TINNITUS AND COCHLEAR IMPLANTATION

IMPACT AND OUTCOMES

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TINNITUS AND COCHLEAR IMPLANTATION:
IMPACT AND OUTCOMES

TINNITUS EN COCHLEAIRE IMPLANTATIE:
IMPACT EN UITKOMSTEN

(met een samenvatting in het Nederlands)

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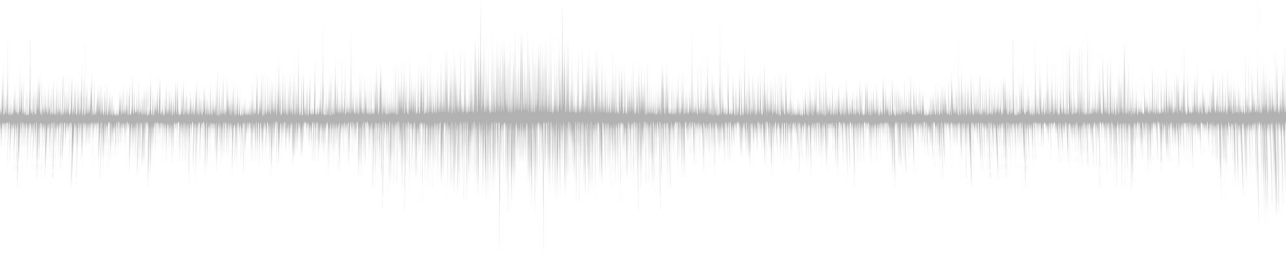
CONTENT OF THESIS

General introduction



In this thesis we discuss multiple subjective (self-reported) instruments and outcomes in the evaluation of cochlear implantation. To understand the importance and relevance of the research questions answered in this thesis, in this introduction we will first describe the physiology of normal hearing, the pathophysiology of hearing loss, tinnitus (a common symptom in patients with hearing loss), cochlear implantation as a possible treatment for hearing loss and tinnitus, and the subjective instruments used for the evaluation of cochlear implantation.

NORMAL HEARING

The ear is a complex sensory organ. The human ear can be divided in three parts: 1) the outer ear which consists of the pinna and the external auditory canal; 2) the middle ear which consists of the tympanic membrane, the middle ear cavity with the three auditory ossicles (malleus, incus, stapes) and 3) the inner ear (labyrinth) which consists of two parts: the cochlea and the vestibular part (Figure 1).[1,2]

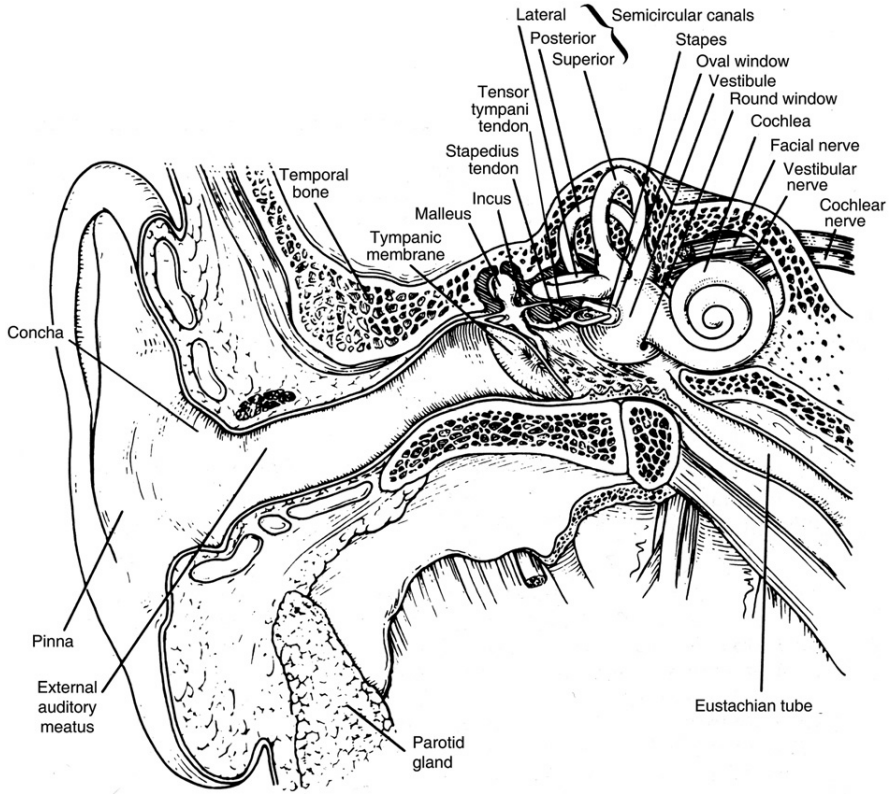


Figure 1. anatomy of the outer, middle and inner ear[3]

The human cochlea is a snail shell-shaped structure with 2 ¾ turns (Figure 1). Uncoiled, the cochlea would form a tube of 35 mm long.[2,4,5] The cochlea consists of three scalae filled with fluid: the cochlear duct or scala media which contains endolymph, and the scala tympani and scala vestibuli both containing perilymph (Figure 2). The scala media forms the inner compartment, the scala tympani and scala vestibuli form the outer compartments. The basilar membrane is located between the scala media and scala tympani and divides these two compartments. The organ of Corti is located on the basilar membrane which is a highly specialized structure, containing hair cells: the sensory hair cells.[3,5] The hair cells consist of one row of inner hair cells (IHCs) and three rows of outer hair cells (OHCs)[3,5]. The inner and outer hair cells are different in shape and function. Humans have approximately 3000 IHCs and each IHC is connected with 10-20 afferent fibers (which transmit auditory information from the cochlea to the central nervous system). The IHCs are the actual sensory receptors, and about 95% of the afferent fibers of the auditory nerve arise from these IHCs. The remaining 5% connect with the more numerous OHCs (approximately 12000).[1–5]

Sound is captured by the pinna and transferred via air through the external auditory canal to the tympanic membrane. Sound waves are then transmitted through the malleus and incus to the stapes footplate.[6] The vibrations of the footplate are transmitted to the oval window, setting the perilymph fluid in the scala vestibuli in motion.[3,5,6] Vibration of the basilar membrane leads to the conversion of mechanical movement to neural impulses

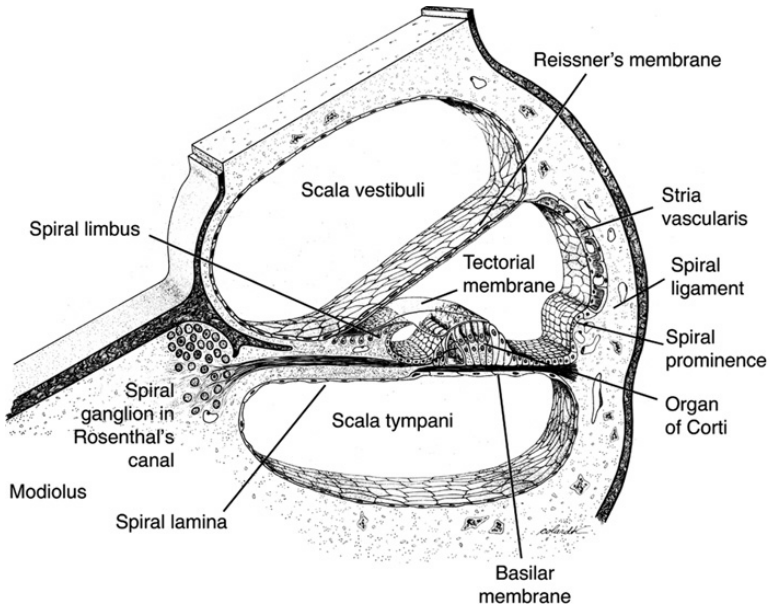


Figure 2. Cross section of one of the turns of the cochlea. The three scalae with associated structures are shown.[3]

in the IHCs, and pass these signals to the brainstem and auditory cortex. The OHCs amplify the vibrations of the basilar membrane.[5,6] The cochlea has a tonotopical organization, which means that each frequency between 20 Hz and 20 kHz will activate another subpopulation of hair cells.[5]

HEARING LOSS

Hearing loss is one of the most common sensory disorders in humans. A Dutch study showed a prevalence of severe hearing loss of 0.74 per 1000 persons.[7]

Two types of hearing loss can be distinguished: conductive hearing loss and sensorineural hearing loss (SNHL). Conductive hearing loss is the result of deficits in the transmission of sounds via the outer or middle ear. The treatment of conductive hearing loss depends on its etiology. Treatment options include medication, surgery or various types of hearing aid. SNHL is the more complex form of hearing loss and is often divided into cochlear and neural (or retrocochlear) hearing loss.[2,8,9] Acquired cochlear hearing loss is often caused by (outer) hair cell damage: noise-induced or age-related (presbycusis). Neural hearing loss is caused by pathologies of the auditory nerve or central auditory nervous system. Also, combinations of cochlear and neural pathologies exist.[1,2] Mostly, SNHL is permanent and worsens with increasing age.[9,10]

To describe the degree of hearing loss, the classification of the American Speech-Language-Hearing Association (ASHA) is often used. Table 1 shows the degree of hearing loss with the hearing loss range in decibels Hearing Level (dB HL).[9,11]

Hearing loss can occur bilaterally (in both ears) or unilaterally (in one ear). In this thesis, we will focus on adult patients with bilateral severe to profound SNHL.

Table 1. Degrees of hearing loss[9]

Degree of hearing loss	Range hearing loss (dB HL)
Normal	-10 – 15
Slight	16 – 25
Mild	26 – 40
Moderate	41 – 55
Moderately severe	56 – 70
Severe	71 – 90
Profound	91 +

COCHLEAR IMPLANTATION – HEARING LOSS

A cochlear implant (CI) is the first effective treatment for severe to profound SNHL. The first CI was implanted in 1961 by the doctors William House and John Doyle in Los Angeles, California. Currently cochlear implantation is standard clinical care for bilateral severe to profound SNHL when hearing aids are no longer effective.[12,13] A CI converts sound into an electronic stimulus, which directly stimulates the acoustic nerve via an electrode placed in the cochlea (Figure 3)[13]. Cochlear implantation has often been proved to be a safe and effective method for improving subjective and objective hearing outcomes in adult as well as pediatric patients.[10,14,15]

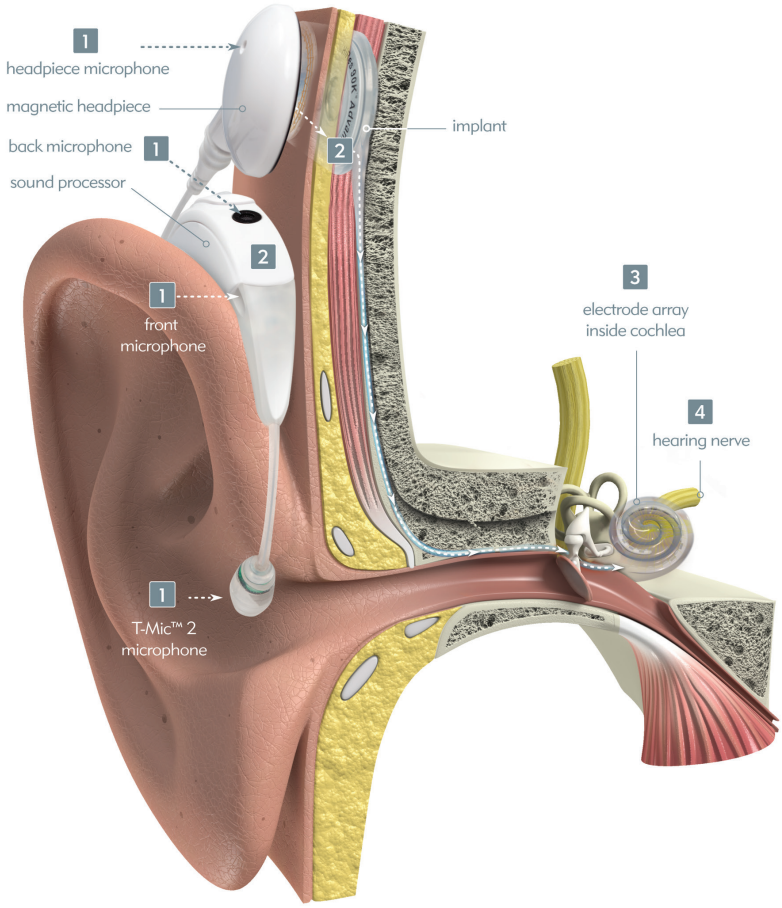


Figure 3. Schematic figure of a cochlear implant. The microphone captures the sound. The sound processor converts sound into signals. The magnetic headpiece transmits the signal to the implant. The electrode stimulates the acoustic nerve. Image courtesy of Advanced Bionics

Candidacy for cochlear implantation has changed through the years. In the beginning, only patients with bilateral profound SNHL were implanted with a CI unilaterally. Nowadays, also patients with some residual hearing are implanted with a CI. The last decades there is a growing interest in bilateral cochlear implantation (BiCI) in patients with bilateral severe to profound SNHL as the advantages of binaural hearing are largely investigated.[16] In most countries, BiCI has become standard clinical care for pediatric patients with bilateral severe to profound SNHL. In the Netherlands (and many other countries) however, in adult patients with bilateral severe to profound SNHL, only unilateral cochlear implantation (UCI) is reimbursed.[12] Therefore, our research group started a multicenter randomized controlled trial (RCT) in 2009 to evaluate the effectiveness and cost-effectiveness of BiCI in adult patients with bilateral severe to profound SNHL. Thirty-eight adult patients were included in this trial and randomly allocated to receive bilateral CIs together in one surgery (simultaneously), or in two surgeries with an interval of 2 years (sequentially). Evaluations on multiple subjective and objective outcomes took place each year after (initial) implantation, until a follow-up period of 4 years was reached. Four of the chapters in this thesis are the result of this RCT.

