (0.2)	
*Turn SP off **	1 (0.2)	
*Change SP settings **	1 (0.2)	
*Drug-based treatment **	1 (0.2)	
*"Strategies do not work" **	3 (0.7)	
No strategy/technique	78 (18.9)	
Night management strategies/techniques		
Listen to sound (without SP)	28 (6.8)	6.0 (5.0-7.0)
Listen to sound (with SP)	32 (7.7)	7.5 (5.8-9.3)
Relaxing activities	81 (19.6)	7.0 (6.0-9.0)
Wear the SP while sleeping	12 (2.9)	8.0 (6.0-10.0)
Other	103 (24.9)	6.0 (5.0-8.0)
*Ignore it **	19 (4.6)	
*Read **	16 (3.9)	
*Mental distraction **	14 (3.4)	
*Breathing exercises **	8 (1.9)	
*Listen to music **	6 (1.5)	
*Take medicines **	6 (1.5)	
*Turn SP on **	4 (1.0)	
*Physical exercises **	2 (0.5)	
*Watch TV **	2 (0.5)	
*Wait to be very tired to sleep **	3 (0.7)	
*No technique/strategy **	18 (4.3)	
No strategy/technique	193 (46.6)	

Tinnitus treatment (previous and current)		
Psychological treatment	32 (7.7)	6.0 (5.0-8.0)
Sound-based treatment	13 (3.1)	6.0 (5.0-7.0)
Drug-based treatment	41 (9.9)	6.0 (5.0-7.0)
Alternative therapies	27 (6.5)	5.0 (5.0-7.5)
Cochlear implant fitting session with an audiologist	58 (14.0)	7.0 (5.0-9.0)
Other	32 (7.7)	5.5 (5.0-8.0)
*Drug-based treatment **	4 (1.0)	
*Relaxation therapies (mindfulness, sophrology) **	3 (0.7)	
*Infusion **	2 (0.5)	
*Sound-based therapy **	1 (0.2)	
*Osteopathy **	1 (0.2)	
*Hypnosis **	1 (0.2)	
*Hyperbaric oxygen therapy **	1 (0.2)	
*Self-performed strategies **	4 (1.0)	
*"Tried everything" **	1 (0.2)	
*No treatment **	14 (3.4)	
No treatment	285 (68.8)	

IQR: interquartile; N: number of CI recipients; SP: sound processor.
Tinnitus management level was rated according to the scale:
0 Very easy – 1 – 2 – 3 – 4 – 5 – 6 – 7 – 8 – 9 – 10 Impossible

Each strategy/technique/treatment was rated according to the scale:
0 Worsens – 1 – 2 – 3 – 4 –5 No change – 6 – 7 – 8 – 9 – 10 Improves
Options marked with an asterisk (*) are extracted from an open field question and grouped into similar themes.

Discussion

In this mixed-method study, we explored the impact of tinnitus on adult CI recipients, situations impacting tinnitus, difficulties associated with tinnitus and their management strategies. The data collected from 136 CI users using a web-based forum discussion showed that tinnitus can affect everyday life of CI users in various ways and highlighted the heterogeneity in their tinnitus experiences. Four themes emerged from the thematic analysis: *tinnitus experience*, *situations impacting tinnitus*, *difficulties associated with tinnitus* and *tinnitus management strategies*. We then developed and conducted a survey in 414 adult CI recipients experiencing tinnitus to assess the themes and sub-themes found in the forum study. While most participants experienced tinnitus independently of the sound processor use, tinnitus was on average perceived as not a problem when wearing the sound processor and a moderate problem when not wearing it. The data collected in the survey highlighted specific situations, difficulties, and management tinnitus strategies, which were often dependent on the sound processor use. The study results highlight the need for further work to explore how to address tinnitus related difficulties identified and how future studies should adapt how they assess tinnitus in CI recipients.

The discussion forum and survey outcomes highlighted the heterogeneity in tinnitus impact on everyday life of CI recipients. Different degrees of tinnitus awareness and annoyance were reported by participants, ranging from *aware but not bothered* to *always bothered* in the discussion forum. This heterogeneity in tinnitus annoyance has also been raised by studies analyzing large databases of CI users, where tinnitus was not a relevant problem in more than 70% of CI users with tinnitus, a moderate problem in around 20% of CI users with tinnitus and a severe or worse problem is less than 10% of CI users[10,15]. Participants did not all report the same difficulties as some had no difficulties associated with tinnitus where others reported several. These differences show that the distress associated with tinnitus is complex and patient specific. Therefore, tinnitus impact cannot be summarized as one common experience in the adult CI population. When exploring tinnitus heterogeneity, it has been suggested by Beukes et al. that subgroups based on tinnitus severity levels should be considered and managed differently[46]. A similar approach could be adopted by clinicians to identify CI users suffering from tinnitus and address their specific needs and associated difficulties.

Most participants experienced tinnitus independently of the sound processor use, but still a third reported having tinnitus only when not wearing the sound processor. This observation outlines the suppression effect on tinnitus of electrical stimulation provided when the sound processor is worn in a third of the participants. However, this effect seems to be patient specific as the other 70% of participants did not report total suppression of tinnitus when wearing their sound processor. Previous studies have shown that electrical stimulation can still reduce tinnitus impact in CI recipients even if it does not completely suppress their tinnitus[10,18,19]. In the current survey, this was assessed using two questions distinguishing tinnitus impact when wearing the sound processor and while not wearing it. Most participants perceived their tinnitus as not a problem or a small problem when wearing their sound processor and as a moderate or big problem without their sound processor. When asked about tinnitus management strategies, one third of recipients reported turning on their sound processor during the day and even a few wore it while sleeping to better manage their tinnitus. Furthermore, difficulties related to tinnitus seem to intensify when not wearing the sound processor. Although not often present according to the low ratings given by the participants, all the difficulties assessed in the survey were significantly more present when not wearing the sound processor. This highlights the limitation of current tinnitus questionnaires, which do not distinguish the two conditions, with or without sound processor. Further work is required to reflect on how future studies including CI recipients should adapt how tinnitus impact is assessed in relation to the status of the sound processor.

The negative impact of hearing tests and CI programming sessions on tinnitus has been clearly reported by many CI recipients. From another perspective, Pierzycki et al. found that 80% of audiologists and 45% of CI recipients reported a negative effect of tinnitus on CI programming, making the programming sessions more difficult and tiresome[47]. They suggested that tinnitus may interfere with the process of refining the CI fitting, mainly because patients may confuse the presented stimuli with their tinnitus, which may challenge the accuracy of the threshold levels set during fitting. By the result of our study, one could reason that the sounds or stimuli presented during hearing tests and CI programming sessions increase tinnitus which could limit the process of CI fitting. This finding is of clinical importance because hearing tests and CI programming sessions remain two essential steps of the CI rehabilitation in order to improve speech perception outcome, the primary intended aim of cochlear implantation.

Further research is required to understand to what extent this impacts hearing outcomes of CI recipients with tinnitus. Nonetheless, when asked about treatment options, recipients rated CI fitting sessions with an audiologist as the most effective option to manage their tinnitus. Further work is needed to better understand how fitting can be optimized both for speech perception and tinnitus reduction and create guidelines for clinical application.

Interestingly, some sub-themes emerging from the forum discussion about tinnitus-related difficulties in CI users coincides with the items from current validated tinnitus impact questionnaires, but not all. Indeed, responses to the open field question in the survey revealed the presence of comorbidities being caused or aggravated by tinnitus in CI recipients (Table A2), such as depressive feelings. In line with our findings, Basso et al. suggested that depression can have a negative effect to hearing-related difficulties and tinnitus impact in the general population experiencing tinnitus[48]. Further work is needed to understand the association and causal relationships between the comorbidities mentioned and tinnitus-related distress in CI recipients. The presence or impact of comorbidities is not assessed by the validated tinnitus questionnaires, whereas they seem to be associated with higher distress in tinnitus patients[46,48,49]. In current clinical practice, asking about comorbidities is not part of diagnostic standards, such as stated by the NICE guidelines on tinnitus developed in 2020[50]. This emphasizes the need for further exploration of essential measurements and diagnostic tools to capture tinnitus-related comorbidities.

It is important to note that 19% of recipients in our studies reported not using any self-performed tinnitus management strategy during the day and 51% not using management strategies at night. Similarly, most participants did not try treatment provided by professionals. Based on the survey question assessing the impact of tinnitus, tinnitus was perceived as a big to very big problem by 28% of recipients in general, by 10.2% of recipients when wearing the sound processor and by 35.2% when not wearing it. These results emphasize that only a small proportion of recipients are seeking help for their tinnitus[10]. Targeting the population still suffering from tinnitus should be a priority to understand and address their needs.

A limitation of the study is that CI recipients suffering from tinnitus might be more inclined to participate in the survey than recipients having tinnitus with minor distress, involving a selection bias. Another limitation in interpreting the study results is a possible recall bias when asking about perceived changes in tinnitus since implantation. The study was restricted to cochlear implants

recipients with a Cochlear Nucleus implant (Cochlear Ltd., Macquarie University, NSW, Australia) and therefore the study population represents only a selection of cochlear implant recipients. However, we do not expect the results with other implant types to be significantly different. Participants presented with different hearing profiles and device configurations, having one or two implants and for some wearing a hearing aid in the other ear. Based on our study, we do not know whether this would have affected the results; future studies may aim to find out. Although participants were instructed to focus only on the difficulties caused by tinnitus, independently of difficulties caused by hearing loss, hearing-related difficulties and psychological problems reported may be due to their associated hearing loss. It can be acknowledged that it is hard to distinguish the difficulties related to the combination of tinnitus and hearing loss. This is also a limitation for our study and for all studies investigating tinnitus impact in CI patients where tinnitus and hearing loss constantly interact with similar factors. The survey was not developed following the COSMIN guidelines[51], mainly because the reliability of the survey was not evaluated. This was beyond the scope of the survey designed in the current study.

To our knowledge, no CI-specific survey has yet been developed to assess the impact of tinnitus on CI recipients in the literature. The mixed-method approach used in our study addressed the gap and identifies the difficulties of CI recipients experiencing tinnitus. The large sample size from six countries around the world depicts a diverse population representative of a typical population of CI recipients with tinnitus. The study provides evidence on the complexity of tinnitus associated with sound processor use and uncovers difficulties and situations associated with tinnitus that are exclusive to CI recipients. The complexity of tinnitus in CI recipients is often not fully addressed by clinicians by fear of unmanageable expectations. Given the findings of our mixed-method study, difficulties and complaints associated with tinnitus should be better identified and understood by clinicians in order to be addressed efficiently.

Conclusion

This study explored the impact of tinnitus on CI recipients. Based on a qualitative analysis, a survey was developed to quantify the items identified (tinnitus presence, tinnitus impact, situations impacting tinnitus, difficulties associated with tinnitus, relationship with CI use, and management strategies). These findings provide insight in the potential benefits of the sound processor use and therefore intracochlear electrical stimulation on tinnitus impact. Clinicians and

industry should focus on the identified difficulties to improve the condition of current and new CI recipients experiencing tinnitus post-implantation.

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Author contributions

KKSA, MS, DH, BvD, ALS and IS conceptualized, designed the study and developed the study protocol. KKSA, MS, DH and ALS contributed to the methodology. IS contributed to the statistical analyses. KKSA and MS contributed to data collection and analyses. KKSA wrote the first version of the manuscript. All authors contributed to the manuscript revision, read and approved the submitted version.

Competing interests

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Data availability statement

The dataset that supports the findings of this study is available in the Supporting Information files.

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Appendix

Table A1. Structure of the developed survey.

	Question	Response type
0	Are you experiencing tinnitus?	Multiple choice (x4)
1a	Do you use a hearing aid?	Binary (yes/no)
1b	[IF YES] On which side do you wear your hearing aid?	Multiple choice (x2)
2	On which side do you wear your sound processor(s)?	Multiple choice (x3)
3	Which type of hearing loss do you have?	Multiple choice (x3)
4	What best describes your tinnitus?	Multiple choice (x2)
5	Where do you hear your tinnitus?	Multiple choice (x7)
6a	Did you have tinnitus before implantation?	Multiple choice (x3)
6b	[IF YES] How much of a problem was your tinnitus before implantation?	Multiple choice (x5)
7a	Did your tinnitus change after implantation?	Multiple choice (x3)
7b	[IF YES] How did it change?	Multiple choice (x7)
8	How many hours per day do you wear your sound processor?	Numerical text
	Please explain if it varies day to day.	Open field text
9	What percentage of your time awake are you consciously AWARE OF your tinnitus?	Numerical rating scale
10	What percentage of your time awake are you ANNOYED by your tinnitus?	Numerical rating scale
11	When you are wearing your sound processor, how much of a problem is your tinnitus?	Multiple choice (x5)
12	When you are not wearing your sound processor, how much of a problem is your tinnitus?	Multiple choice (x5)
13	In general, how much of a problem is your tinnitus?	Multiple choice (x5)
14	Does your tinnitus make it difficult to fall asleep or stay asleep?	Numerical rating scale (x2)
15	Does your tinnitus make you feel tired?	Numerical rating scale (x2)
16	Does your tinnitus make you feel stressed?	Numerical rating scale (x2)
17	Does your tinnitus make you feel depressed?	Numerical rating scale (x2)
18	Does your tinnitus make you feel anxious?	Numerical rating scale (x2)

19	Does your tinnitus make you angry?	Numerical rating scale (x2)
20	Does your tinnitus make it difficult to concentrate?	Numerical rating scale (x2)
21	Does your tinnitus make it difficult to work or perform other tasks such as home maintenance, schoolwork, or caring for children or others?	Numerical rating scale (x2)
22	Does your tinnitus make it difficult to hear clearly?	Numerical rating scale (x2)
23	Does your tinnitus make it difficult to listen to radio or television?	Numerical rating scale (x2)
24	Does your tinnitus make it difficult to follow conversations in a group or in meetings?	Numerical rating scale (x2)
25	Does your tinnitus interfere with your ability to enjoy social activities?	Numerical rating scale (x2)
26	Does your tinnitus cause or aggravate other health problems?	Multiple choice (x3)
27	How do the following situations affect your tinnitus?	Numerical rating scale (x10)
28a	Are there any other situations where your tinnitus gets better?	Binary (yes/no)
28b	[IF YES] Please provide details	Open field text
29a	Are there any other situations where your tinnitus gets worse?	Binary (yes/no)
29b	[IF YES] Please provide details	Open field text
30a	What strategies/techniques do you use to manage your tinnitus during the day?	Multiple choice (x9)
30b	What effect does this strategy/technique have on your tinnitus?	Numerical rating scale
31a	What strategies/techniques do you use to manage your tinnitus when you want to sleep?	Multiple choice (x6)
31b	What effect does this strategy/technique have on your tinnitus?	Numerical rating scale
32a	Which treatments have you had or are currently receiving to manage your tinnitus?	Multiple choice (x7)
32b	What effect does this treatment have on your tinnitus?	Numerical rating scale
33	How easy is it to manage your tinnitus in general	Numerical rating scale (x2)

Table A2. Comorbidities caused or aggravated by tinnitus.

Comorbidities	**N (%)** (*n* = 80)
Anger	1 (1.25)
Anxiety	6 (7.5)
Balance disorders	12 (15.0)
Cold symptoms	3 (3.7)
Concentration difficulties	3 (3.7)
Depression	10 (12.5)
DFNA9 symptoms	1 (1.25)
Fatigue	10 (12.5)
Hearing difficulties	2 (2.5)
Hyperacusis	1 (1.25)
Hypertension	6 (7.5)
Migraine	11 (13.8)
Meniere's attack	2 (2.5)
Muscle tension	1 (1.25)
Neck pain	6 (7.5)
Psychosomatic complaint	1 (1.25)
Personality disorder	1 (1.25)
Sadness	1 (1.25)
Shoulder pain	2 (2.5)
Sleep disorders	8 (10.0)
Social isolation	1 (1.25)
Stress	11 (13.8)
Teeth grinding	1 (1.25)
Temporomandibular joint disorder	1 (1.25)

All comorbidities are extracted from an open field question and grouped into similar themes.

Table A3. Themes, sub-themes and codes from the thematic analysis.

Theme	Sub-themes	Codes
Tinnitus experience	Awareness/Annoyance	Always bothered
		Bothered intermittently
		Always aware, not bothered
	Dependency of the sound processor use	Aways aware, only bothered when not wearing the sound processor
		Only aware when not wearing the sound processor
	Dependency on the implantation side	Aware in the non-implanted ear
Situations impacting tinnitus	Bedtime	When going to sleep or sleeping
		When waking up
	Environmental change	During extreme change in weather
		During change in atmospheric pressure
	Mental state	When being anxious
		When being stressed
		When being mentally tired
		After a concentration effort
		When bringing attention to tinnitus
	Physical state	When being physically tired
		After intense physical effort
		When being sick
	Sound environment	When being in a quiet environment
		When being in a loud or noisy environment
		During a hearing test or a CI programming session
		During group conversations
		During auditory overstimulation
	Sound processor status	When the sound processor is on
		When the sound processor is off
Tinnitus-related difficulties	Auditory-related difficulties	Communication difficulties
		Hearing difficulties
		Sensitivity to sounds
	Comorbidities worsening	Dizziness
		Hyperacusis
		Migraine
		Pain
	Concentration difficulties	

	Difficulties at work	
	Fatigue	
	Sleep disorders	
	Psychological problems	Anxiety
		Angriness
		Depression
		Stress
	Social isolation	
Tinnitus management strategies	Change in CI use	Turn the sound processor on
		Turn the sound processor off
		Wear the sound processor while sleeping
	Change in CI settings	Change volume
		Change sensitivity
		Personalized CI fitting
	Self-performed avoidance strategies	Isolation
		Avoid noise environment
		Avoid physical effort
	Self-performed distraction activities	Reading
		Listening to TV or music
		Walk
		Physical activity
	Self-performed stress management	Breathing exercises
		Mindfulness, meditation
		Relaxation
		Sophrology
		Sleep or rest
	Therapies provided by professionals	Behavioral therapy
		Group support
		Cranial massages
		Hearing or sound therapy
		Homeopathy
		Osteopathy
		Failure of care