More recent developments in candidacy for cochlear implantation involve patients with unilateral SNHL or incapacitating tinnitus.[17–19]

TINNITUS

Tinnitus is defined as a sound sensation without the presence of an external source of the sound. Patients often experience the sound as ringing or buzzing in the ears. Subjective tinnitus is the most common type of tinnitus and it means that the patient experiences a sound in the head or ear, whereas the physician cannot confirm the presence of this sound by physical examination.[20,21] In objective tinnitus, the sound is observed by both the patient and the physician.[1,18] This sound arises from an internal physical source and it has often an identifiable cause. When the cause of objective tinnitus is of vascular origin, for example an aneurysm or arteriovenous malformation, the sound is pulsatile. A clicking, vibrational sound can be explained by muscular contractions due to myoclonus.[22] Subjective tinnitus is the most common sort of tinnitus and the focus of this thesis will be on this type of tinnitus only. Therefore, in the remaining of this and further chapters the term 'tinnitus' refers to subjective tinnitus only.

Tinnitus is a common problem, with largely varying prevalence rates between 5% and 49%. This large range can be explained by the lack of standardized measures for tinnitus which results in uncertainties about the true prevalence.[23] As tinnitus is a subjective symptom, questionnaires are used to measure the presence and burden of tinnitus[24].

The exact cause of tinnitus is unknown. In the majority of the individuals tinnitus is accompanied by SNHL.[21,25] Especially in patients with severe SNHL, the prevalence of tinnitus is high. Prevalence rates of preoperative tinnitus in CI patients for example range between 66% and 86%.[26] There are many different hypotheses about the mechanisms by which tinnitus can occur[27]. The former hypothesis about tinnitus was of peripheral origin.

More recent theories focus on involvement of central auditory structures. Neuroplastic changes in these structures, such as changes in tonotopic organization or an enhanced neuronal synchrony or firing rate, can result in a tinnitus sensation.[28,29]

An extensive amount of treatment options exists for the management of tinnitus, although the efficacy of a lot of these therapies is inconclusive[30,31]. Psychological therapy, which includes psychoeducation, tinnitus retraining therapy and cognitive behavioral therapy, is used for coping and achieving habituation to the tinnitus, curing is not the purpose[29]. Tinnitus-specific cognitive behavioral therapy is the most effective of these psychological therapies[31]. The treatment of comorbidities, in particular depression, is also recommended. Many different drugs have been studied, but until now no drug therapy for tinnitus exists. When tinnitus is accompanied with hearing loss, general sound enrichment can be recommended, or technical devices like hearing aids or CIs are known to reduce tinnitus complaints.[30,31].

COCHLEAR IMPLANTATION – TINNITUS

Already in 1981 House and Brackmann[32] reported improvement in tinnitus sensation in CI patients and therefore recommended CI procedures in patients with severe tinnitus. Since then a lot of studies focused on this 'side effect' of cochlear implantation. Although a CI can reduce tinnitus complaints, increase of tinnitus and even newly induced tinnitus has also been reported in a minority of patients.[26]

SUBJECTIVE INSTRUMENTS

As mentioned above, questionnaires are used for the measurement of tinnitus. A questionnaire is a subjective (self-reported) instrument. In the evaluation of the effectiveness and cost-effectiveness of cochlear implantation, a wide range of instruments is used. Examples of objective hearing instruments are speech perception in silence and noise tests or localization tests. In many CI centers, the clinical evaluation of cochlear implantation only encompass objective hearing tests regarding speech perception in silence. It can be questioned whether such tests fully represent a patient's everyday listening situation. For that reason, Patient Reported Outcomes Measures (PROMs) gain in importance and the healthcare system is moving towards a more patient-centered system[33–35]. PROMs capture patients' subjective experience of illness, impairment and disability[36]. Subjective outcomes in the evaluation of cochlear implantation include quality of life (QoL), quality of hearing (QoH) and tinnitus questionnaires.

Another reason for the growing importance of QoL instruments, is the increasing importance of cost-effectiveness of treatments in today's healthcare. An often used method to evaluate cost-effectiveness is a cost-utility analysis[37]. In these analyses, the outcomes of self-reported health-related QoL instruments are leading. Therefore, QoL outcomes have become important instruments in the current healthcare system.

OUTLINE OF THIS THESIS

This thesis consists of two parts. The first part focuses on the effect of cochlear implantation on tinnitus, investigated with different study designs and in different patient groups. The second part focuses on subjective instruments and outcomes in the evaluation of cochlear implantation.

In **Chapter 1.1** we systematically reviewed the literature on the effect of UCI in adult patients with bilateral severe to profound SNHL. In **Chapter 1.2** we evaluated the 10 year results of the Department of Otorhinolaryngology, Head and Neck Surgery from the University Medical Center Utrecht (UMCU) regarding the effect of UCI on tinnitus in adult patients with bilateral severe to profound SNHL, which was a retrospective study. In **Chapter 1.3** we used parts of the data from chapter 1.2, to develop a prediction model for tinnitus recovery following UCI. In **Chapter 1.4** we evaluated the effect of BiCI on tinnitus in adult patients with bilateral severe to profound SNHL. This was a descriptive study which presents the tinnitus data collected as part of the above mentioned RCT on the benefits of simultaneous versus sequential BiCI.

The second part of this thesis focuses on subjective instruments and outcomes in the evaluation of cochlear implantation. All data used in this part of the thesis was collected as part of the RCT. In **Chapter 2.1** the agreement between different general health utility instruments in cochlear implantation is evaluated and recommendations are made for the use of instruments in future cochlear implant research. In **Chapter 2.2** we studied the correlation between subjective and objective hearing tests. In **Chapter 2.3** we present the long-term (4 years) subjective outcomes of the RCT using longitudinal data-analyses.

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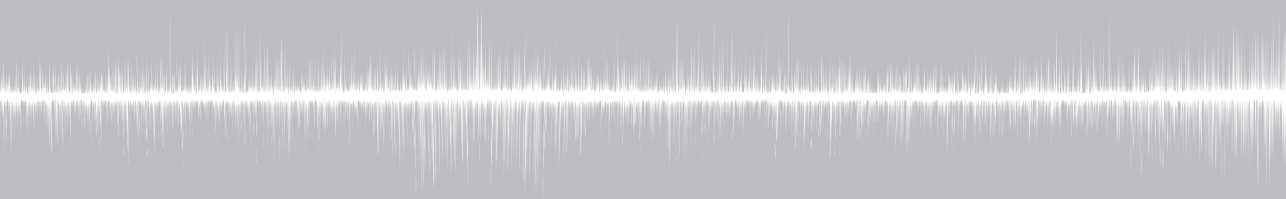

Part one

Cochlear implantation and tinnitus

Chapter 1.1

The effect of cochlear implantation on tinnitus in patients with bilateral hearing loss: a systematic review

Laryngoscope 2015;125(11):2584-92

Geerte GJ Ramakers
Alice van Zon
Inge Stegeman
Wilko Grolman

ABSTRACT

Objectives
To present an overview of the effect of cochlear implantation on tinnitus in adults with bilateral sensorineural hearing loss.

Data sources
PubMed, Cochrane Library, CINAHL, and Embase databases were searched for articles from database inception up to January 13, 2015.

Methods
A systematic search was conducted. Original studies reporting on cochlear implantation and the effect on tinnitus, measured with a tinnitus questionnaire, were included. The directness of evidence and risk of bias were assessed. Studies with a moderate or high directness of evidence and a low or moderate risk of bias were included for analysis. The pre- and postimplantation tinnitus scores were extracted.

Results
In total, 786 unique articles were retrieved. Although there was lack of high level of evidence studies, 10 articles satisfied the eligibility criteria. Overall, there was a reduction of mean tinnitus score. There was a decrease in tinnitus score in 25% to 72%, and a total suppression of tinnitus after implantation was reported in 8% to 45% of patients. Tinnitus was stable in 0% to 36% of patients, and increase of tinnitus occurred in 0% to 25%. Tinnitus induction rates in the patients without preoperative tinnitus varied from 0% to 10%.

Conclusions
There are no high level of evidence studies concerning cochlear implantation and the effect on tinnitus. Overall, current literature shows that there is a decrease of mean tinnitus questionnaire score after unilateral cochlear implantation. However, there is also a chance of increasing burden of existing tinnitus, and the induction of tinnitus is reported.

INTRODUCTION

Tinnitus is a disturbing phenomenon, with a high prevalence in sensorineural hearing-impaired patients. The prevalence rates in previous studies differ, ranging from 67% to 86% in cochlear implant (CI) candidates.[1]

Unilateral cochlear implantation is a common treatment for patients with bilateral sensorineural hearing loss. An often reported additional benefit of this treatment is the subjective reduction of tinnitus.[1,2] Quaranta et al. showed total tinnitus suppression rates varying from 2% to 83%[1]. However, an increase of existing tinnitus, varying from 2% to 9% of patients, as well as a new onset of tinnitus, is described[1]. The induction of tinnitus occurs in 1% to 5% of patients according to recent studies describing the complications following cochlear implantation[3,4].

Most studies that report on the effect of cochlear implantation on tinnitus have been published in the last decade. However, a current systematic review of the literature following evidenced-based medicine (EBM) principles is still lacking.[1,5,6]

Therefore, the objective of this study was to systematically review the effect of unilateral and bilateral cochlear implantation on tinnitus in adults with bilateral sensorineural hearing loss.

METHODS

For this systematic review, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement is used.[6]

Search strategy

A systematic search was performed in PubMed, Cochrane Library, CINAHL, and Embase databases from inception up to January 13, 2015. The search terms tinnitus and cochlear implantation and all their synonyms were combined. Table 1 presents a complete overview of the search syntaxes.

Study selection

Two of the authors (G.G.J.R., A.v.Z.) independently screened the title and abstract for all of the retrieved articles, and subsequently they screened the full-text of eligible studies against the inclusion criteria. Original articles on cochlear implantation and the effect on tinnitus in adults with bilateral sensorineural hearing loss were selected. Only studies in which tinnitus was evaluated with a questionnaire before and after implantation were included. Studies not on humans; written in languages other than English, German, or Dutch; case reports (n<5); and studies with a nonretrievable abstract or full text were excluded. Furthermore, we excluded studies in which a CI was provided in an experimental setting. Disagreement between the authors was resolved by discussion (see Figure 1 for selection criteria).

Table 1. Search strategy (date of search January 13, 2015)

Database	Search	Syntax	Results
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]	465
	#2	((cochlear[Title/Abstract]) AND implant*[Title/Abstract]) OR (cochlear[Title/Abstract] AND prosthes*[Title/Abstract]) OR (cochlear[Title/Abstract] AND prosthesis[Title/Abstract] AND system[Title/Abstract]) OR (cochlear[Title/Abstract] AND prosthetic[Title/Abstract] AND devices[Title/Abstract]) OR (auditory[Title/Abstract] AND prosthes*[Title/Abstract]) OR CI[Title/Abstract]) OR implant*[Title/Abstract]) OR prosthes*[Title/Abstract]) OR "cochlear implants"[MeSH Terms]) OR "cochlear implantation"[MeSH Terms])	
	#3	#1 AND #2	
Cochrane	Modeled search strategy designed for Cochrane		174
CINAHL	Modeled search strategy designed for CINAHL		71
Embase	Modeled search strategy designed for Embase, not Medline		195

Assessing quality of studies

The directness of evidence and risk of bias were investigated by using predefined criteria by the previous mentioned two authors independently. A criterion was assessed as satisfactory, unsatisfactory, or unclear if it was not reported.

Assessing the directness of evidence involved evaluation of the study population, therapy, and reported outcome (refer to Table 2 for the criteria). A high directness of evidence was defined as a positive score on all the criteria, moderate directness was scored when the study met three out of the four criteria, and a low directness of evidence was scored if the study met less than three criteria.

The risk of bias was assessed by the evaluation of six criteria, based on The Cochrane Collaboration's tool for assessing risk of bias[7] and adapted to our needs: blinding, treatment allocation, standardization of therapy, standardization of outcome, selective reporting, and completeness of data. Studies were classified as having a low risk of bias when they met five or six criteria, as moderate if they complied with at least three criteria, and the remaining studies were classified as high risk of bias.