References

1. De Ridder, D. et al. Tinnitus and tinnitus disorder: Theoretical and operational definitions (an international multidisciplinary proposal). in Progress in Brain Research vol. 260 1–25 (Elsevier B.V., 2021).
2. Stegeman, I. et al. Tinnitus and its associations with general health and hearing loss. Prog. Brain Res. Press. (2021).
3. McCormack, A., Edmondson-Jones, M., Somerset, S. & Hall, D. A systematic review of the reporting of tinnitus prevalence and severity. Hearing Research (2016) doi:10.1016/j.heares.2016.05.009.
4. Biswas, R. et al. Tinnitus prevalence in Europe: a multi-country cross-sectional population study. Lancet Reg. Heal. - Eur. 12, 100250 (2022).
5. Jarach, C. M. et al. Global Prevalence and Incidence of Tinnitus: A Systematic Review and Meta-analysis. JAMA Neurol. (2022) doi:10.1001/jamaneurol.2022.2189.
6. Quaranta, N., Wagstaff, S. & Baguley, D. M. Tinnitus and cochlear implantation. International Journal of Audiology vol. 43 245–251 (2004).
7. Ramakers, G. G. J., Van Zon, A., Stegeman, I. & Grolman, W. The effect of cochlear implantation on tinnitus in patients with bilateral hearing loss: A systematic review. Laryngoscope 125, 2584–2592 (2015).
8. Peter, N., Liyanage, N., Pfiffner, F., Huber, A. & Kleinjung, T. The Influence of Cochlear Implantation on Tinnitus in Patients with Single-Sided Deafness: A Systematic Review. Otolaryngol. - Head Neck Surg. (2019) doi:10.1177/0194599819846084.
9. Assouly, K. K. S., van Heteren, J. A. A., Stokroos, R. J., Stegeman, I. & Smit, A. L. Cochlear implantation for patients with tinnitus - A systematic review. Prog. Brain Res. 260, 27–50 (2021).
10. Assouly, K. K. S. et al. Analysis of a Cochlear Implant Database: Changes in Tinnitus Prevalence and Distress After Cochlear Implantation. Trends Hear. 26, 23312165221128430 (2022).
11. Pierzycki, R. H. & Kitterick, P. T. Insomnia, Anxiety and Depression in Adult Cochlear Implant Users With Tinnitus. Ear Hear. (2020) doi:10.1097/aud.0000000000000900.
12. James, C. J. et al. The Listening Network and Cochlear Implant Benefits in Hearing-Impaired Adults. Front. Aging Neurosci. 13, 1–13 (2021).
13. Opperman, E., le Roux, T., Masenge, A. & Eikelboom, R. H. The effect of tinnitus on hearing-related quality of life outcomes in adult cochlear implant recipients. Int. J. Audiol. 0, 1–9 (2020).
14. Andersson, G., Freijd, A., Baguley, D. M. & Idrizbegovic, E. Tinnitus distress, anxiety, depression, and hearing problems among cochlear implant patients with tinnitus. J. Am. Acad. Audiol. (2009) doi:10.3766/jaaa.20.5.5.

15. Assouly, K. K. S., Arts, R. A. G. J., Graham, P. L., van Dijk, B. & James, C. J. Influence of tinnitus annoyance on hearing-related quality of life in cochlear implant recipients. Sci. Rep. 12, 14423 (2022).

16. Gomersall, P. A., Baguley, D. M. & Carlyon, R. P. A Cross-Sectional Questionnaire Study of Tinnitus Awareness and Impact in a Population of Adult Cochlear Implant Users. Ear Hear. 40, 135–142 (2019).

17. Assouly, K. K. S. et al. Systematic Review on Intra- and Extracochlear Electrical Stimulation for Tinnitus. Brain Sci. 11, (2021).

18. Ramos Macías, A. et al. One-Year Results for Patients with Unilateral Hearing Loss and Accompanying Severe Tinnitus and Hyperacusis Treated with a Cochlear Implant. Audiol. Neurotol. 23, 8–19 (2018).

19. Mertens, G., De Bodt, M. & Van de Heyning, P. Cochlear implantation as a long-term treatment for ipsilateral incapacitating tinnitus in subjects with unilateral hearing loss up to 10 years. Hear. Res. 331, 1–6 (2016).

20. M. D. Fetters, L. A. Curry, and J. W. Creswell, "Achieving integration in mixed methods designs-principles and practices.," Health Serv. Res., vol. 48, no. 6 Pt 2, pp. 2134–2156, Dec. 2013, doi: 10.1111/1475-6773.12117.

21. D. A. Hall, A. Hibbert, M. Vesala, M. Kerr, and S. Harrison, Web-based discussion forums reveal the person-centered relevance and importance of tinnitus, 1st ed. Elsevier B.V., 2021.

22. E. Genitsaridi, D. J. Hoare, T. Kypraios, and D. A. Hall, "A review and a framework of variables for defining and characterizing tinnitus subphenotypes," Brain Sci., vol. 10, no. 12, pp. 1–21, 2020, doi: 10.3390/brainsci10120938.

23. H. M. Levitt, M. Bamberg, J. W. Creswell, D. M. Frost, R. Josselson, and C. Suárez-Orozco, "Journal article reporting standards for qualitative primary, qualitative meta-analytic, and mixed methods research in psychology: The APA Publications and Communications Board task force report.," Am. Psychol., vol. 73, no. 1, pp. 26–46, Jan. 2018, doi: 10.1037/amp0000151.

24. E. O. Im and W. Chee, "Practical guidelines for qualitative research using online forums.," Comput. Inform. Nurs., vol. 30, no. 11, pp. 604–611, 2012, doi: 10.1097/nxn.0b013e318266cade.

25. V. Braun and V. Clarke, "Using thematic analysis in psychology," Qual. Res. Psychol., vol. 3, no. 2, pp. 77–101, 2006, doi: 10.1191/1478088706qp063oa.1

26. M. B. Meikle et al., "The tinnitus functional index: Development of a new clinical measure for chronic, intrusive tinnitus," Ear Hear., 2012, doi: 10.1097/AUD.0b013e31822f67c0.

27. F. Kuk, "Tinnitus Handicap Questionnaire (THQ)," High Defin. Hear., pp. 17–18, 1990.

28. S. L. Smith and M. Fagelson, "Development of the self-efficacy for tinnitus management questionnaire," J. Am. Acad. Audiol., vol. 22, no. 7, pp. 424–440, 2011, doi: 10.3766/jaaa.22.7.4.

29. B. S. Greenberg and M. C. Carlos, "The sound-sensitive tinnitus index: Psychometric properties of a scale to assess the impact of tinnitus exacerbated by sound," Noise Heal., vol. 21, no. 100, pp. 98–107, 2019, doi: 10.4103/nah.NAH_29_18.

30. P. H. Wilson and J. L. Henry, "Tinnitus cognitions questionnaire: Development and psychometric properties of a measure of dysfunctional cognitions associated with tinnitus," Int. Tinnitus J., vol. 4, no. 1, pp. 23–30, 1998.

31. P. H. Wilson, J. Henry, M. Bowen, and G. Haralambous, "Tinnitus reaction questionnaire: psychometric properties of a measure of distress associated with tinnitus.," J. Speech Hear. Res., vol. 34, no. 1, pp. 197–201, Feb. 1991.

32. C. W. Newman, G. P. Jacobson, and J. B. Spitzer, "Development of the Tinnitus Handicap Inventory," Arch. Otolaryngol. Neck Surg., vol. 122, no. 2, pp. 143–148, Feb. 1996, doi: 10.1001/archotol.1996.01890140029007.

33. R. S. Hallam, TQ Manual of the Tinnitus Questionnaire. London: The Psychological Corporation. 1996.

34. R. Tyler, H. Ji, A. Perreau, S. Witt, W. Noble, and C. Coelho, "Development and validation of the tinnitus primary function questionnaire.," Am. J. Audiol., vol. 23, no. 3, pp. 260–272, Sep. 2014, doi: 10.1044/2014_AJA-13-0014.

35. C. J. Schmidt, R. D. Kerns, S. Griest, S. M. Theodoroff, R. H. Pietrzak, and J. A. Henry, "Toward development of a tinnitus magnitude index," Ear Hear., vol. 35, no. 4, pp. 476–484, 2014, doi: 10.1097/AUD.0000000000000017.

36. V. Kennedy, S. Chéry-Croze, D. Stephens, S. Kramer, H. Thai-Van, and L. Collet, "Development of the International Tinnitus Inventory (ITI): A patient-directed problem questionnaire," Audiol. Med., vol. 3, no. 4, pp. 228–237, 2005, doi: 10.1080/16513860500470474.

37. R. J. Budd and R. Pugh, "Tinnitus coping style and its relationship to tinnitus severity and emotional distress," J. Psychosom. Res., vol. 41, no. 4, pp. 327–335, 1996, doi: 10.1016/S0022-3999(96)00171-7.

38. T. E. Fuller, R. F. F. Cima, E. Van den Bussche, and J. W. S. Vlaeyen, "The Fear of Tinnitus Questionnaire: Toward a Reliable and Valid Means of Assessing Fear in Adults with Tinnitus.," Ear Hear., vol. 40, no. 6, pp. 1467–1477, 2019, doi: 10.1097/AUD.0000000000000728.

39. R. Moschen et al., "Validation of the Chronic Tinnitus Acceptance Questionnaire (CTAQ-I): the Italian version.," Acta Otorhinolaryngol. Ital. organo Uff. della Soc. Ital. di Otorinolaringol. e Chir. Cerv.-facc., vol. 39, no. 2, pp. 107–116, Apr. 2019, doi: 10.14639/0392-100X-2144.

40. J. B. Halford and S. D. Anderson, "Tinnitus severity measured by a subjective scale, audiometry and clinical judgement.," J. Laryngol. Otol., vol. 105, no. 2, pp. 89–93, Feb. 1991, doi: 10.1017/s0022215100115038.

41. V. Westin, S. C. Hayes, and G. Andersson, "Is it the sound or your relationship to it? The role of acceptance in predicting tinnitus impact.," Behav. Res. Ther., vol. 46, no. 12, pp. 1259–1265, Dec. 2008, doi: 10.1016/j.brat.2008.08.008.

42. M. Kleinstäuber, K. Jasper, I. Schweda, W. Hiller, G. Andersson, and C. Weise, "The Role of Fear-Avoidance Cognitions and Behaviors in Patients with Chronic Tinnitus. Cogn Behav Ther. 2013;42(2):84–99.

43. García AA. Cognitive Interviews to Test and Refine Questionnaires. Public Health Nurs. 2011.

43. García AA. Cognitive Interviews to Test and Refine Questionnaires. Public Health Nurs. 2011.

44. Patrick DL, Burke LB, Gwaltney CJ, Leidy NK, Martin ML, Molsen E, et al. Content validity - Establishing and reporting the evidence in newly developed patient-reported outcomes (PRO) instruments for medical product evaluation: ISPOR PRO good research practices task force report: Part 2 - Assessing respondent understanding. Value Heal. 2011;14:978–88.

45. Hall DA, Zaragoza Domingo S, Hamdache LZ, Manchaiah V, Thammaiah S, Evans C, et al. A good practice guide for translating and adapting hearing-related questionnaires for different languages and cultures. Int J Audiol. 2018 Mar;57(3):161–75.

46. Beukes EW, Manchaiah V, Allen PM, Andersson G, Baguley DM. Exploring tinnitus 758 heterogeneity. Prog Brain Res. 2021;260:79–99.

47. Pierzycki RH, Corner C, Fielden CA, Kitterick PT. Effects of Tinnitus on Cochlear Implant Programming. Trends Hear [Internet]. 2019;23:233121651983662. Available from: http://journals.sagepub.com/doi/10.1177/2331216519836624.

48. Basso L, Boecking B, Brueggemann P, Pedersen NL, Canlon B, Cederroth CR, et al. Chapter 3 - Subjective hearing ability, physical and mental comorbidities in individuals with bothersome tinnitus in a Swedish population sample. In: Schlee W, Langguth B, Kleinjung T, Vanneste S, De Ridder DBT-P in BR, editors. Tinnitus - An Interdisciplinary Approach Towards Individualized Treatment: From Heterogeneity to Personalized Medicine [Internet]. Elsevier; 2021. p. 51–78. Available from: https://www.sciencedirect.com/science/article/pii/S0079612320302144

49. Pinto PCL, Marcelos CM, Mezzasalma MA, Osterne FJ V, de Melo Tavares de Lima MA, Nardi AE. Tinnitus and its association with psychiatric disorders: systematic review. J Laryngol Otol. 2014 Aug;128(8):660–4.

50. National Institute for Health and Care Excellence. Tinnitus : assessment and management [Internet]. NICE Guideline 155. 2020. Available from: www.nice.org.uk/guidance/ng155.

51. Gagnier JJ, Lai J, Mokkink LB, Terwee CB. COSMIN reporting guideline for studies on measurement properties of patient-reported outcome measures. Qual Life Res. 2021;30(8):2197–218.

10

Summary and general discussion

The aim of the thesis was to provide high level evidence on the effect of electrical stimulation of the auditory nerve through cochlear implants on tinnitus. Three main research objectives were defined for this thesis :

1. assess the effect of electrical stimulation through a cochlear implant on tinnitus impact
2. investigate the influence of cochlear implant related factors on tinnitus outcomes
3. explore the impact of tinnitus on cochlear implant recipients. This final chapter summarizes the conclusion related to each of the objectives, discusses some limitations encountered and provides suggestions for clinical implications and future directions.

Summary of findings

PART I : EFFECT OF ELECTRICAL STIMULATION THROUGH A COCHLEAR IMPLANT ON TINNITUS

A cochlear implant is a standard treatment for people with severe to profound hearing loss who do not benefit from hearing aids, where reduction in tinnitus distress is observed as a secondary benefit in addition to restoration of hearing function. It is still unclear what the effect of electrical stimulation with a cochlear implant is for patients receiving a cochlear implant for their tinnitus as a primary complaint and not for hearing loss. To fill this gap, the first part of the thesis evaluated the effect of electrical stimulation through a cochlear implant on tinnitus using different study designs. In this part, two different populations were studied : patients receiving a cochlear implant for tinnitus as a primary complaint **(Chapter 2 - 4)** and patients receiving a cochlear implant for hearing loss **(Chapter 5)**.

In **Chapter 2**, we systematically reviewed the literature on the effect of electrical stimulation through a cochlear implant on tinnitus as a primary complaint. The seven studies included reported a statistically significant and clinically relevant tinnitus reduction after implantation. However, all studies concerned only patients with tinnitus as a primary complaint and accompanying single-sided deafness or asymmetrical hearing loss. Moreover, all included studies had small sample sizes and considerable risk of bias. Higher level of evidence is needed before considering cochlear implant as an effective treatment for tinnitus. To overcome the large heterogeneity in the studies, an individual patient data (IPD) meta-analysis will be conducted as a follow-up project of the systematic

review, as described in **Chapter 3**. The IPD meta-analysis will provide a more accurate estimate of treatment efficacy for tinnitus as a primary complaint and help identify individual factors influencing treatment outcomes.

Based on the systematic review, there was no high level of evidence of the effect of intracochlear electrical stimulation as an intervention for primary tinnitus complaint in case of bilateral moderate to severe hearing loss. Therefore, we aimed to design a high-quality study to assess the effect of cochlear implantation on patients with moderate to severe tinnitus and moderate to severe bilateral hearing loss. The highest level of evidence for therapeutic studies is a randomized controlled trial. In **Chapter 4,** we described the study protocol of the ongoing randomized controlled trial, which has been published to improve transparency and avoid publication bias. So far, the trial recruitment has been limited due to strict inclusion criteria based on criteria for hearing loss and mental status and is still ongoing at the University Medical Center Utrecht. Future results will be made accessible in a peer-review open access journal after the completion of the trial.

In the study described in **Chapter 5**, the change in tinnitus prevalence and distress after implantation was assessed in 300 patients receiving cochlear implant(s) for their bilateral severe to profound hearing loss. Tinnitus prevalence decreased from 55.8% pre-operatively to 44.3% post-implantation. However, tinnitus distress was low for most participants after implantation with 93.7% having no to mild tinnitus distress and 6.3% experiencing high levels of distress. Tinnitus associated distress decreased post-implantation, with a cohort population reported on average a “slight” tinnitus handicap pre- and post-implantation. No association was found between the measured tinnitus impact scores at 12 months post-implantation and patient characteristics available in the study. Further research is needed to understand the factors influencing changes in tinnitus.

PART II : INFLUENCE OF COCHLEAR IMPLANT RELATED FACTORS ON TINNITUS OUTCOMES

As shown in **Chapter 5**, in patients receiving a cochlear implant for their hearing loss, changes in tinnitus outcomes are heterogeneous and hardly predictable. In this second part, we investigated two cochlear implant related factors that might influence tinnitus outcomes : electrode array position and electrical stimulation pattern.

In the study described in **Chapter 6**, we found no influence of electrode design or position on tinnitus impact and characteristics in 25 single-sided deaf patients implanted with a cochlear implant. However, this study should be replicated with a bigger sample size before generalizing this result. In **Chapter 7**, we systematically reviewed the effect of intra- and extracochlear electrical stimulation for tinnitus relief. All studies showed subjective tinnitus improvement during or after electrical stimulation using different stimulation patterns. Due to a considerable bias in the included studies, no conclusions could be drawn on the influence of specific electrical stimulation parameters (electrode location, current level, pulse rate, polarity) on tinnitus and how the stimulation pattern could be optimised for tinnitus relief.

PART III : IMPACT OF TINNITUS ON COCHLEAR IMPLANT RECIPIENTS

According to previous literature, still a small proportion of cochlear implant recipients are experiencing moderate to severe tinnitus. Using two different approaches, in the third part of this thesis, we explored the impact of tinnitus on these patients still experiencing tinnitus. In the study described in **Chapter 8**, we analysed a cochlear implant databases of 2322 implanted patients to assess the relationship between tinnitus annoyance and hearing-related quality of life in cochlear implant recipients. In this study, we showed that hearing-related quality of life varied significantly with tinnitus annoyance, age and unilateral versus bilateral implants, where tinnitus annoyance was the most important predictive factor.

To better understand the impact of tinnitus on cochlear implant recipients, we adopted a mixed method approach in **Chapter 9** to explore the impact of tinnitus from a patient point of view. The mixed-method approach consisted of two parts : (1) an exploratory sequential design involving collecting qualitative exploratory data and (2) using the findings to develop a survey for cochlear implant users to quantitatively measure the impact of tinnitus in cochlear implant users. For the qualitative study, a web-based forum discussion was used to collect qualitatively rich data from a large and diverse pool of cochlear implant users. Four themes emerged from the thematic analysis of the forum discussion : tinnitus experience, situations impacting tinnitus, difficulties associated with tinnitus and tinnitus management strategies. We then developed a survey to quantitatively measure the themes emerging from the qualitative study in a large group of cochlear implant users experiencing tinnitus. Four hundred and fourteen participants participated to the developed survey. Thanks to the survey, we showed that tinnitus presence and impact can be

associated with the sound processor use. For most cochlear implant recipients, tinnitus seemed to increase when performing a hearing test or cochlear implant programming session and when being tired, stressed or sick. Difficulties such as fatigue, stress, concentration, group conversation and hearing difficulties were frequently reported and usually intensified when not wearing the sound processor. Further research is needed to understand the complex interaction between the sound processor use and change in tinnitus presence and impact. Finally, clinicians and industry partners should address the different needs of patient identified in the study to improve the condition of current and new cochlear implant recipients who experience tinnitus after implantation.

Clinical implications and future directions

The following section presents suggestions for clinical implications and future directions for the establishment of cochlear implant as a treatment option for tinnitus.