Discrepancies between the reviewers were discussed until consensus was reached. All studies with a low directness of evidence and/or a high risk of bias were excluded for further review.

Data extraction

The same two authors extracted study characteristics and outcome data of the included studies. Our main outcome was the difference in pre- and postimplantation score, based on one or more of the tinnitus questionnaires. We extracted or computed the pre- and postimplantation scores based on the tinnitus questionnaires and the difference between these scores.

Another outcome was the effect of cochlear implantation on tinnitus in the individual patient, also based on tinnitus questionnaire scores. For this outcome, patients were classified in the following categories: total suppression, decrease, stable, and increase of tinnitus. When possible, data for newly induced tinnitus were also extracted.

Questionnaires

For all tinnitus questionnaires that were used to objectify tinnitus perception, a higher score meant a higher tinnitus burden. For the most commonly used questionnaire, the Tinnitus Handicap Inventory (THI), the total score represents the severity of the tinnitus as well: slight (0–16), mild (18–36), moderate (38–56), severe (58–76), or catastrophic (78–100).[8,9]

Meta-analysis

To find out whether a meta-analysis could be performed, we compared the study characteristics on heterogeneity and calculated the heterogeneity of effect size using Cochrane's I^2,using Review Manager (RevMan, version 5.3; The Cochrane Collaboration, London, United Kingdom).[10] We decided not to pool the data if I^2 was higher than 50%, because this corresponds to a notable heterogeneity.[11]

RESULTS

Search strategy and study selection

Our search identified a total of 905 articles, of which 786 were unique. After screening of title, abstract, and full text, 768 articles were excluded using the EBM methodology. The remaining 18 articles were eligible for further analysis (Figure 1).[12–29]

Assessing quality of studies

The critical appraisal is presented in Table 2. The directness of evidence was found high in 12 studies[12,13,15,16,19–24,28,29] and moderate in six studies[14,17,18,25–27]. None of these studies had a low directness of evidence. All studies were prospective or retrospective case series.

In 10 studies[12,13,16,18,20–22,26,27,29] the risk of bias was moderate, and in eight studies[14,15,17,19,23–25,28] the risk of bias was high. Adequate randomization, treatment allocation, and blinding were not achieved in any of the included studies. Only one study scored unsatisfactory on standardization of therapy[17]. Two studies did not use a validated questionnaire to score the tinnitus perception[15,27]. One study did not report which questionnaire was used[17], and in three studies patients completed the questionnaires concerning preoperative tinnitus retrospectively[19,23,24]. Five studies gave an inadequate description of the inclusion and exclusion criteria of their study population[12,14,16,25,28]. In 11 studies[14,15,17,19,21–25,28,29] there was 10% or more missing data or the completeness of data was unclear.

As a result, 10 studies with a moderate risk of bias and moderate or high directness of evidence remained for complete data extraction[12,13,16,18,20–22,26,27,29].

Data extraction

Large clinical heterogeneity between studies—such as differences between study designs, implant types, test conditions (CI on vs. CI off, implanted ear vs. contralateral ear vs. bilateral), follow-up duration, analyzed group, and outcome measures—and the lack of studies with a low risk of bias made it undesirable to pool the extracted data. This was confirmed by calculating the heterogeneity of effect size using Cochrane's I^2, for the studies using THI questionnaires. The I^2 was 78%, which means that there was substantial heterogeneity.[10,11] Therefore, we had to use descriptive analysis instead.

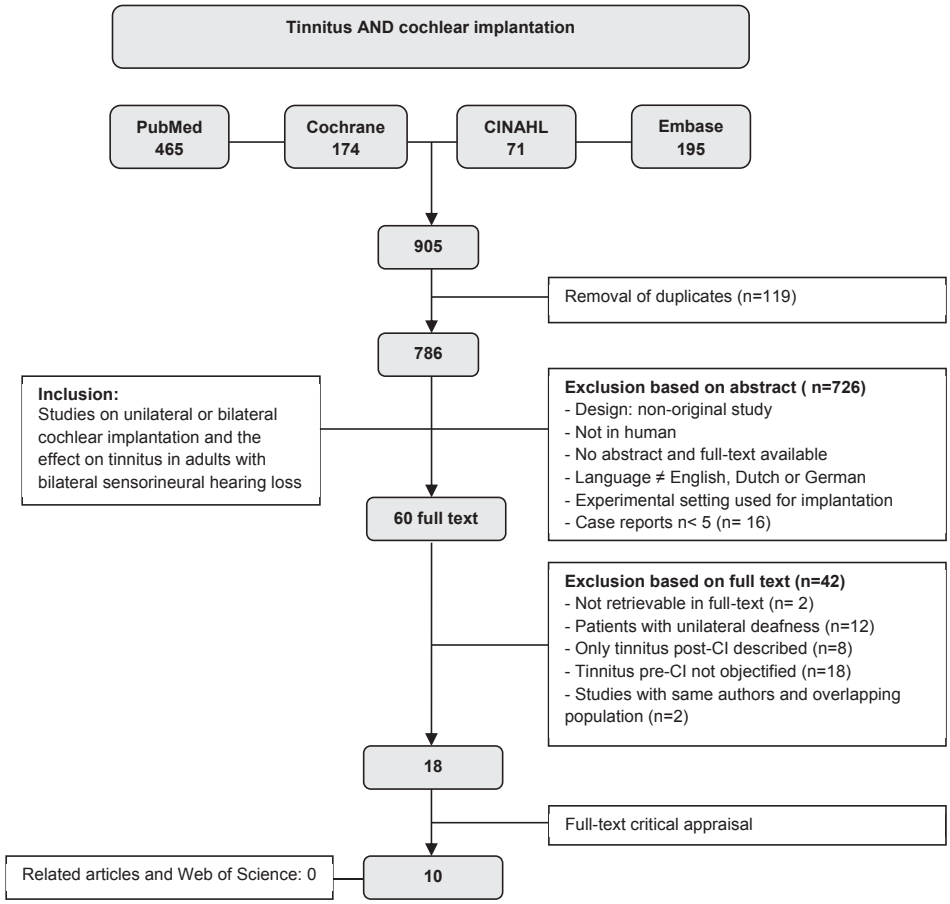

Figure 1. Flowchart of study selection process. CI=cochlear implant.

Table 2. Assessment of quality of included studies

			Directness of evidence					Risk of bias						
Study	Sample size (n)	Study design	Patients	Therapy	Outcome	Follow up	DoE	Blinding	Treatment allocation	Standardization (T)	Standardization (O)	Selective reporting	Complete data	RoB
Amoodi 2011	142	RCS	●	●	●	●	H	O	O	●	●	O	●	M
Bovo 2011	51	PCS	●	●	●	●	H	O	O	●	●	●	●	M
Daneshi 2005	20	PCS	●	●	●	O	M	O	O	●	●	O	?	H
Demajumdar 1999	99	PCS	●	●	●	●	H	O	O	●	O	●	?	H
Di Nardo 2007	30	PCS	●	●	●	●	H	O	O	●	●	O	●	M
Ito 1994	30	PCS	●	●	●	?	M	O	O	O	O	●	?	H
Kim 2013	35	RCS	●	●	●	O	M	O	O	●	●	●	●	M
Kloostra 2015	152	RCS	●	●	●	●	H	O	O	●	O	●	O	H
Kompis 2012	174	PCS	●	●	●	●	H	O	O	●	●	●	●	M
Mick 2014	40	RCS	●	●	●	●	H	O	O	●	●	●	O	M
Olze 2011	43	RCS	●	●	●	●	H	O	O	●	●	●	?	M
Olze, Gräbel 2012	40	RCS	●	●	●	●	H	O	O	●	O	●	?	H
Olze, Szczepek 2012	32	RCS	●	●	●	●	H	O	O	●	O	●	?	H
Pan 2009	244	PCS	●	●	●	?	M	O	O	●	●	O	O	H
Quaranta 2008	89	PCS	●	●	●	O	M	O	O	●	●	●	●	M
Ruckenstein 2001	38	PCS	●	●	●	?	M	O	O	●	O	●	●	M
Tyler 1995	82	PCS	●	●	●	●	H	O	O	●	●	O	O	H
Vallés-Varela 2013	20	RCS	●	●	●	●	H	O	O	●	●	●	?	M

Directness of evidence:
Patients: ● = patients with bilateral sensorineural hearing loss and tinnitus , O = other. Therapy: ● = unilateral or bilateral cochlear implantation, O = other. Outcome: ● = evaluation of tinnitus perception after implantation, O = no information about tinnitus. Follow up: ● = ≥ 6 months, O = < 6 months.
Level of directness of evidence: A high directness of evidence was defined as a positive score on all criteria, moderate as a positive score on three out of the four criteria, and a low directness of evidence if they complied with less than three criteria.
Risk of bias:
Blinding: ● = blinding of patient, researcher, observer; O = no blinding. Treatment allocation: ● = randomized or concealed, O = neither randomization nor concealment. Standardization of therapy (T): ● = implant type mentioned, O = not described or no standard protocol. Standardization of outcome (O): ● = the same validated tinnitus questionnaires were used to objectify tinnitus before and after implantation prospectively, O = no validated questionnaires used or not the same questionnaire before and after implantation or questionnaires for the preimplantation situation were completed retrospectively. Selective reporting: ● = well-defined and adequately described inclusion and exclusion criteria; O = inadequate description of sample selection. Completeness of outcome data: ● = <10% missing data, O ≥10% missing data.
Level of risk of bias: Studies were classified as having a low risk of bias when they complied with six or five criteria, as moderate if they complied with at least three criteria, and the remaining studies were classified as high risk of bias.
● = satisfactory; O = unsatisfactory; ?=unclear, DoE= directness of evidence; H= high; M= moderate; PCS= prospective case serie; RCS= retrospective case serie; RoB= risk of bias.

Study characteristics

Study characteristics are described in Table 3. The sample size of the study populations varied from 20 to 174 patients. Most studies included CI candidates with or without preoperative tinnitus. In three studies, only patients with bilateral hearing loss and preoperative tinnitus perception were included[12,27,29]. Mick et al.[21] compared the effect of cochlear implantation in patients with Ménière's disease and matched controls. All other studies focused on patients with bilateral profound hearing loss without one specific cause.

All studies reported on unilateral implanted patients. In two of the included studies, all patients within the study received the same type of cochlear implant[18,29]. In the other studies, several brands and types of cochlear implants were used. For the measuring of tinnitus, six studies used the THI[12,13,16,18,21,26], one study used the Tinnitus Questionnaire (TQ)[22], and in six studies another type of questionnaire was used only or in combination with the THI or TQ[13,16,18,20,27,29].

Tinnitus questionnaire scores

Table 4 shows the outcome measures of the analyzed studies. All six studies that used the THI as an outcome measure found a significant reduction of the THI score after cochlear implantation[12,13,16,18,21,26]. However, Mick et al.[21] found a significant reduction only in the Ménière group. Preimplantation scores ranged from 20.0 to 50.5. After cochlear implantation all mean scores decreased, and the postimplantation scores varied from 7.0 to 32.3[12,13,16,18,21,26]. The study with the highest mean preoperative THI score also showed the largest mean reduction of 40.4 on the THI score[18]. The other studies showed a decrease in THI score varying from 13.6 to 19.5. The tinnitus evaluation plot in Figure 2 shows the pre- and postoperative THI scores for all individual studies. A significantly reduced postimplantation score was also seen in the study that used the TQ for the evaluation of tinnitus, with the score reduced from 30.9 to 23.6 after implantation[22]. Four studies[13,16,18,20] used a visual analogue scale (VAS) score for loudness of tinnitus. The preimplantation loudness score ranged from 5.4 to 6.3, with postimplantation scores varying from 1.4 to 2.8[13,16,18,20]. In two studies[13,18], the annoyance of tinnitus was scored in a VAS. The scores were 4.2 and 5.8 before implantation, with a significant reduction to 2.3 and 1.3, respectively, after implantation[13,18]. Some studies used other tinnitus questionnaires as outcome measures; they all reported a reduction after cochlear implantation[18,27,28].