RECOMMENDATIONS FOR FUTURE STUDIES

Appropriate patient selection is one key point to ensure the benefit of cochlear implants for patients with tinnitus. The patient selection in future studies should rely on sufficient hypothesis-driven evidence from prediction models or studies on the effect of electrical stimulation on tinnitus in different subgroups. Based on the available evidence at this stage, subtyping patients at least by hearing profiles and tinnitus severity or impact should be considered in studies to reduce heterogeneity of the study population. Hearing profile distinction could be made based on the ear affected by hearing loss : bilateral hearing loss, asymmetrical hearing loss and unilateral hearing loss, also called single-sided deafness. Tinnitus impact, such as emotional distress, cognitive dysfunction or autonomic arousal leading to behavioural changes and functional disability[1], should always be used to distinguish between patients with different tinnitus-related distress, who may be affected differently by treatment. In **Chapter 2 and 9**, we showed that tinnitus presence, impact and related difficulties in cochlear implant recipients are highly dependent on the use of sound processor(s). Based on this, studies using cochlear implant should always consider providing tinnitus questionnaires in two situations; with and without the sound processor. Overall, researchers and clinicians should be aware of patient subtypes and variability in tinnitus evaluation and consider them when designing a study or counselling patients with tinnitus and hearing loss.

TINNITUS AS A NEW INDICATION FOR COCHLEAR IMPLANTATION

Cochlear implantation may be an effective treatment for patients with severe tinnitus who do not respond to conventional treatments. Currently, the cochlear implant is only labelled as a medical device and reimbursed for severe to profound hearing loss. Despites considerable risk of bias in the included studies, in the systematic review in **Chapter 2**, we found statistically significant and clinically relevant reduction in tinnitus distress in patients with accompanying single-sided deafness and asymmetrical hearing loss. More recently, a randomized controlled trial on the effect of cochlear implantation for single-sided deafness and asymmetrical hearing loss included a cost-utility analysis and showed that cochlear implantation led to significant improvements in quality of life in patients with single-sided deafness and asymmetrical hearing loss, particularly in patients with associated severe tinnitus[2]. In France, these results led to an expansion of cochlear implant indication for patients with single-sided deafness and severe tinnitus. The ongoing research projects described in **Chapter 3** and **Chapter 4** will provide higher level evidence on the effect of electrical stimulation through cochlear implant as a potential treatment option for patients with tinnitus as a primary complaint and accompanying hearing loss. The future results may lead to the expansion of the indication criteria for standard clinical cochlear implant in the Netherlands and other countries. As a further step, a cost-utility analysis should be carried out to demand the reimbursement of this treatment for patients seeking help for tinnitus.

PREDICTING TINNITUS OUTCOMES PRIOR TO IMPLANTATION

Among patients receiving cochlear implant(s) for bilateral severe to profound hearing loss, the effect of electrical stimulation through cochlear implants on tinnitus seems to vary widely. As described in **Chapter 5**, negative effects such as tinnitus induction leading to moderate tinnitus in the most severe case was observed in 9.2% of the cohort and worsening of tinnitus with no more than one degree of severity of distress was reported in 1.3% of the cohort population. To date, it is still unclear why some cochlear implant recipients experience negative effects while the majority of recipients experience positive effects on tinnitus. Few studies have tried to find predictors for having positive or negative effects of tinnitus after cochlear implantation, but no consistent predictive factors were found between studies, partly due to small sample sizes of studies and high risk of bias of the presented models[3–6]. In **Chapter 5**, we could not find association between the self-reported tinnitus

distress at 12 months after implantation and patient characteristics available in the study. Based on the outcomes of **Chapter 6** and **Chapter 7**, electrode position or electrical stimulation patterns were not identified as factors related to tinnitus impact. This could be related to methodological limitations as discussed in **Chapter 6** and **Chapter 7** and the low reporting quality of the included studies in **Chapter 7**. Furthermore, the variability of tinnitus outcomes following cochlear implantation might be associated with several factors such as patient characteristics, hearing characteristics, tinnitus characteristics prior to surgery, mental health characteristics, trauma provoked by the implantation procedure and cochlear implant related factors. With the described IPD meta-analysis in **Chapter 4**, we aim to predict the effect of cochlear implantation on tinnitus in individual patients with tinnitus as a primary complaint. Identifying factors which influence tinnitus changes after implantation will help clinicians to better counsel and manage patient expectations prior to implantation, and even contribute to the better understanding of the suppressing effect of electrical stimulation.

UNDERSTANDING UNDERLYING TINNITUS MECHANISMS THROUGH ELECTRICAL STIMULATION

Knowledge out of studies assessing the effect of electrical stimulation through cochlear implants on tinnitus might also contribute to the understanding of mechanisms underlying tinnitus generation as discussed in **Chapter 7**. The fact that tinnitus can be reduced in the ipsilateral ear but also in the contralateral ear when the cochlear implant is switched on and that tinnitus often comes back when the cochlear implant is switched off brings valuable information on the underlying tinnitus mechanisms. Several research groups such as Eggermont et al. or Knipper et al. used tinnitus reduction through cochlear implants as an argument to support their tinnitus models[7,8]. Therefore, research on electrical stimulation through cochlear implants for tinnitus is of interest to the whole tinnitus research community. Likewise, residual inhibition after electrical stimulation should be further monitored in studies to better understand the mechanisms of actions with the potential to optimize electrical stimulation for tinnitus relief.

PROOF OF PRINCIPLE FOR FUTURE TINNITUS TREATMENT

Electrical stimulation through cochlear implants could be used as a proof of principle for tinnitus relief. Understanding its mechanisms of actions could lead to the development of a tinnitus dedicated device stimulating the auditory nerve without damaging hearing. Indeed, although having the advantage of proximity to stimulate the targeted auditory nerve, an important limitation of cochlear implants is the invasive nature of the electrode array placed inside the cochlea, which presents only limited risk for patients with severe to profound hearing loss for whom damage to the cochlea does not affect their current conditions. The length of the cochlear implant electrode array has been defined with the goal of stimulating the apical regions of the cochlea to restore hearing, whereas a dedicated tinnitus implant could be designed differently, without a long and invasive electrode array. As described in **Chapter 7**, several studies tried to compare the effect of intra- and extracochlear electrical stimulation applied on different stimulated electrode locations or different numbers of activated electrodes on tinnitus without finding a consensus so far. Further research is needed to understand the mechanisms of actions involved in tinnitus suppression and define the requirements for the design of a tinnitus dedicated device that effectively suppresses tinnitus. The development of a less invasive device could offer an acceptable and effective treatment for a broader population of tinnitus sufferers, including patients with normal hearing. The acceptance and long-term effect of such a device must be evaluated before such treatment can be considered as a perspective of tinnitus treatment in normal hearing patients.

PATIENT-CENTRED APPROACH

To date, there is no cure for tinnitus and symptom reduction is the highest achievable goal. This statement to patients could in turn lead to an increase in the psychological burden patients experience[9]. As suggested in **Chapter 9**, difficulties and complaints associated with tinnitus should be better identified and understood by clinicians to be addressed efficiently. A personalized therapy could then be offered depending on patients' needs. For tinnitus help seekers, cochlear implant programming should be guided by the goal of maximizing speech perception abilities as well as reducing tinnitus. There are currently no guidelines on cochlear implant fitting aiming to reduce tinnitus. Further work in collaboration with audiologists is needed to better understand how fitting can be optimized both for speech perception and tinnitus reduction

and create guidelines integrating these findings. By the outcomes of the systematic review in **Chapter 7**, we could not conclude on how the stimulation pattern could be optimised for tinnitus relief. To evaluate the influence of electrical stimulation parameters on tinnitus, a deeper understanding of the mechanisms involved in tinnitus suppression is needed with use of objective measures and more appropriate study designs.

INTERDISCIPLINARY INTERNATIONAL COLLABORATION AS A KEY FOR SUCCESS

This thesis is the result of an international collaboration between industry, clinic and academia. This synergy enables the development of high-quality research projects with an interdisciplinary team that shares the same interest in assessing the potential of electrical stimulation through cochlear implants as a treatment for tinnitus. The content of the thesis could not have been as rich without the exchange of expertise through interdisciplinary international collaboration. The study described in **Chapter 5** resulted from a collaboration with the Ear Science Institute in Australia. The mixed-method approach described in **Chapter 9** was conducted with the collaboration of the University of Nottingham in the United Kingdom and Cochlear Ltd. Given the challenge of collecting large datasets, the collaboration between research centres and the harmonization of findings across independent studies can help to build evidence. The IPD meta-analysis described in **Chapter 4** will result from collaborations and data sharing with research groups conducting studies on the effect of electrical stimulation through cochlear implants on tinnitus. This thesis was also a scientific contribution to the Horizon 2020-funded European consortium TIN-ACT, which aims to understand how fundamental neural mechanisms of tinnitus can be studied in animal models and human tinnitus patients, and how additional research techniques can be used to cure tinnitus. This dynamic and scientific environment enables interdisciplinary and diverse training, as well as fruitful exchanges and collaborations with leading European tinnitus researchers. Establishing multi-centre collaborations with international centres and interdisciplinary actors should be extended to coordinate efforts and accelerate findings. This would help to reach consensus on tinnitus diagnosis and management, establish tinnitus guidelines and finally build a tinnitus patient pathway where all tinnitus patients can find a suitable treatment depending on their profile and needs.

Conclusion

This thesis contributed to a higher level of evidence and a better understanding of the effect of electrical stimulation of the auditory nerve as a treatment option for tinnitus. We have shown that electrical stimulation through cochlear implants showed overall a positive effect on tinnitus in patients with tinnitus as a primary complaint. However, there are several considerations before drawing conclusions on the potential of electrical stimulation through cochlear implants as a viable treatment for tinnitus for patients with accompanying hearing loss. This thesis underlines the importance of patient selection and appropriate tinnitus evaluation after cochlear implantation in research studies and clinical practices. In addition, it contributed to a better understanding of the impact of tinnitus on cochlear implant recipients, which findings can be used to further promote a patient-centred approach. Further research is needed to predict tinnitus outcomes after implantation and ideally to better understand the mechanisms of actions of electrical stimulation. Through collaboration between clinicians, scientists and industrial partners, a curative treatment for tinnitus could be developed through electrical stimulation of the auditory nerve.

References

1. De Ridder, D. et al. Tinnitus and tinnitus disorder : Theoretical and operational definitions (an international multidisciplinary proposal). in Progress in Brain Research vol. 260 1–25 (Elsevier B.V., 2021).
2. Marx, M. et al. Cochlear Implantation and Other Treatments in Single-Sided Deafness and Asymmetric Hearing Loss : Results of a National Multicenter Study Including a Randomized Controlled Trial. Audiol. Neurootol. 26, 414–424 (2021).
3. Dixon, P. R. et al. Predicting Reduced Tinnitus Burden after Cochlear Implantation in Adults. Otol. Neurotol. 41, 196–201 (2020).
4. Ramakers, G. G. J. et al. Development and internal validation of a multivariable prediction model for tinnitus recovery following unilateral cochlear implantation : A cross-sectional retrospective study. BMJ Open 8, 1–9 (2018).
5. Kim, D. K. et al. Prospective, Multicenter Study on Tinnitus Changes after Cochlear Implantation. Audiol. Neurotol. 21, 165–171 (2016).
6. Kloostra, F. J. J., Arnold, R., Hofman, R., Burgerhof, J. G. M. & Dijk, P. Models to predict positive and negative effects of cochlear implantation on tinnitus. Laryngoscope Investig. Otolaryngol. 1–5 (2018) doi :10.1002/lio2.224.
7. Eggermont, J. J. & Kral, A. Somatic memory and gain increase as preconditions for tinnitus : Insights from congenital deafness. Hear. Res. 333, 37–48 (2016).
8. Knipper, M. et al. The neural bases of tinnitus : lessons from deafness and cochlear implants. Journal of Neuroscience vol. 40 7190–7202 (2020).
9. Cima, R. et al. Doctors disagree, patients suffer : The case of heterogeneous tinnitus management across Europe. (2017) doi:doi:10.34894/TISAGC.

Nederlandse samenvatting

De algemene inleiding in **Hoofdstuk 1** geeft een kort overzicht van de definitie van tinnitus, de gevolgen ervan en de huidige beperkingen voor het vinden van een behandeling. Het doel van dit proefschrift was op hoog niveau bewijs te leveren over het effect van elektrische stimulatie van de gehoorzenuw door middel van cochleaire implantaten op tinnitus. Drie belangrijke onderzoeksdoelstellingen werden gedefinieerd voor dit proefschrift:

1. het effect van elektrische stimulatie via cochleaire implantaten op tinnitus beoordelen,

2. de invloed van cochleaire implantaatgerelateerde factoren op de resultaten van tinnitus te onderzoeken,

3. de impact van tinnitus op ontvangers van cochleaire implantaten analyseren.

Het laatste hoofdstuk, **Hoofdstuk 10**, vat de conclusie samen met betrekking tot elk van de doelstellingen, bespreekt enkele beperkingen, en geeft suggesties voor klinische implicaties en toekomstige richtingen.

DEEL I: EFFECT VAN ELEKTRISCHE STIMULATIE VIA EEN COCHLEAIR IMPLANTAAT OP TINNITUS

Een cochleair implantaat is een standaardbehandeling voor mensen met ernstig tot zeer ernstig gehoorverlies die geen baat hebben bij hoortoestellen, met vermindering van de tinnitus-symptomen als secundair voordeel naast het herstel van de hoorfunctie. Het is nog onduidelijk wat het effect is van elektrische stimulatie met een cochleair implantaat voor patiënten die een cochleair implantaat krijgen voor hun tinnitus als primaire klacht en niet voor hun gehoorverlies. Om deze leemte op te vullen werd in het eerste deel van het proefschrift het effect van elektrische stimulatie door middel van cochleaire implantaten op tinnitus geëvalueerd met behulp van verschillende studieopzetten. In dit deel werden twee verschillende populaties bestudeerd: patiënten die een cochleair implantaat kregen voor tinnitus als primaire klacht **(Hoofdstuk 2-4)** en patiënten die een cochleair implantaat kregen voor gehoorverlies **(Hoofdstuk 5)**.

In **Hoofdstuk 2** hebben we de literatuur over het effect van elektrische stimulatie via een cochleair implantaat op tinnitus als primaire klacht systematisch beoordeeld. De zeven geïncludeerde studies rapporteerden een statistisch significante en klinisch relevante vermindering van tinnitus na implantatie. Alle studies includeerden echter alleen patiënten met tinnitus als primaire klacht en

begeleidende enkelzijdige doofheid of asymmetrisch gehoorverlies. Bovendien hadden alle geïncludeerde studies een kleine steekproefomvang en een aanzienlijk risico op vertekening. Er is meer bewijs nodig voordat cochleair implantaat wordt beschouwd als een effectieve behandeling voor tinnitus. Om de grote heterogeniteit in de studies te ondervangen, zal als vervolgproject op de systematische review, zoals beschreven in **Hoofdstuk 3**, een meta-analyse van individuele patiëntgegevens (IPD) worden uitgevoerd. De IPD meta-analyse zal een nauwkeuriger schatting opleveren van de effectiviteit van de behandeling voor tinnitus als primaire klacht en zal helpen bij het identificeren van individuele factoren die van invloed zijn op de uitkomsten van de behandeling.

Op basis van de systematische review was er geen hoog niveau van bewijs voor het effect van intracochleaire elektrische stimulatie als interventie voor primaire tinnitus symptomen bij bilateraal matig tot ernstig gehoorverlies. Daarom hebben wij getracht een hoogwaardige studie te ontwerpen om het effect van cochleaire implantatie bij patiënten met matige tot ernstige tinnitus en matig tot ernstig bilateraal gehoorverlies te beoordelen. Het hoogste bewijsniveau voor therapeutische studies is een gerandomiseerde gecontroleerde studie. In **Hoofdstuk 4** hebben wij het studieprotocol beschreven van de lopende gerandomiseerde gecontroleerde studie. Dit protocol werd gepubliceerd om de transparantie te verbeteren en publicatiebias te vermijden. Tot dusver is de werving voor het onderzoek beperkt door strikte inclusiecriteria op basis van gehoorverlies en mentale status, en het onderzoek loopt nog steeds in het Universitair Medisch Centrum Utrecht. De toekomstige resultaten zullen na voltooiing van de studie toegankelijk worden gemaakt in een peer-review open access tijdschrift.

De in **Hoofdstuk 5** beschreven studie beoordeelde de verandering in prevalentie van tinnitus en ongemak na implantatie bij 300 patiënten die cochleaire implantaten kregen voor hun bilateraal ernstig tot zeer ernstig gehoorverlies. De prevalentie van tinnitus daalde van 55,8% pre-operatief tot 44,3% post-implantatie. De meeste deelnemers ervoeren echter weinig postoperatieve tinnitus: 93,7% ervoer geen tot weinig tinnitus en 6,3% ervoer veel tinnitus. Tinnitus geassocieerde last nam af na implantatie, met een cohort populatie die gemiddeld een "milde" tinnitus handicap rapporteerde voor en na implantatie.

Er werd geen verband gevonden tussen de gemeten tinnitusimpactscores op 12 maanden na implantatie en de in de studie beschikbare patiëntkenmerken. Verder onderzoek is nodig om de factoren te begrijpen die van invloed zijn op de veranderingen in tinnitus die worden ervaren door patiënten door cochleair implantatie.

DEEL II: INVLOED VAN COCHLEAIRE IMPLANTAAT-GERELATEERDE FACTOREN OP DE RESULTATEN VAN TINNITUS

Zoals aangetoond in **Hoofdstuk 5**, zijn veranderingen in tinnitusuitkomsten bij patiënten die cochleaire implantaten krijgen voor hun gehoorverlies heterogeen en nauwelijks voorspelbaar. In dit tweede deel onderzochten we twee cochleaire implantaatgerelateerde factoren die de tinnitusuitkomsten zouden kunnen beïnvloeden: de positie van de elektrode array en het elektrische stimulatiepatroon. In de studie beschreven in **Hoofdstuk 6** vonden we geen invloed van elektrodeontwerp of -positie op de impact en kenmerken van tinnitus bij 25 enkelzijdig dove patiënten geïmplanteerd met een cochleair implantaat. Deze studie moet echter worden herhaald met een grotere steekproefgrootte voordat dit resultaat kan worden gegeneraliseerd. In **Hoofdstuk 7** hebben we het effect van intra- en extracochleaire elektrische stimulatie voor verlichting van tinnitus systematisch beoordeeld. Alle studies toonden subjectieve verbetering van de tinnitus tijdens of na elektrische stimulatie met verschillende stimulatiepatronen. Vanwege significante bias in de geïncludeerde studies konden geen conclusies worden getrokken over de invloed van specifieke elektrische stimulatie parameters (elektrode locatie, stroom niveau, puls frequentie, polariteit) op tinnitus en hoe het stimulatie patroon geoptimaliseerd zou kunnen worden voor verlichting van tinnitus.