Effect of cochlear implantation

In five of the studies that used the THI, some data about tinnitus suppression, decrease, stable, and increase rates were extractable or computable[12,13,16,18,26]. Total suppression of tinnitus according to the THI score was found in 30%[16] and 37%[12]. A decrease, but not total suppression, of the tinnitus was found in 29% to 72% of patients[12,13,16]. In 0% to 30% of patients, the tinnitus was stable, and an increase was found in 0% to 25%.[12,13,16,18] Quaranta et al. was the only study in which data in different conditions were extractable. Total suppression of bilateral tinnitus was present in 41% of patients when the CI was off and in 56% when the CI was on.[26] This study made a distinction between the implanted and

Table 3. Study characteristics

Study	Study design	Sample size, no.	Preoperative tinnitus, no.	Age, years (SD)	Implant indication	FU, mo	Implant type	Questionnaire
Amoodi 2011 Canada	RCS	142	142	54.2 (14.7)	Postlingual bilateral deafness, different causes	12	Advanced Bionics, Cochlear, Med-El	THI
Bovo 2011 Italy	PCS	51	36	46.0 (17.5)	Postlingual bilateral deafness, different causes	6	Advanced Bionics, Cochlear, Med-El	THI-Italian, Loudness VAS, Annoyance VAS
Di Nardo 2007 Italy	PCS	30	20	43.3 (15.8)	Postlingual bilateral deafness, causes not mentioned	6	Advanced Bionics, Cochlear, Med-El, Neurelec	THI, Loudness VAS, Annoyance (mild/moderate/ severe)
Kim 2013 South Korea	RCS	35	22	40.6 (17.5)	Profound bilateral sensorineural hearing loss	3 - 42	Cochlear	THI, Loudness VAS, Annoyance VAS, Effect on life VAS
Kompis 2012 Switzerland	PCS	174	125	51.2	NE	6	Advanced Bionics, Cochlear, Med-El, Neurelec	Loudness VAS, 10-Q
Mick 2014 Canada	RCS	MD: 20	MD: 15*	MD: 68.2 (11.6)	Ménière	12	Advanced Bionics, Cochlear, Med-El	THI
		C: 20	C: 6*	C: 68.4 (11.2)	Other			
Olze 2011 Germany	RCS	43	39	51.7 (16.9)	Postlingual bilateral deafness, different causes	9 - 24	Cochlear, Med-El	TQ
Quaranta 2008 Italy	PCS	89	62	49.5†	Pre- and postlingual bilateral deafness, different causes	>3	Advanced Bionics, Cochlear, Med-El	THI
Ruckenstein 2001 USA	PCS	38	38	54 (13)	Bilateral deafness, causes not mentioned	NE	Advanced Bionics, Cochlear	Tinnitus rating scale‡
Vallés-Varela 2013 Spain	RCS	20	20	NE	Bilateral deafness, causes not mentioned	6/12	Cochlear	Modified THI, VAS

* There were tinnitus data available for these patients only. It is not clear whether the rest of patients did not suffer from tinnitus or this information is missing.
†mean age of evaluated patients: only patients with bilateral tinnitus preoperative (n=41)
‡Tinnitus rating scale, score 1-5: 1= no tinnitus; 2= tinnitus present, not annoying; 3= tinnitus present, an annoyance but does not cause psychological distress; 4= tinnitus severe, causes distress but does not impair activities of daily living; 5= tinnitus debilitating
C= control; FU= follow-up; MD= Ménière's disease; NE= not extractable; PCS= prospective case series; RCS= retrospective case series; SD= standard deviation; THI= Tinnitus Handicap Inventory; TQ= Tinnitus Questionnaire; VAS= Visual Analogue Scale; 10-Q= 10-question tinnitus questionnaire.

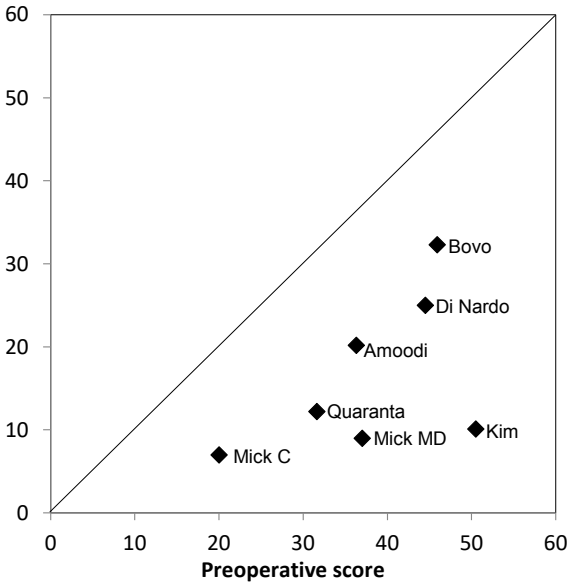

Figure 2. Tinnitus Evaluation Plot for mean Tinnitus Handicap Inventory score per study. Mick MD= patients in the study of Mick et al. with Ménière's disease; Mick C= control patients in the study of Mick et al.

contralateral ear as well, which resulted in a total suppression of tinnitus of 56% and 66% in the implanted ear with the CI off and on, respectively. In the contralateral ear, these suppression rates were 54% and 66% in off and on conditions, respectively.[26] In the study of Vallés-Varela et al., the distinction between the implanted and contralateral ear was made as well, but different categories were used.[29] The authors found a quantitative improvement in the implanted ear in 65% and in the contralateral ear in 50% of patients[29].

In the study that used the TQ as an outcome measure, total suppression was seen in 8%. A decrease in TQ score was seen in 56% of the patients. The tinnitus score was stable in 36%, and in none of the patients was there an increase of tinnitus.[22]

Total suppression rates measured with other questionnaires than the THI and TQ ranged from 20% to 45%[13,16,20,27]. In 25% to 51% of patients there was a decrease[13,16,20,27]. In 5% to 25%[13,16,27] these scores were stable, and in 0% to 11% of the patients the scores increased decrease[13,16,20,27].

Overall, the total suppression rates from all the different questionnaires combined varied from 8% to 45%[12,13,16,20,22,27]. A decrease, without complete suppression of tinnitus, was seen in 25% to 72% of patients[12,13,16,20,22,27]. There was stable tinnitus in 0% to 36% and increasing scores in 0% to 25% of patients.[12,13,16,18,20,22,27]

In some of the studies, including patients with and without preoperative tinnitus, the development of newly induced tinnitus after cochlear implantation could be studied. These induction rates varied from 0% to 10%.[18,20,26]

DISCUSSION

In this study, we described the results of a systematic review on the effect of cochlear implantation on tinnitus in patients with bilateral sensorineural hearing loss. One finding is that the current best available evidence on this topic only consists of nonrandomized, low or moderate level of evidence studies, and there is lack of studies on bilateral cochlear implantation.

The current review reports a decrease in mean tinnitus questionnaires scores after unilateral implantation in all analyzed studies where the primary outcome was extractable.[12,13,16,18,21,22,26,27,29] The overall total tinnitus suppression rates varied from 8% to 45% of patients after cochlear implantation.[12,13,16,20,22,27] Decrease of tinnitus was seen in 25% to 72% of patients [12,13,16,20,22,27],and for 0% to 36% of the patients the tinnitus was stable. Increase of tinnitus occurred in 0% to 25% of patients.[12,13,16,18,20,22,27] The development of newly induced tinnitus after cochlear implantation varied from 0% to 10% in the patients without preoperative tinnitus.[18,20,26]

The major strength of our study is that we present the first systematic review on this topic, which is characterized by a transparent search strategy, a transparent study selection process with strict inclusion and exclusion criteria, a transparent critical assessment of studies, and comprehensive outcome tables of all individual studies.

When interpreting the results, the following considerations need to be taken into account. Besides the lack of high-quality evidence, there was also large clinical heterogeneity between the studies. Pooling results from poor quality, nonrandomized study types is not recommended.[30]

All studies were retrospective or prospective case series[12,13,16,18,20–22,26,27,29], which means that all patients in these articles received treatment. These study designs are often used for studies on unintentional effects of an intervention.[30] In the included articles, the indication for cochlear implantation in all patients was bilateral deafness, and change in tinnitus was the unintentional effect. Because of this, randomization and blinding were not achieved in all the studies. Moreover, blinding of observer and patient for cochlear implantation is regarded as impossible. The original Cochrane Tool for assessing Risk of Bias we used in the current study is developed for the assessment of risk of bias in RCT's and not for case series. The use of this tool can be seen as a possible limitation of the current study.

The heterogeneity between the studies consisted of differences between study designs, implant types, test conditions, follow-up duration, analyzed groups, and outcome measures. In some of the retrospective studies, the design resulted in missing data or exclusion of patients with missing data, which led to smaller analyzed groups.[12,18,21,22] An additional weakness in some studies was the lack of information that is relevant for interpreting results and draw conclusions. For example, not all studies reported on the distinction between implanted and contralateral ear and differences between CI on and off conditions.[12,13,16,18,20–22,27]

The most used outcome measure in this review was the THI. This questionnaire is an internationally validated questionnaire developed by Newman et al.[8] Another often-used questionnaire for the evaluation of tinnitus is the TQ.[31] A problem with these and other

Table 4. Results

Study	Questionnaire	Analyzed group	Preimplantation score, mean (SD)	Postimplantation score, mean (SD)	Difference score, mean (SD)	Statistics, *p* value	Effect on tinnitus in %(no.)				
							Total suppression	Decrease	Stable	Increase	Newly induced tinnitus, %(no.)*
Amoodi 2011	THI	Only patients with pre- and postoperative tinnitus (n=89)	36.3	20.2	-16.0 (2.3)	<.01	37%(53)	29%(41)	29%(41)	5%(7)	NA
Bovo 2011	THI-Italian, Loudness VAS Annoyance VAS	Only patients with preoperative tinnitus (n=36)	45.9 (24.9)	32.3 (25.3)	-13.6	<.01	-	72%(26)	3%(1)	25%(9)	NA
			6.3 (2.3)	2.7 (2.8)	-3.6	<.01	36%(13)	42%(15)	17%(6)	6%(2)	NA
			4.2 (2.0)	2.3 (2.1)	-1.9	<.01	31%(11)	44%(16)	14%(5)	11%(4)	NA
Di Nardo 2007	THI Loudness VAS Annoyance (mild/ moderate/severe)	Only patients with preoperative tinnitus (n=20)	44.5	25	-19.5	<.05	30%(6)	35%(7)	30%(6)	5%(1)	0%(0)
			5.9	2.8	-3.1	NE	40%(8)	25%(5)	25%(5)	10%(2)	
			NE	NE	NE	NE	40%(8)	35%(7)	20%(5)	5%(1)	
Kim 2013	THI Loudness VAS Annoyance VAS Effect on life VAS	Only patients with preoperative tinnitus (n=22)	50.5 (28.7)	10.1 (15.8)	-40.4	<.01	NE	NE	0%(0)	0%(0)	0%(0)
			5.4 (2.8)	1.4 (1.0)	-4.0	<.01	NE	NE	NE	NE	NE
			5.8 (3.2)	1.3 (2.1)	-4.5	<.01	NE	NE	NE	NE	NE
			6.0 (3.3)	1.1 (2.0)	-4.9	<.01	NE	NE	NE	NE	NE
Kompis 2012	Loudness VAS 10-Q	Only patients with preoperative tinnitus (n=125)	NE	NE	NE	NE	20%(25)	28-51%	NE	7-9%	10%(5)
			NE	NE	NE	NE					
Mick 2014	THI	NE	MD:37.0†	MD:9.0†	NE	MD: <.001	NE	NE	NE	NE	NE
			C:20.0†	C:7.0†	NE	C: .087	NE	NE	NE	NE	NE
Olze 2011	TQ	Only patients with preoperative tinnitus (n=39)	30.9 (18.8)	23.6 (15.8)	-7.3	<.01	8%(3)	56%(22)	36%(14)	0%(0)	0%(0)

Quaranta 2008	THI	Only patients with preoperative bilateral tinnitus (n=41) in different conditions‡	31.6 (24)	12.2 (20)	-19.4	<.01	CI on: 56%(23) CI off: 41%(14)	NE	NE	NE	6%(2)
Ruckenstein 2001	Tinnitus rating scale	Only patients with preoperative tinnitus (n=38)	3.8	1.8	-2.0	Significant:NE	45%(17)	50%(19)	5%(2)	0%(0)	NA
Vallés-Varela 2013	Modified THI	Only patients with preoperative bilateral tinnitus (n=20)	NE	NE	NE	NE	NE	NE	NE	NE	NA
	VAS		5.1 (1.9)§	3.3 (1.6)§	-1.8	NE	NE	NE	NE	NE	NA

*percentage of the patients without preoperative tinnitus. †median instead of mean. ‡conditions: implanted ear, contralateral ear, CI on, CI off. § score for the ear with more intense tinnitus. C= control; CI= cochlear implant; MD= Ménière's disease; NE= not extractable; SD= standard deviation; THI=Tinnitus Handicap Inventory; TQ= Tinnitus Questionnaire; VAS= Visual Analogue Scale; 10-Q= 10-question tinnitus questionnaire; NA= not applicable.

tinnitus questionnaires is that they are not validated to measure the effectiveness of therapies.[32] We had to exclude three studies where patients completed the questionnaires about the preoperative tinnitus perception retrospectively, because this is an unreliable method.[19,23,24]

All the reported tinnitus questionnaires are developed for tinnitus patients and not particularly for deaf or CI patients with tinnitus. The fact that there is no commonly accepted questionnaire to evaluate the effect of therapy on tinnitus has resulted in the use of various questionnaires, making comparison between studies difficult. The development of a questionnaire for this purpose is needed. Furthermore, well-defined prospective cohort studies are also needed to provide a higher level of evidence for the effect of cochlear implantation in bilaterally deafened patients with tinnitus.

CONCLUSION

This systematic review provides an evaluation of current literature. Unfortunately, due to methodological considerations, no firm conclusions on the effectiveness of CI on tinnitus in adults with bilateral sensorineural hearing loss can be drawn. Existing literature reports a decrease of tinnitus after unilateral cochlear implantation. This suggests that cochlear implantation can be an effective treatment strategy for the reduction of tinnitus in this patient category. However, because an increase of tinnitus and newly induced tinnitus were also reported, a positive effect of cochlear implantation on the individual patient experiencing tinnitus cannot be predicted for certain.

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Chapter 1.2

Tinnitus following cochlear implantation; 10-year results of a tertiary care center

Submitted

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ABSTRACT

Objective
(1) to give an overview of prevalence and severity rates of tinnitus before and after cochlear implantation and changes in tinnitus after cochlear implantation; (2) to explore characteristics of patients with tinnitus induction; (3) to investigate the effect of turning the cochlear implant (CI) processor 'on' and 'off' on tinnitus severity.

Design
Retrospective study.

Study sample
137 patients with bilateral deafness who underwent unilateral cochlear implantation in a 10-year period, completed a questionnaire concerning preoperative and postoperative tinnitus.

Results
87 patients (64%) experienced tinnitus before cochlear implantation. Following cochlear implantation, tinnitus completely recovered in 35 (40%), decreased in 16 (19%) and increased in 9 (10%) patients. Induction of new tinnitus after implantation occurred in 7 patients (14%). Age, gender, prelinguality, preoperative speech perception and difference in residual hearing after surgery differed between patients with and without tinnitus induction. Significant decreases in median Visual Analogue Scale (VAS) scores were seen when turning the CI processor 'on' in patients with postoperative tinnitus.

Conclusion
In the majority of patients, cochlear implantation had a positive effect on preoperative tinnitus. However, induction of tinnitus also occurred. Turning the CI processor 'on' had a positive effect on tinnitus severity in patients with postoperative tinnitus.

INTRODUCTION

Subjective tinnitus is a common experienced phenomenon in patients with severe sensorineural hearing loss[1]. The exact cause of subjective tinnitus is unknown. One hypothesis is that tinnitus is the result of overactivity of the central auditory system due to lack of peripheral input[1,2]. Following this hypothesis, restoring the peripheral auditory input could lead to a decrease of this neural overactivity and thus might reduce tinnitus perception.

Currently, unilateral cochlear implantation is standard clinical care for adult patients with bilateral, severe sensorineural hearing loss[3]. Prevalence rates of preoperative tinnitus in cochlear implant (CI) candidates range from 66% to 86%[4]. A suppression of this tinnitus following cochlear implantation is often reported[5]. However, an increase of tinnitus and even newly induced tinnitus can also occur following cochlear implantation[5–8].

Most studies so far investigated the general effect of cochlear implantation on tinnitus severity by comparing preoperative and postoperative severity scores. Few studies specifically investigated the direct effect of turning the CI processor 'on' and 'off' on tinnitus severity. Quaranta et al. for example reported that turning the CI processor 'on' resulted in a total absence of tinnitus in 22% of patients who were still experiencing tinnitus while the CI processor was 'off '[9]. Greenberg et al. found a total or partial suppression of tinnitus in the ipsilateral ear with the CI processor 'on' in 57% of patients compared to 28% with the CI processor 'off'[10]. In both studies, turning the CI processor 'on' also resulted in increase of tinnitus in a couple of patients[9,10].

The reasons why some patients experience less tinnitus following cochlear implantation while other patients experience more tinnitus, are barely investigated and misunderstood. Pan et al. investigated characteristics of patients who developed tinnitus following cochlear implantation[11]. Probably due to the small sample size (11 of 91 patients developed tinnitus), no significant differences were found[11]. A recent study of Arts et al. investigated a possible relationship between deterioration of residual hearing due to CI surgery and postoperative tinnitus increase or induction[6]. They concluded that there was no association between deterioration of residual hearing and postoperative tinnitus induction.

The current study aims to give an overview of prevalence and severity rates of tinnitus before and after cochlear implantation and changes in tinnitus following cochlear implantation in our tertiary care center. Also, characteristics of patients with tinnitus induction will be explored. Furthermore, the effect of turning the CI processor 'on' and 'off' on tinnitus severity will be investigated.

METHODS

Ethics approval

This study was designed and conducted in accordance with the Declaration of Helsinki and an exemption of full review was obtained from the Medical Ethics Committee of the University Medical Center Utrecht (UMCU) (WAG/mb/16/003184). All included participants provided written informed consent.

Study design and participants

This study was conducted at the Department of Otorhinolaryngology, Head and Neck Surgery from the UMCU in the Netherlands. A questionnaire, together with an information letter and informed consent form, was sent out to all adult patients with bilateral severe to profound hearing loss who underwent unilateral cochlear implantation between January 1st 2006 and December 31st 2015, who were still under care of the UMCU and had at least 6 months experience with the CI. Patients were first approached in June 2016. The patients who did not respond to the first invitation received a second invitation for participation in August 2016. For all patients who returned the completed informed consent form and questionnaire, additional patient information was extracted from the medical file.

Questionnaire

The questionnaire contained a general and a tinnitus specific part. The general part included questions concerning demographic characteristics as ethnicity and education and tinnitus related comorbidity (anxiety, depression, sleep, chronic pain and dizziness disorders). The tinnitus questionnaire included questions concerning the preoperative and postoperative presence, severity, and localization of tinnitus, and tinnitus change postoperatively (improved, stable or worsened). The severity of tinnitus preoperatively was assessed with a multiple choice question with the following answer possibilities: mild/moderate/severe. If patients were currently suffering from tinnitus, they were asked to complete a Visual Analogue Scale (VAS) ranging from 0 (low) to 10 (high) concerning the tinnitus loudness, annoyance and pitch both with their CI processor turned 'on' and 'off'. Furthermore, they were asked to complete the tinnitus handicap inventory (THI)[12]. This questionnaire comprises a 12-item functional subscale, an 8-item emotional subscale and a 5-item catastrophic subscale. The total score of this questionnaire represents the overall severity of tinnitus: slight (0-16), mild (18-36), moderate (38-56), severe (58-76) or catastrophic (78-100)[12].

Data collection

Other demographic, deafness related and surgery related patient characteristics were extracted from the medical files. Demographic characteristics included age at time of surgery and gender. Deafness related characteristics included etiology, duration and severity of deafness. Surgery related characteristics included duration of follow-up, surgical approach (cochleostomy/ direct round window), full or partial insertion of the electrode and brand of CI (Cochlear/MedEl/Advanced Bionics). Hearing performance was evaluated with Pure-Tone Audiometry (PTA) and Consonant-Vowel-Consonant (CVC) tests preoperatively and postoperatively. PTA was tested in a soundproof cabin at the frequencies of 0.125, 0.25, 0.5, 1, 2, 4, and 8 kHz and was performed according to international standards (ISO 8253-1) on a Decos Audiology Workstation (Decos Technology Group, Noordwijk, the Netherlands). If a tone frequency was not heard by the patient, a threshold value of 130 decibel hearing level (dB HL) (5 dB above the maximum stimulation level) was used. The CVC phoneme test resulted in a percentage correct phoneme score (ranging from 0 – 100%).

The presence and localization of tinnitus preoperatively was assessed with a standard checklist prior to the surgery as well. As this information was prospectively collected, we used this data, when available, instead of the retrospectively collected data concerning preoperative tinnitus presence and localization.

Missing data

In case the prospectively collected data concerning preoperative tinnitus presence or localization were missing, the retrospectively collected preoperative tinnitus data were used. In case the retrospectively collected data concerning preoperative or postoperative tinnitus presence were also missing, the patient was contacted by telephone or e-mail.

In case of missing values in the THI questionnaire of a patient, the missing value was imputed with the mean question score of that patient. In case of a complete missing THI questionnaire, the patient was excluded from THI score analyses. In case of complete missing VAS scores, the patient was excluded from VAS score analyses.

Statistical methods

Baseline characteristics for patients with and without preoperative tinnitus were presented. The distribution of the data was checked visually using histograms. Normally distributed data were presented as mean and standard deviation (SD), not normally distributed data were presented as median and interquartile range (IQR).

This study has a largely descriptive character. Prevalence and severity rates of preoperative tinnitus were calculated. Changes in tinnitus following cochlear implantation were described. Incidence rates of newly induced tinnitus postoperatively were calculated. Characteristics of the patients with tinnitus induction and the patients without tinnitus induction were presented. Also the severity of postoperative tinnitus was described, using the THI total score and subdomain scores (functional, emotional and catastrophic). The median THI scores were presented for the total group, and also for subgroups of patients based on the change in tinnitus following cochlear implantation compared to the preoperative situation: decrease, no change, increase or induction of tinnitus.

Median VAS loudness, VAS annoyance and VAS pitch scores for CI turned 'on' and 'off' were presented for the total group and for each subgroup of patients. In order to measure the effect of turning the CI processor 'on' on tinnitus severity, the median VAS scores in the 'off' and 'on' condition in the total group were compared using the Wilcoxon signed rank test. The Bonferroni correction was used to correct for multiple testing, resulting in a p-value <0.017 which was considered statistically significant.

IBM SPSS Statistics version 22.0 was used for the analyses.

RESULTS

Participants

Between January 1st 2006 and December 31st 2015, 322 eligible patients underwent cochlear implantation in the UMCU (Figure 1). In the end, 137 patients were included in this study. The median follow up duration was 3.78 years (IQR:1.81-6.35).

Missing data

The number of missing data in baseline characteristics are shown in Table 1. In eight patients with postoperative tinnitus, 1-8 items of the THI were missing, which were imputed by the mean item score of that patient. In one patient, the THI questionnaire was missing completely. The VAS scores were missing completely in one patient as well. The CI was explanted in one patient and therefore this patient was excluded from the THI score and VAS score analyses.

Patients with preoperative tinnitus

The prevalence of preoperative tinnitus was 64% (87/137). Baseline characteristics of patients with and without preoperative tinnitus are presented in Table 1.

Preoperative tinnitus characteristics

The severity of preoperative tinnitus was mild in 15 (17%), moderate in 26 (30%) and severe in 22 (25%) of the patients. The information concerning the preoperative severity was missing in 24 (28%) patients.

The tinnitus was localized bilaterally in 61 (70%) patients, in the right ear only in 10 (11%) patients and in the left ear only in 16 (18%) patients

Change in tinnitus following cochlear implantation

Thirty-five patients with preoperative tinnitus (40%) reported complete recovery of tinnitus at the moment of completing the questionnaire and 16 patients (18%) reported a decrease. Twenty-four patients (28%) stated that their current tinnitus complaints were the same as before surgery. Increase of tinnitus in the years after surgery was reported by 9 (10%) patients. Three patients (3%) were still experiencing tinnitus at the moment of completing the questionnaire, but the information concerning the change in tinnitus (decrease/no change/increase) was missing.

Figure 2 shows information about the localization of the CI compared to the localization of the preoperative tinnitus for each subgroup of tinnitus change. As the figure shows, a CI at the ipsilateral as well as contralateral side of the tinnitus side could lead to improvement.

Patients with tinnitus induction

Fifty patients did not experience tinnitus preoperatively. Four patients (8%) reported that they had temporary tinnitus complaints postoperatively, with a median duration of 0.61 (range: 0.25-5) years. Induction of chronic tinnitus occurred in 7 patients (14%).