DEEL III: IMPACT VAN TINNITUS OP PATIËNTEN MET EEN COCHLEAIR IMPLANTAAT

Volgens eerdere literatuur ervaart een klein deel van de ontvangers van cochleaire implantaten nog steeds matige tot ernstige tinnitus. In het derde deel van dit proefschrift gebruikten we twee verschillende benaderingen om de impact van tinnitus te onderzoeken op deze patiënten die nog steeds tinnitus ervaren. In de studie beschreven in Hoofdstuk 8, analyseerden we een cochleair implantaat database van 2322 geïmplanteerde patiënten om de relatie tussen tinnitus hinder en gehoorgerelateerde kwaliteit van leven bij cochleair implantaat ontvangers te beoordelen. In deze studie toonden we aan dat de gehoorgerelateerde levenskwaliteit significant varieerde met tinnitushinder,

leeftijd, en unilaterale versus bilaterale implantaten, waarbij tinnitushinder de meest significante voorspeller was.

Om de impact van tinnitus op ontvangers van cochleaire implantaten beter te begrijpen, gebruikten we in Hoofdstuk 9 een gemengde methode om de impact van tinnitus te onderzoeken vanuit het standpunt van de patiënt. De mixed-method approach bestond uit twee delen: (1) een exploratief sequentieel design dat kwalitatieve verkennende gegevens verzamelde en (2) een hieruit ontwikkelde enquête voor kwantitatieve analyse Voor de kwalitatieve studie werd een webgebaseerde forumdiscussie gebruikt om kwalitatief rijke gegevens te verzamelen van een grote en diverse groep gebruikers van cochleaire implantaten. Uit de thematische analyse van de forumdiscussie kwamen vier thema's naar voren: tinnituservaring, situaties die tinnitus beïnvloeden, moeilijkheden in verband met tinnitus, en strategieën voor tinnitusbeheer. Vervolgens ontwikkelden we een enquête om de thema's die uit de kwalitatieve studie naar voren kwamen kwantitatief te meten in een grote groep gebruikers van cochleaire implantaten die tinnitus ervaren. Vierhonderdveertien deelnemers namen deel aan de ontwikkelde enquête. Dankzij de enquête toonden we aan dat de aanwezigheid en de impact van tinnitus in verband kunnen worden gebracht met het gebruik van de geluidsprocessor. Voor de meeste CI-gebruikers leek de tinnitus toe te nemen bij het uitvoeren van een hoortest of CI-programmeersessie en bij vermoeidheid, stress of ziekte. Moeilijkheden zoals vermoeidheid, stress, concentratie, groepsgesprekken en gehoorproblemen werden vaak gemeld en namen meestal toe wanneer de geluidsprocessor niet werd gedragen. Verder onderzoek is nodig om de complexe interactie tussen het gebruik van de geluidsprocessor en veranderingen in de aanwezigheid en de impact van tinnitus te begrijpen. Deze bevindingen leiden tot het advies voor clinici en industriële partners om zich meer te richten op de verschillende behoeften van patiënten die in het onderzoek naar voren kwamen, om de conditie te verbeteren van huidige en nieuwe CI-ontvangers die na implantatie tinnitus ervaren.

CONCLUSION

Dit proefschrift heeft bijgedragen aan een hoger bewijsniveau en een beter begrip van het effect van elektrische stimulatie van de gehoorzenuw als behandelingsoptie voor tinnitus. We hebben aangetoond dat elektrische stimulatie via cochleaire implantaten over het algemeen een positief effect heeft op tinnitus bij patiënten met tinnitus als primaire klacht. Er zijn echter verschillende overwegingen voordat conclusies worden getrokken over het potentieel van elektrische stimulatie door middel van cochleaire implantaten

als een levensvatbare behandeling van tinnitus voor patiënten met bijbehorend gehoorverlies. Dit proefschrift onderstreept het belang van patiëntenselectie en passende tinnitusevaluatie na cochleaire implantatie in onderzoeksstudies en klinische praktijken. Daarnaast heeft het bijgedragen aan een beter begrip van de impact van tinnitus op dragers van cochleaire implantaten, welke bevindingen kunnen worden gebruikt om een patiëntgerichte benadering verder te promoten. Verder onderzoek is nodig om tinnitusresultaten na implantatie te voorspellen en idealiter om de werkingsmechanismen van elektrische stimulatie beter te begrijpen. Door samenwerking tussen clinici, wetenschappers en industriële partners zou een genezende behandeling voor tinnitus kunnen worden ontwikkeld door middel van elektrische stimulatie van de gehoorzenuw.

Résumé

L'introduction générale du **chapitre 1** donne un bref aperçu de la définition des acouphènes, de leurs impacts et des limites actuelles dans la recherche d'un traitement pour les acouphènes. L'objectif de cette thèse est de fournir des preuves de haut niveau sur l'effet de la stimulation électrique du nerf auditif via les implants cochléaires sur les acouphènes. Trois objectifs de recherche principaux ont été définis pour cette thèse :

1. Évaluer l'effet de la stimulation électrique via les implants cochléaires sur les acouphènes
2. Étudier l'influence des facteurs liés aux implants cochléaires sur les acouphènes
3. Analyser l'impact des acouphènes sur les porteurs d'implants cochléaires. Ce dernier chapitre résume les conclusions relatives à chacun des objectifs, discute de certaines limites et propose des suggestions concernant les implications cliniques et les orientations futures.

PARTIE I : EFFET DE LA STIMULATION ÉLECTRIQUE VIA UN IMPLANT COCHLÉAIRE SUR LES ACOUPHÈNES

L'implant cochléaire est un traitement standard pour les personnes atteintes d'une perte auditive sévère à profonde qui ne perçoivent pas de bénéficie pas d'appareils auditives, la réduction des acouphènes étant un bénéfice secondaire en plus de la restauration de l'audition. L'effet de la stimulation électrique via un implant cochléaire n'est toujours pas clair pour les patients qui reçoivent un implant cochléaire pour leurs acouphènes en tant que plainte principale et non pour leur perte auditive. Pour combler cette lacune, la première partie de la thèse a évalué l'effet de la stimulation électrique via les implants cochléaires sur les acouphènes en utilisant différents modèles d'étude. Dans cette partie, deux populations différentes ont été étudiées : les patients qui ont reçu un implant cochléaire pour les acouphènes en tant que plainte principale **(chapitres 2-4)** et les patients qui ont reçu un implant cochléaire pour une perte auditive **(chapitre 5)**.

Dans le **chapitre 2**, nous avons procédé à une analyse systématique de la littérature sur l'effet de la stimulation électrique via un implant cochléaire sur les acouphènes en tant que plainte principale. Les sept études incluses ont toutes fait état d'une réduction statistiquement significative et cliniquement pertinente

des acouphènes après l'implantation. Cependant, toutes les études n'incluaient que des patients dont l'acouphène était la principale plainte qui présentaient une perte auditive unilatérale ou asymétrique. En outre, toutes les études incluses avaient un échantillon de petite taille et un risque élevé de biais. Des preuves supplémentaires sont nécessaires avant que les implants cochléaires puissent être considérés comme un traitement efficace des acouphènes. Pour surmonter la grande hétérogénéité des études, une méta-analyse des données individuelles des patients (Individual Patient Data, IPD) est en cours afin de mettre à jour et d'approfondir les résultats de la revue systématique, comme décrit au **chapitre 3**. Cette méta-analyse fournira une estimation plus précise de l'efficacité du traitement sur les acouphènes en tant que plainte primaire et aidera à identifier les facteurs individuels influençant les résultats du traitement.

D'après la revue systématique, il n'y avait pas de niveau de preuve élevé pour l'effet de la stimulation électrique intra-cochléaire en tant qu'intervention pour les symptômes primaires de l'acouphène dans les pertes auditives bilatérales modérées à sévères. Nous avons donc mis en place une étude de haute qualité pour évaluer l'effet de l'implantation cochléaire chez les patients souffrant d'acouphènes modérés à sévères et ayant une perte auditive bilatérale modérée à sévère. Le niveau de preuve le plus élevé pour les études thérapeutiques est un essai contrôlé randomisé. Dans le **chapitre 4**, nous avons décrit le protocole de l'essai contrôlé randomisé en cours. Ce protocole a été publié pour améliorer la transparence et éviter les biais de publication. Jusqu'à présent, le recrutement de l'étude a été limité par des critères d'inclusion stricts basés sur la perte auditive et l'état mental des patients. L'étude est toujours en cours au Centre médical universitaire d'Utrecht (UMC Utrecht) aux Pays-Bas. Une fois l'étude terminée, les résultats seront publiés dans un journal scientifique en libre accès.

L'étude décrite dans le **chapitre 5** a évalué l'évolution de la prévalence et de la gêne des acouphènes après l'implantation chez 300 patients ayant reçu des implants cochléaires pour leur perte auditive bilatérale sévère à profonde. La prévalence des acouphènes a diminué de 55,8 % avant l'opération à 44,3 % après l'implantation. Cependant, la plupart des participants ont ressenti peu d'acouphènes après l'opération : 93,7 % ont ressenti peu ou pas d'acouphènes et 6,3 % ont ressenti beaucoup d'acouphènes. Le fardeau associé aux acouphènes a diminué après l'implantation, la population de la cohorte ayant signalé une incapacité "légère" liée aux acouphènes en moyenne avant l'opération.