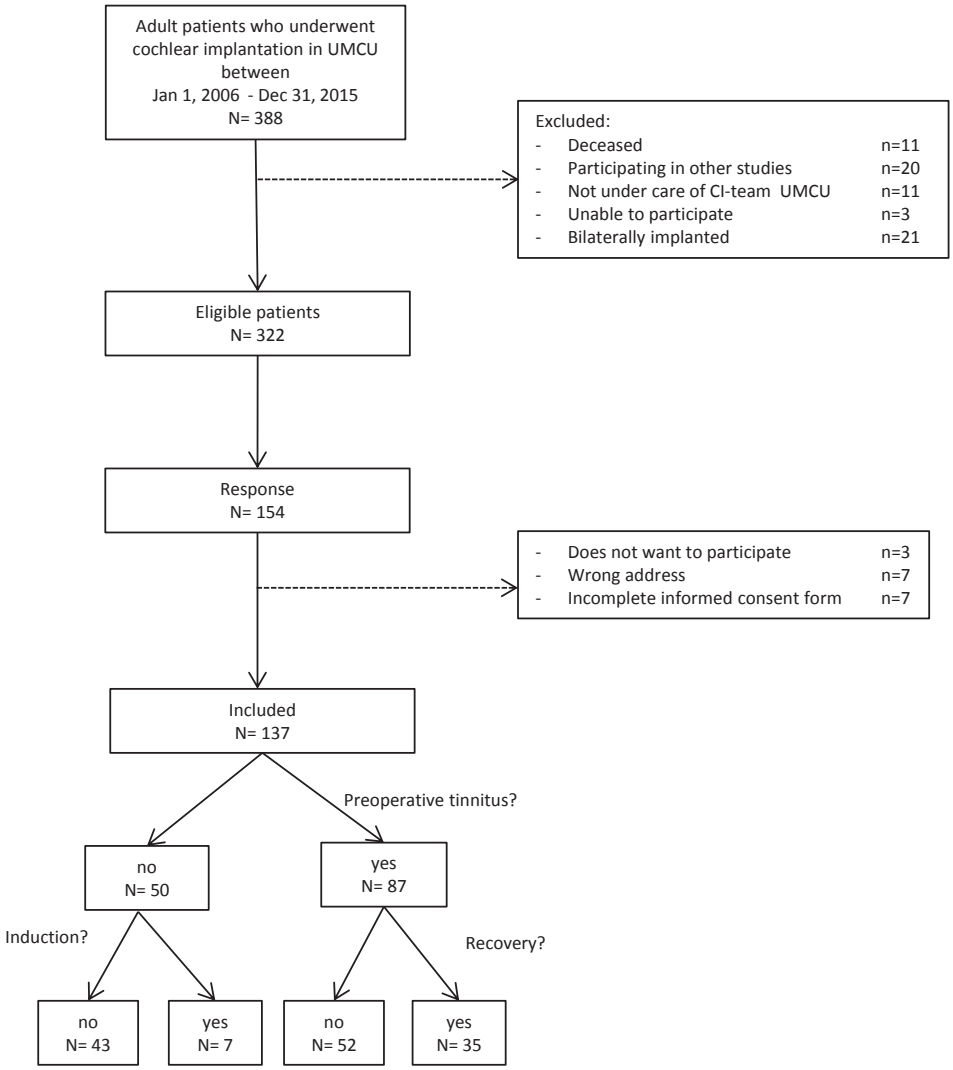

Figure 1. Flowchart of the study

In one of the patients with tinnitus induction, the CI was explanted at the moment of completing the questionnaire because of pain, tinnitus and low hearing performance. The tinnitus burden decreased after the explantation.

Tinnitus characteristics

The median THI score of patients with induced tinnitus was 22 [6-44]. In 3 of the patients (43%), the tinnitus was reported in the implanted ear, in 1 patient (14%) in the non-

implanted ear, in 2 patients (29%) in both ears and in 1 patient (14%) in the implanted ear and in the head.

Table 2 shows the characteristics of the patients with and without tinnitus induction following cochlear implantation. The largest differences were that patients with tinnitus

Table 1. Baseline characteristics of patients with and without preoperative tinnitus

	Preoperative tinnitus	
	Yes (n=87)	**No (n=50)**
Age, yr, mean (SD)	60.9 (13.1)	58.0 (16.4)
Male gender, n (%)	46 (53)	22 (44)
Education level, low/moderate/high, n(%)	34(39)/28(32)/21(24)	27(54)/8(16)/12(24)
	Missing: 4	Missing: 3
Depression in history, n (%)	5 (6)	1 (2)
	Missing: 1	Missing: 1
Anxiety disorder in history, n (%)	3 (3)	1 (2)
	Missing: 1	Missing: 1
Sleep disorder in history, n (%)	14 (16)	5 (10)
	Missing: 1	Missing: 1
Pain disorder in history, n (%)	4 (5)	1 (2)
	Missing: 1	Missing: 1
Dizziness disorder in history, n (%)	22 (25)	4 (8)
	Missing: 1	Missing: 1
Prelingual deaf, n (%)	6 (7)	10 (20)
Duration of deafness operated ear, yr, median [IQR]	10.2 [2.3-26.9]	8.2 [4.1-35.0]
Etiology of deafness operated ear		
Progressive	35 (40)	27 (54)
Congenital	9 (10)	11 (22)
Meningitis	4 (5)	3 (6)
Postnatal infection	9 (10)	3 (6)
Traumatic	4 (5)	0 (0)
Otosclerosis	7 (8)	3 (6)
Sudden deafness	3 (3)	2 (4)
Menière's disease	14 (16)	0 (0)
Iatrogenic, n (%)	2 (2)	1 (2)
Preoperative CVC score, median [IQR]	37.0 [13.5-61.5]	33 [10.0-54.0]
Preoperative PTA operated ear, mean (SD)	104.8 (17.2)	101.7 (14.0)
Preoperative low FI operated ear, median [IQR]	103.3 [90.0-118.3]	104.2 [94.6-116.7]

SD: standard deviation; yr: year; IQR: interquartile range; CVC: consonant-vowel-consonant; PTA: pure tone average, average threshold over frequencies 0.125-8 kilo hertz; Low FI: fletcher index, mean 0.5, 1, 2 kHz

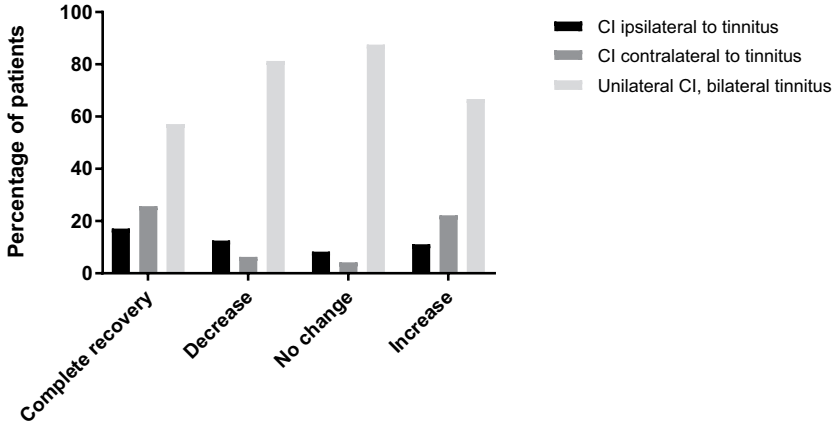

Figure 2. Localization of the cochlear implant (CI) compared to the localization of preoperative tinnitus

induction had a younger median age at time of surgery (53.4 years compared to 62.9 years), were mostly women (86% compared to 51%), had a higher percentage of prelinguality (43% compared to 16%), had a lower median preoperative CVC score (22.0 compared to 40.0), and had a smaller deterioration of residual hearing after surgery (difference in PTA score 11.4 compared to 22.5). The preoperative PTA was higher, while the postoperative PTA was lower in the patients with tinnitus induction compared to the patients without tinnitus induction (preoperative PTA 106.4 compared to 100.7 and postoperative PTA 123.9 compared to 130.0).

Tinnitus severity postoperatively

In total, 59 patients experienced tinnitus postoperatively at the moment of completing the questionnaire. In 52 of these patients the tinnitus was also present preoperatively and 7 of these patients suffered from newly induced tinnitus.

The median THI total score was 20 [8-44], functional score 10 [4-25], emotional score 2 [0-12] and catastrophic score 4 [1.5-9] (Figure 3). As Figure 3 shows, the questionnaire scores were highest in the patients with increased tinnitus (median THI total score of 48) and lowest in patients with stabilized tinnitus (median THI total score of 15).

Effect of turning CI processer 'on'

The median VAS loudness, annoyance and pitch scores decreased significantly when turning the CI processor 'on' (Figure 4). As shown in Figure 4, the differences in VAS scores between the CI 'on' and 'off' condition were biggest in the patients with decreased tinnitus complaints following cochlear implantation.

Table 2. Characteristics of patients with and without tinnitus induction

	Tinnitus induction (n=7)	**No tinnitus induction (n=43)**
Baseline characteristics		
Age, yr, median [IQR]	53.4 [38.0-62.2]	62.9 [47.5-72.3]
Male gender, n (%)	1 (14)	21 (49)
Education level, low/moderate/high, n (%)	1 (14) / 2 (29) / 3 (43)	26 (61) / 6 (14) / 9(21)
	Missing:1	Missing: 2
Prelingual deaf, n (%)	3 (43)	7 (16)
Duration of deafness operated ear, yr, median [IQR]	6.2 [2.4-40.5]	8.2 [4.3-31.1]
Etiology of deafness operated ear		
Progressive	3 (43)	24 (56)
Congenital	2 (29)	9 (21)
Meningitis	1 (14)	2 (5)
Postnatal infection	0 (0)	3 (7)
Otosclerosis	0 (0)	3 (7)
Sudden deafness	0 (0)	2 (5)
Iatrogenic n (%)	1 (14)	0 (0)
Preoperative CVC score Median [IQR]	22.0 [9.0-32.0]	40.0 [10.5-55.8]
Preoperative PTA operated ear Mean (SD)	106.4 [98.6-120-0]	100.7 [90.7-110.7]
Preoperative low FI operated ear Median [IQR]	110 [101.7-121.7]	103.3 [93.3-115.0]
Per- and postoperative characteristics		
Follow up duration yr, median [IQR]	5.2 [3.0-9.1]	3.7 [1.8-5.5]
Insertion electrode Full/partial, n (%)	6 (86) / 1 (14)	40 (93) / 3 (7)
Surgical approach Cochleostomy/direct round window, n (%)	5 (71) / 1 (14)	30 (70) / 8 (19)
	Missing: 1	Missing: 5
Brand CI Cochlear/MedEl/Advanced Bionics, n (%)	5 (71) / 2 (29) / 0 (0)	14 (33) / 24 (56) / 5 (12)
Time of CI usage Daily/occasionally/non-user, n (%)	3 (43) / 3 (43) / 1 (14)	40 (93) / 1 (2) / 1 (2)
Postoperative CVC score Median [IQR]	75.0 [27.0-87.4]	76.0 [61.0-89.0]
Postoperative PTA operated ear unaided Median [IQR]	123.9 [117.9-127.1]	130.0 [121.8-130.0]
Difference in PTA score operated ear unaided (= deterioration of residual hearing) Median [IQR]	11.4 [-0.1-19.6]	22.5 [10.4-35.4]
Postoperative low FI operated ear unaided Median [IQR]	125.8 [119.9-130.0]	130.0 [121.3-130.0]
Difference in low FI operated ear	12.5 [-0.2-16.7]	23.3[10.8-31.3]

SD: standard deviation; yr: year; IQR: interquartile range; CVC: consonant-vowel-consonant; PTA: pure tone average, average threshold over frequencies 0.125-8 kilo hertz; Low FI: fletcher index, mean 0.5, 1, 2 kHz

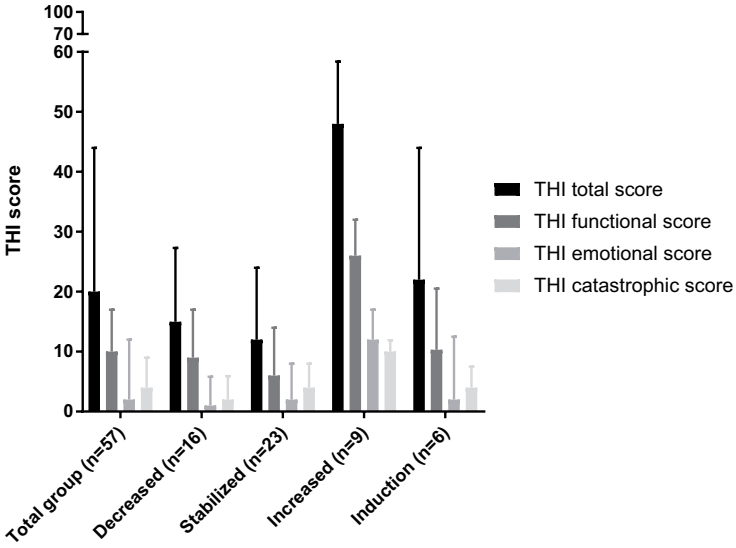

Figure 3. Tinnitus severity postoperatively for different groups of patients. Legend: Medians with IQR are presented.

DISCUSSION

Key findings

The current study used retrospective data of 137 patients who underwent unilateral cochlear implantation in a 10-year period, to give an overview of prevalence and severity rates of tinnitus before and after cochlear implantation.

The prevalence of preoperative tinnitus was 64%. Complete recovery of tinnitus was reported in 40% of these patients, decrease in 18%, no change in 28% and increase in 10% of patients. Induction of tinnitus occurred in 7 patients without preoperative tinnitus (14%).

In all patients who were (still) experiencing tinnitus postoperatively, the median THI total score was 20, indicating a mild overall tinnitus handicap. VAS loudness, annoyance and pitch scores significantly decreased when turning CI processor 'on'.

Comparison with literature

The current study shows that cochlear implantation had a beneficial effect on preoperative tinnitus in the majority of patients, which is in agreement with previous literature[5]. The rates on tinnitus induction following cochlear implantation are widely varying in literature, with rates from 0 to 20%[5–8]. The incidence found in the current study is within this range. However, we assume that the prevalences of preoperative as well as postoperative tinnitus in the current study as well as in literature could be an overestimation, as a result of bias due to retrospective study designs. Patients who do not suffer from tinnitus may be less inclined to return a questionnaire concerning tinnitus (i.e. sampling bias)[10]. Also, the onset of new

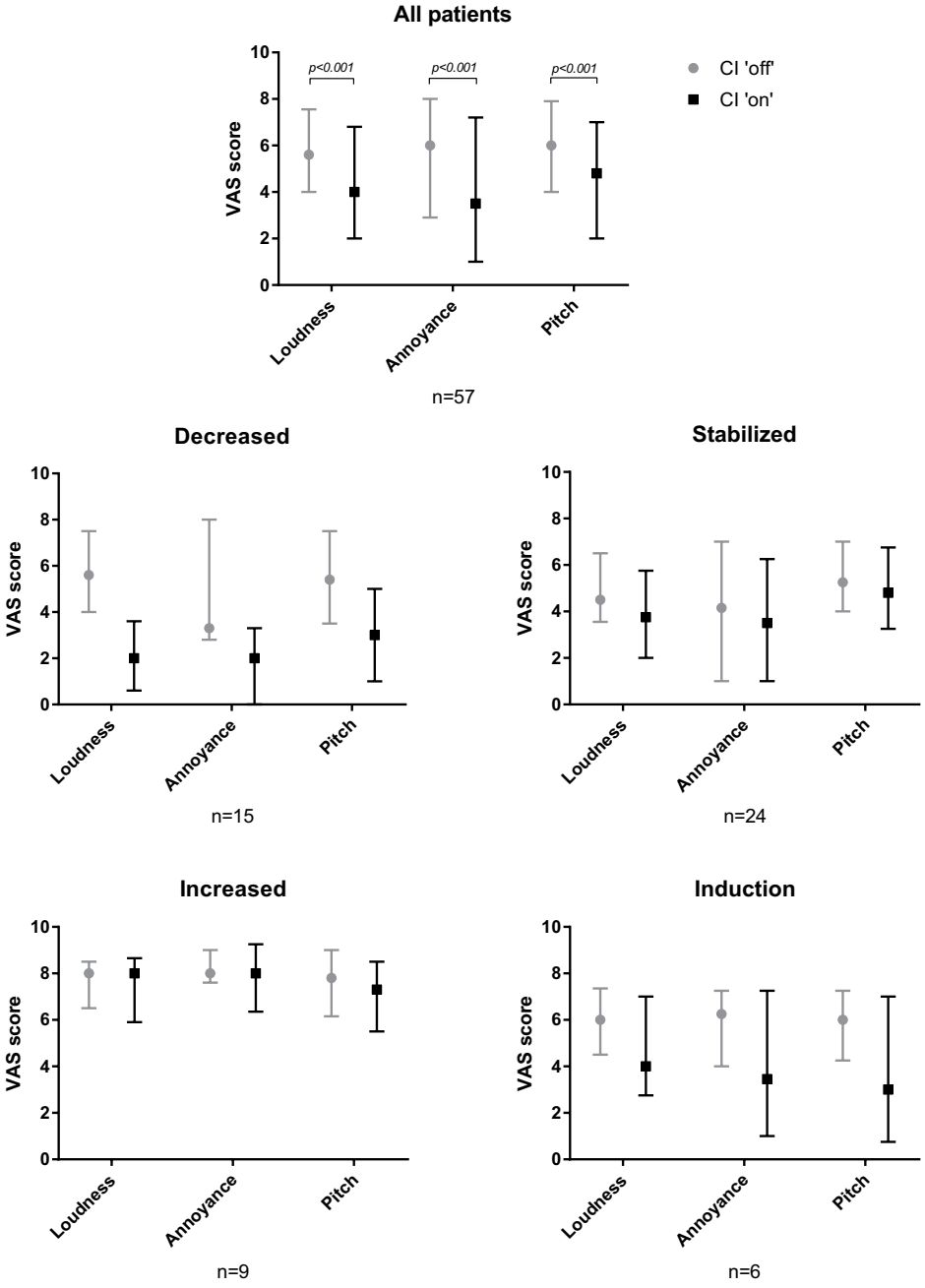

Figure 4. VAS scores when turning CI processor 'on' and 'off' for different groups of patients. The median VAS scores in the 'off' and 'on' condition in the total group were compared using the Wilcoxon signed rank test.

tinnitus could be independent of the cochlear implantation itself, as, due to the relatively long follow-up period, not solely the effect of the CI surgery or activation is investigated, but also an effect of time and age.

We tried to identify differences between patients with and without tinnitus induction following cochlear implantation. The largest differences were: a younger age, higher percentage of female gender, higher percentage of prelinguality, lower preoperative CVC score and smaller deterioration of residual hearing after surgery in patients with tinnitus induction compared to patients without tinnitus induction. Due to the small sample of patients with tinnitus induction (7 out of 50 patients), we were unable to perform statistical analyses. Therefore, we could not draw firm conclusions based on the current study. A previous study of Pan et al. encountered the same problem[11].

In this study of Pan et al., 11 of 91 patients (12%) suffered from newly developed tinnitus following cochlear implantation. They found a shorter duration of profound hearing loss in patients with induced tinnitus, but none of the tested characteristics differed statistically significantly between patients with and without tinnitus induction[11]. In the current study, patients with tinnitus induction had a smaller deterioration of residual hearing after surgery than patients without tinnitus induction. This is an interesting finding which is contradictory to the hypothesis investigated by Arts et al.[6]. These authors assumed that deterioration of residual hearing due to traumatic insertion of the electrode may trigger tinnitus postoperatively. In their retrospective study 25 of 131 patients (19%) suffered from newly developed tinnitus following cochlear implantation. No statistically significant association was found between perioperative deterioration of hearing thresholds and tinnitus induction[6]. To further investigate differences between patients with and without tinnitus induction following cochlear implantation, a larger study is needed in a prospective setting.

Our study showed that turning the CI processor 'on' generally had a positive effect on tinnitus, which is in agreement with previous literature[9,10]. Different from these previous studies, we tried to quantify the effect of turning the CI processor 'on' and 'off' on tinnitus severity scores in patients with bilateral deafness. The median VAS loudness, annoyance and pitch scores decreased statistically significantly from 5.6, 6.0 and 6.0 to 4.0, 3.5 and 4.8, respectively when turning the CI processor 'on'.

The exact mechanisms on how a CI influences tinnitus severity remain unknown. One possible explanation for the reduction of tinnitus after cochlear implantation is the electrical stimulation of the CI itself[13]. Another possible explanation is improvement of auditory abilities which lead to a situation where the patient can focus his/her auditory attention on sounds other than tinnitus (acoustic masking)[14]. These theories would suggest that the tinnitus will increase or return when turning the CI processor 'off'. The fact that we found higher VAS scores when CI 'off' compared to CI 'on' situation, can contribute to the latter theory. This theory, however, does not explain the sustained suppression of tinnitus when the CI processor is turned 'off' [9], which was found in 40% of patients in our study. The facts that tinnitus improvement as well as deterioration can be seen when the CI processor is switched 'on' as well as 'off' and in the ipsilateral, contralateral and both ears[9,15], indicate the difficulties in tinnitus mechanisms.

Future research is needed to further investigate which patients with tinnitus are most likely to benefit from cochlear implantation and for which patients cochlear implantation will most likely lead to increased or even newly induced tinnitus. Our research group will investigate possible predictors for tinnitus recovery following cochlear implantation[16] (Chapter 1.3).

Strengths and limitations

This retrospective study gives an overview of prevalence and severity rates of tinnitus before and after unilateral cochlear implantation in our tertiary care center. Multiple research questions were investigated.

There are several shortcomings to our study. One of the limitations is the retrospective study design, which could have resulted in recall bias by the relatively long follow up period. We tried to minimize this bias by using the prospectively measured data concerning preoperative tinnitus presence and localization. However, information concerning preoperative tinnitus severity was asked retrospectively with a single question instead of a more valid measurement as the THI for example. Furthermore, the PTA results of this study could be biased by the use of a cutoff value of 130 dB HL for all frequencies when a tone was not heard by the patient. It is questionable whether 130 dB HL is the correct cutoff value to use and whether it is correct to use the same cutoff value for all frequencies. Another possible limitation of this study is the selection of the included patients. Only 137 of 322 eligible patients (43%) were included. Non-response bias could have occurred. We tried to minimize this bias by sending a reminder to the patients who did not respond after the first invitation. Due to ethical limitation, we were not able to determine differences between responders and non-responders. Another limitation is the relatively small sample size, especially in the different subgroups of change in tinnitus. Therefore this study has a largely descriptive character. The small sample sizes in the tinnitus induction group for example (n=7) withheld us from performing statistical tests to identify differences between the patients with and without tinnitus induction.

CONCLUSION

In the majority of patients, unilateral cochlear implantation had a positive effect on preoperative tinnitus. However, induction of tinnitus also occurred in 14% of patients without preoperative tinnitus. Differences were seen in characteristics between patients with tinnitus induction compared to patients without induction, however the small sample size withheld us from drawing firm conclusions. In all patients who were experiencing tinnitus postoperatively, the tinnitus overall handicap was mild and turning the CI processor ‘on’ had a positive effect on VAS loudness, annoyance and pitch scores.

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Chapter 1.3

The development and internal validation of a multivariable prediction model for tinnitus recovery following unilateral cochlear implantation: a cross-sectional retrospective study

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ABSTRACT

Objective
To develop and internally validate a prediction model for tinnitus recovery following unilateral cochlear implantation.

Design
A cross-sectional retrospective study.

Setting
A questionnaire concerning tinnitus was sent to patients with bilateral severe to profound hearing loss, who underwent unilateral cochlear implantation at the University Medical Center Utrecht, the Netherlands, between January 1st 2006 and December 31st 2015.

Participants
Of 137 included patients, 87 patients experienced tinnitus preoperatively. Data of these 87 patients was used to develop the prediction model.

Primary and secondary outcome measures
The outcome of the prediction model was tinnitus recovery. Investigated predictors were: age, gender, duration of deafness, preoperative hearing performance, tinnitus duration, severity and localization, follow-up duration, localization of cochlear implant (CI) compared to tinnitus side, surgical approach, insertion depth of the electrode, CI brand, and difference in hearing threshold following cochlear implantation. Multivariable backward logistic regression was performed. Missing data were handled using multiple imputation. The performance of the model was assessed by the calibrative and discriminative ability of the model. The prediction model was internally validated using bootstrapping techniques.

Results
The tinnitus recovery rate was 40%. A lower preoperative Consonant-Vowel-Consonant (CVC) score, unilateral localization of tinnitus and larger deterioration of residual hearing at 250 Hz revealed to be relevant predictors for tinnitus recovery. The area under the receiver operating characteristics curve (AUC) of the initial model was 0.722 [IQR: 0.703-0.729]. After internal validation of this prediction model, the AUC decreased to 0.696 [IQR: 0.667-0.700].

Conclusion and Relevance
Lower preoperative CVC score, unilateral localization of tinnitus and larger deterioration of residual hearing at 250 Hz were significant predictors for tinnitus recovery following unilateral cochlear implantation. The performance of the model developed in this retrospective study is promising. However, before clinical use of the model, the conduction of a larger prospective study is recommended.

INTRODUCTION

Tinnitus is a common problem, but uncertainty exists about its true prevalence. Estimates range between 5% and 43%.[1] In the majority of the individuals, tinnitus is accompanied by sensorineural hearing loss[2,3]. Currently, standard clinical care for adult patients with bilateral severe to profound sensorineural hearing loss is unilateral cochlear implantation[4]. Prevalence rates of preoperative tinnitus in cochlear implant (CI) patients range from 66% to 86%[5].

Partial or complete suppression of tinnitus is often reported as a beneficial side effect of cochlear implantation[6]. A recent systematic review reported recovery (complete suppression) of tinnitus in 8% to 45% of patients and a decrease of tinnitus in 25% to 72% of patients with preoperative tinnitus[6]. However, an increase of tinnitus burden was also reported in 0% to 25% of patients. Even newly induced tinnitus after cochlear implantation can occur in 0% to 20% of patients without preoperative tinnitus[6–9]. Cochlear implantation as a single treatment for invalidating tinnitus with or without unilateral sensorineural hearing loss is still part of debate in the literature[10].

Which CI patients with preoperative tinnitus will recover from tinnitus after cochlear implantation and which patients will not, is barely investigated. A prediction model for tinnitus recovery following cochlear implantation to identify these different groups, would be of great importance. Firstly, a prediction model would enable clinicians to counsel patients preoperatively about the expectations regarding their tinnitus recovery. Secondly, knowledge about predictive factors that can be influenced could lead to adjustments in the patient's lifestyle or treatment strategy in order to increase the chance of tinnitus recovery.