PARTIE II : INFLUENCE DES FACTEURS LIÉS À L'IMPLANT COCHLÉAIRE SUR L'ÉVOLUTION DES ACOUPHÈNES

Comme nous l'avons démontré au **chapitre 5**, les changements dans l'évolution des acouphènes chez les patients recevant un implant cochléaire pour leur perte auditive sont hétérogènes et difficiles à prédire. Dans cette deuxième partie, nous avons étudié deux facteurs liés à l'implant cochléaire qui pourraient influencer l'évolution des acouphènes : la position du porte-électrodes et le schéma de stimulation électrique. Dans l'étude décrite au **chapitre 6**, nous n'avons trouvé aucune influence de la conception ou de la position des électrodes sur l'impact et les caractéristiques des acouphènes chez 25 patients sourds unilatéraux porteurs d'un implant cochléaire. Cependant, cette étude doit être répétée avec un échantillon plus important avant que ce résultat puisse être généralisé. Dans le **chapitre 7,** nous avons évalué systématiquement l'effet de la stimulation électrique intra- et extra-cochléaire sur le soulagement des acouphènes. Toutes les études ont montré une amélioration subjective des acouphènes pendant ou après la stimulation électrique avec différents schémas de stimulation. En raison d'un biais important dans les études incluses, aucune conclusion n'a pu être tirée sur l'influence de paramètres spécifiques de stimulation électrique (emplacement de l'électrode, niveau de courant, fréquence d'impulsion, polarité) sur les acouphènes et sur la manière dont le schéma de stimulation pourrait être optimisé pour le soulagement des acouphènes.

PARTIE III : IMPACT DES ACOUPHÈNES SUR LES PATIENTS PORTEURS D'UN IMPLANT COCHLÉAIRE

Selon la littérature antérieure, une petite proportion de porteurs d'implants cochléaires souffrent encore d'acouphènes modérés à sévères. Dans la troisième partie de cette thèse, nous avons utilisé deux approches différentes pour étudier l'impact des acouphènes sur les patients qui souffrent encore d'acouphènes. Dans l'étude décrite au **chapitre 8**, nous avons analysé une base de données d'implants cochléaires de 2322 patients implantés pour évaluer la relation entre la gêne des acouphènes et la qualité de vie liée à l'audition chez les porteurs d'implants cochléaires. Dans cette étude, nous avons montré que la qualité de vie liée à l'audition variait de manière significative avec la gêne des acouphènes, l'âge et les implants unilatéraux par rapport aux implants bilatéraux, la gêne des acouphènes étant le prédicteur le plus significatif.

Pour mieux comprendre l'impact des acouphènes sur les porteurs d'implants cochléaires, nous avons utilisé dans le **chapitre 9** une méthode mixte pour

examiner l'impact des acouphènes du point de vue du patient. L'approche à méthode mixte se composait de deux parties : (1) une conception séquentielle exploratoire qui recueillait des données exploratoires qualitatives et (2) une enquête élaborée à partir de celles-ci pour une analyse quantitative. Pour l'étude qualitative, un forum de discussion en ligne a été utilisé pour collecter des données qualitativement riches auprès d'un groupe important et diversifié d'utilisateurs d'implants cochléaires. Quatre thèmes ont émergé de l'analyse thématique de la discussion du forum : l'expérience des acouphènes, les situations affectant les acouphènes, les difficultés liées aux acouphènes et les stratégies de gestion des acouphènes. Nous avons ensuite développé une enquête pour mesurer quantitativement les thèmes émergeant de l'étude qualitative dans un grand groupe d'utilisateurs d'implants cochléaires souffrant d'acouphènes. Quatre cent quatorze participants ont pris part à l'enquête élaborée. Grâce à l'enquête, nous avons montré que la présence et l'impact des acouphènes peuvent être associés à l'utilisation d'un processeur de son. Pour la plupart des utilisateurs d'implants cochléaires, les acouphènes semblaient augmenter pendant un test auditif ou une session de programmation d'IC et lorsqu'ils étaient fatigués, stressés ou malades. Des difficultés telles que la fatigue, le stress, la concentration, les conversations de groupe et les problèmes d'audition ont été fréquemment signalées et généralement augmentées lorsque le processeur de son n'était pas porté. Des recherches supplémentaires sont nécessaires pour comprendre l'interaction complexe entre l'utilisation du processeur de son et les changements dans la présence et l'impact des acouphènes. Ces résultats conduisent à conseiller aux cliniciens et aux partenaires de l'industrie de se concentrer davantage sur les différents besoins des patients identifiés dans l'étude afin d'améliorer l'état des receveurs actuels et nouveaux d'IC qui souffrent d'acouphènes après l'implantation.

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Curriculum Vitae

Kelly Kérène Simy Assouly was born on March 3rd, 1995, in Villeurbanne, France. After she graduated from secondary school in Lyon, she studied Health Science Engineering at Telecom Physique Strasbourg, France, where she specialised in Innovative Therapies. After a master's thesis at the Federal Polytechnic School of Lausanne (EPFL) in Switzerland, she obtained a Master's degree in Biomedical Engineering at Telecom Physique Strasbourg and an MSc in Micro and Nanoelectronics at the University of Strasbourg in 2018. During the years of study, she performed several internships in clinical neuroscience research projects such as the Brain & Mindfulness project at the Neuroscience Research Centre of Lyon (CRNL) in France and the Walk Again project at the Alberto Santos Dumont Association for Research Support (AASDAP), in Sao Paulo, Brazil. In November 2018, she started her PhD at the Department of Otorhinolaryngology, Head and Neck surgery of the University Medical Center Utrecht in Utrecht, the Netherlands, and at the Cochlear Technology Centre in Mechelen, Belgium, which led to this thesis. For this position, she got a Marie Skłodowska-Curie Research Fellowship as an early-stage researcher in the TinACT project, a European Union's Horizon 2020 funded project investigating the diagnosis, causes and treatment of tinnitus, where her research focuses on the treatment of tinnitus through cochlear implants. In addition to her PhD, she is the Media Promotion Coordinator of the TRI Academy, an international education program on tinnitus research. In May 2023, she started working as a Clinical Project Manager and Research Engineer at the Cochear Technology Center to develop research projects on adjacent auditory therapies such as tinnitus and vestibular disorders.

List of publications

Assouly KKS, van Heteren JAA*, Stokroos RJ, Stegeman I, Smit AL. Cochlear implantation for patients with tinnitus - A systematic review. Prog Brain Res. 2021;260:27-50. doi: 10.1016/bs.pbr.2020.06.013. Epub 2020 Oct 14. PMID : 33637223.

Van Heteren JAA, Arts RAGJ, Killian MJP, **Assouly KKS**, van de Wauw C, Stokroos RJ, Smit AL, George ELJ. Sound therapy for cochlear implant users with tinnitus. Int J Audiol. 2021 May;60(5):374-384. doi: 10.1080/14992027.2020.1832266. Epub 2020 Oct 19. PMID: 33074733.

Assouly K, Smit AL, Stegeman I, Rhebergen KS, van Dijk B, Stokroos R. Cochlear implantation for tinnitus in adults with bilateral hearing loss : protocol of a randomised controlled trial. BMJ Open. 2021 May 18;11(5):e043288. doi: 10.1136/bmjopen-2020-043288. Erratum in: BMJ Open. 2022 Jul 6;12(7):e043288corr1. PMID: 34006544; PMCID: PMC8130732.

Simoes JP, Daoud E, Shabbir M, Amanat S, **Assouly K**, Biswas R, Casolani C, Dode A, Enzler F, Jacquemin L, Joergensen M, Kok T, Liyanage N, Lourenco M, Makani P, Mehdi M, Ramadhani AL, Riha C, Santacruz JL, Schiller A, Schoisswohl S, Trpchevska N, Genitsaridi E. Multidisciplinary Tinnitus Research : Challenges and Future Directions From the Perspective of Early Stage Researchers. Front Aging Neurosci. 2021 Jun 11;13:647285. doi: 10.3389/fnagi.2021.647285. Erratum in : Front Aging Neurosci. 2021 Aug 09;13:730758. PMID: 34177549; PMCID: PMC8225955.

Assouly KKS, Dullaart MJ, Stokroos RJ, van Dijk B, Stegeman I, Smit AL. Systematic Review on Intra- and Extracochlear Electrical Stimulation for Tinnitus. Brain Sci. 2021 Oct 24;11(11):1394. doi: 10.3390/brainsci11111394. PMID: 34827395; PMCID: PMC8615734.

Assouly KKS, Smit AL, Eikelboom RH, Sucher C, Atlas M, Stokroos RJ, Stegeman I. Analysis of a Cochlear Implant Database : Changes in Tinnitus Prevalence and Distress After Cochlear Implantation. Trends Hear. 2022 Jan-Dec;26:23312165221128431. doi: 10.1177/23312165221128431. PMID: 36154765; PMCID: PMC9515522..

Assouly KKS, Smit AL, Stegeman I. Effect of electrical stimulation with a cochlear implant on tinnitus impact : protocol of an individual patient data meta-analysis. BMJ Open. 2022 Jun 17;12(6):e063432. doi: 10.1136/bmjopen-2022-063432. PMID: 35715189; PMCID: PMC9208004.

Assouly KKS, Arts RAGJ, Graham PL, van Dijk B, James CJ. Influence of tinnitus annoyance on hearing-related quality of life in cochlear implant recipients. Sci Rep. 2022 Aug 24;12(1):14423. doi: 10.1038/s41598-022-18823-3. PMID: 36002556; PMCID: PMC9402917.

Idriss SA, Reynard P, Marx M, Mainguy A, Joly CA, Ionescu EC, **Assouly KKS,** Thai-Van H. Short- and Long-Term Effect of Cochlear Implantation on Disabling Tinnitus in Single-Sided Deafness Patients : A Systematic Review. J Clin Med. 2022 Sep 26;11(19):5664. doi: 10.3390/jcm11195664. PMID: 36233532; PMCID: PMC9572534.

Assouly KKS, Shabbir M, van Dijk B, Hoare DJ, Akeroyd MA, Stokroos RJ, Stegeman I, Smit AL. The impact of tinnitus on adult cochlear implant recipients : a mixed-method approach. PLoS ONE. 2023 April 20; 18(4): e0284719. https://doi.org/10.1371/journal.pone.0284719

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