To date, only few studies investigated possible predictors for tinnitus improvement following cochlear implantation. The prospective study of Kim et al.[11] did this as a secondary analysis of their study. Three factors significantly predicted tinnitus outcome: the preoperative auditory steady-state response (ASSR), which is an electrophysiological test that evaluates hearing thresholds, the Tinnitus Handicap Inventory (THI) score, which indicates tinnitus severity and the final Beck's Depression Index (BDI) score, which indicates depression severity[11]. No information was given on the performance of this model and this model was not internally or externally validated. The study of Pan et al.[12] tried to identify differences between patients with and without tinnitus recovery, but no clear differences were found[12].

A study conducting, developing and validating a multivariable clinical prediction model is lacking. Therefore, the aim of the current study was to develop and internally validate a clinical model that predicts tinnitus recovery following unilateral cochlear implantation in patients with bilateral severe to profound hearing loss and preoperative tinnitus.

METHODS

We conducted and reported this study using the transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD) statement[13].

The 10-year results concerning prevalence rates of tinnitus in our center are previously reported using the same database as the current study[14] (Chapter 1.2).

Ethics approval

This study was designed and conducted in accordance with the Declaration of Helsinki[15] and an exemption of full review was obtained from the Medical Ethics Committee of the University Medical Center Utrecht (UMCU) (WAG/mb/16/003184). Exemption was obtained because participants had to complete a short questionnaire only and were not subject to procedures or required to follow rules of behavior. All included participants provided written informed consent.

Study design and participants

This retrospective study was conducted at the Department of Otorhinolaryngology, Head and Neck Surgery from the UMCU. A self-developed questionnaire was sent out to all adult patients with bilateral severe to profound hearing loss who underwent unilateral cochlear implantation between January 1st 2006 and December 31st 2015, who were still under care of the UMCU and had at least 6 months experience with the CI. Patients were first approached in June 2016. The patients who did not answer the first invitation received a second invitation for participation in August 2016. For all patients who returned the completed informed consent form and questionnaire, additional patient information needed for the prediction model was extracted from the medical file. The flowchart of the study is presented in Figure 1.

Outcome

The outcome that is predicted by the prediction model is tinnitus recovery after cochlear implantation. Tinnitus recovery was defined as the presence of tinnitus preoperatively and complete absence of tinnitus postoperatively at the moment of completing the questionnaire. Complete absence was defined as absence of tinnitus in all situations: when the CI was switched 'on' and 'off'. The presence of tinnitus preoperatively was assessed in a standard preoperative checklist and collected from the medical file. The presence of tinnitus postoperatively was assessed with the questionnaire.

Potential predictors

Potential predictors based on clinical relevance and literature included a wide range of demographic, deafness related, tinnitus related and surgery related factors[8,11,16]. Information concerning these possible predictors was collected from the medical file and information not available in the medical file was collected with the questionnaire.

Demographic factors, age at time of surgery and gender, were collected from the medical file. Deafness related factors were extracted from the medical file and included prelinguality, duration of deafness, etiology of deafness and preoperative and postoperative hearing performance.

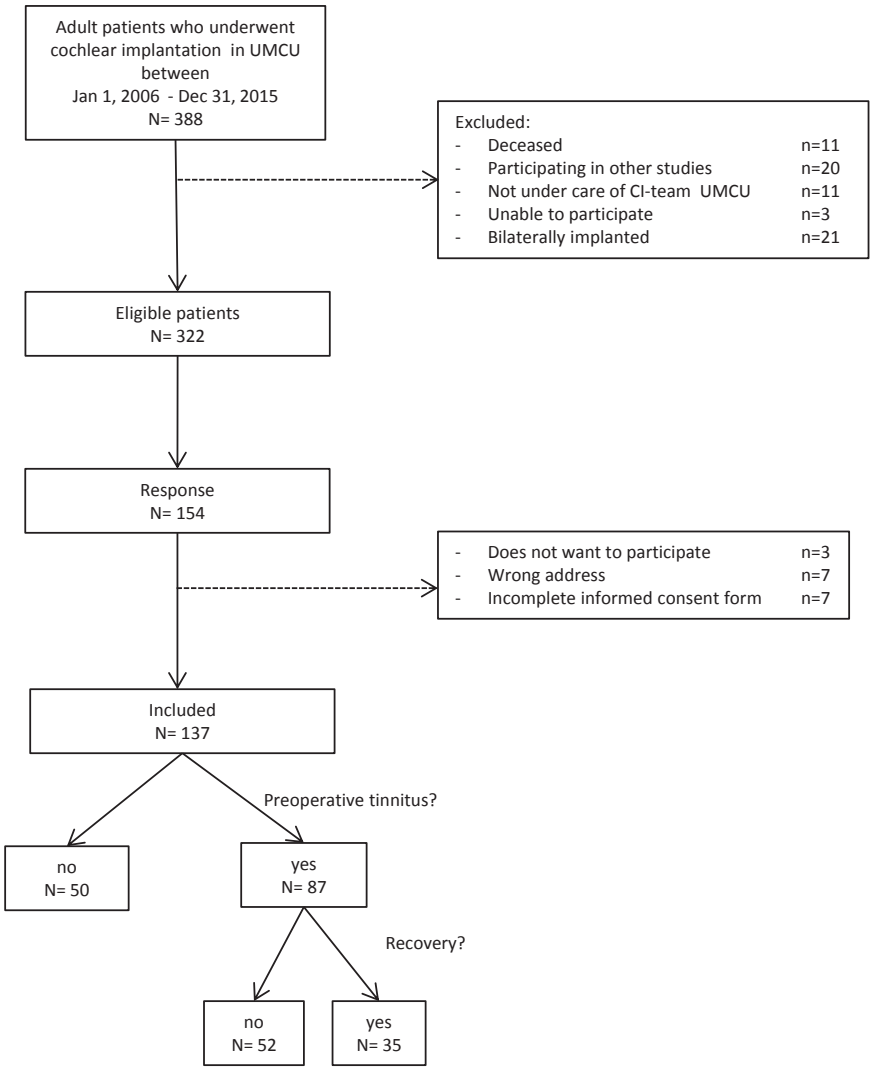

Figure 1. Flowchart of the study

Hearing performance was measured using two hearing tests: the Consonant-Vowel-Consonant (CVC) test, which results in a percentage correct score and audiometric hearing thresholds measured by pure-tone audiometry (PTA) at frequencies 125, 250, 500, 1000, 2000, 4000, 8000 Hertz (Hz), which results in a threshold per frequency in decibel hearing level (dBHL). If a frequency was not heard by the patient, a threshold value of 130 dBHL was used as cutoff value[14].

Tinnitus related factors collected with the questionnaire were: preoperative tinnitus duration, tinnitus severity (mild/moderate/severe) and tinnitus related comorbidity as depression and anxiety. The localization of tinnitus was asked in a standard preoperative checklist and collected from the medical file.

Surgery related factors were extracted from the medical file and included the time between surgery and completing the questionnaire (follow-up duration), localization of CI compared to tinnitus side, surgical approach (cochleostomy or round window), full or partial insertion of the electrode, brand of CI, and deterioration of hearing after surgery. Deterioration of hearing was defined as difference in hearing threshold after surgery per frequency in the operated ear (pure tone threshold shortly after surgery minus threshold shortly before surgery).[8,11,16]

Missing data

Outcome: There were no missings in preoperative tinnitus data. Eight patients were contacted by telephone to solve the missings in retrospectively collected data concerning postoperative tinnitus presence.

Predictors: Duration of tinnitus was missing in 45%, severity of tinnitus was missing in 28%, surgical approach in 6%, preoperative CVC score in 2%, difference in thresholds at 250-8000 Hz in 12% and difference at 125 Hz in 13% of patients.

The Little's missing completely at random (MCAR) test and independent t-tests and chi-square tests with missing data indicator as group variable were used to differentiate between MCAR and not MCAR data. Our missing data was most likely MCAR for the variables surgical approach and preoperative CVC score and most likely missing at random for the duration of tinnitus, severity of tinnitus and the hearing thresholds[17]. In either way, multiple imputation is a decent method[17]. Therefore, multiple imputation was performed for all of above mentioned predictor variables with missing data using the multivariate imputation by chained equation (MICE) procedure with the predictive mean matching method. Variables with more than 40% missing data were only imputed and not used as predictor. Fifteen multiple imputed datasets were created, as the total percentage of missing observations was about 15%. All results from the pooled dataset are reported. Rubin's rules were used to pool the regression coefficient estimates from the imputed datasets. As a sensitivity analysis the results of the original dataset with missing data are also reported.

Statistical methods

Baseline characteristics of patients with and without tinnitus recovery were presented. Normally distributed data were presented as mean and standard deviation (SD), not normally distributed data were presented as median and interquartile range (IQR).

For the final prediction model, we attempted to not cross the 10 event/non-events per predictor variable (EPV) criterion[18]. Therefore, we firstly selected the most important potential predictors based on clinical relevance, literature and the baseline descriptives. Univariable logistic regression with the remaining predictors as covariate and tinnitus recovery (no=0, yes=1) as the dependent variable was performed afterwards.

As recommended in the TRIPOD statement, Akaike's information criterion (p<0.157) was used to select a predictor after univariable screening. The most relevant predictors after univariable screening were used in the final multivariable logistic regression model and backward stepwise selection was applied for removal of a predictor (p<0.157). In case there was multicollinearity between variables, the variable with the best predictive value (i.e. combination of p-value and type of predictor variable) was selected.

The performance of a prediction model can be assessed by the calibrative and discriminative ability of the model. Calibration refers to the agreement between the predicted outcomes and the observed outcomes[19,20]. A calibration curve will present the predicted and observed probabilities for deciles of patients in the first imputed dataset[20]. The calibration will also be assessed with the Hosmer and Lemeshow test for goodness of fit in all imputed datasets and the range of *p*-values is reported. A *p*-value >0.05 means a good fit of the model, as it indicates that there is no significant difference between the predicted and observed outcomes. The discrimination of the model is the ability of the model to distinguish between patients who did recover from tinnitus and patients who did not recover from tinnitus[19]. The discrimination will be assessed with the area under receiver operating characteristics (ROC) curve (AUC) in each imputed dataset and the median AUC with IQR will be reported[21]. An AUC ranges from 0.5 (no discrimination above chance) to 1 (perfect discrimination).

Especially in small datasets there is a high chance that the prediction model is overfitted, i.e. too much adapted to the data. To adjust the prediction model for overfitting, bootstrapping techniques (250 bootstraps) were used, which is called internal validation. This procedure generates a calibration slope that can be used to adjust the regression coefficients (and indirect the odds ratios (OR)) and the AUC[21].

R version 3.0.3 was used for the internal validation, IBM SPSS Statistics version 22.0 was used for all other analyses.

RESULTS

Participants

Between January 1st 2006 and December 31st 2015, 322 eligible patients underwent unilateral cochlear implantation in the UMCU (Figure 1). Eventually, 137 patients were included in this study. All patients received a CI because of severe to profound hearing loss and the presence or severity of tinnitus were not part of the indication criteria. The prevalence of preoperative tinnitus was 64%. The data of these 87 patients was used to develop the prediction model. The recovery rate of tinnitus was 40%. Worsening of tinnitus in the years after surgery was reported by 9 (10%) patients.

Prediction model

Table 1 presents the baseline characteristics of the patients with and without tinnitus recovery. The median follow-up period was 5.3 [IQR: 2.4-7.1] years in the patients with tinnitus recovery and 3.5 [IQR: 1.5-6.1] years in the patients without tinnitus recovery.

Table 1. Baseline characteristics of patients with and without recovery of preoperative tinnitus

	Recovery (n=35)	No recovery (n=52)
Demographics		
Age in years, median [IQR]	67.7 [58.3-71.2]	60.0 [51.7-66.2]
Male, n (%)	20 (57)	26 (50)
Deafness related factors		
Prelinguality, n (%)	3 (9)	3 (6)
Duration of deafness operated ear in years, median [IQR]	9.7 [2.1-34.6]	10.3 [2.5-23.1]
Etiology of deafness operated ear, n (%)		
Progressive	18 (51)	17 (33)
Congenital	3 (9)	6 (12)
Meningitis	1 (3)	3 (6)
Postnatal infection	4 (11)	5 (10)
Traumatic	1 (3)	3 (6)
Otosclerosis	2 (6)	5 (10)
Sudden deafness	0 (0)	3 (6)
Menière's disease	5 (14)	9 (17)
Iatrogenic	1 (3)	1 (2)
Preoperative CVC score, median [IQR]	33.0 [0.0-58.0]	45.0 [24.3-64.0]
		Missing: 2
Preoperative PTA threshold operated ear in dBHL, mean (SD)	100.8 (16.8)	106.7 (17.3)
	Missing: 1	Missing: 1
Tinnitus related factors		
Tinnitus duration preoperative in years, median [IQR]	10.0 [4.6-16.3]	17.3 [10.0-30.0]
	Missing: 25	Missing: 14
Tinnitus severity preoperative, n (%)		
Mild	2 (14)	13 (27)
Moderate	7 (50)	19 (39)
Severe	5 (36)	17 (35)
	Missing: 21	Missing: 3
Localization tinnitus, n (%)		
Right ear	6 (17)	4 (8)
Left ear	9 (26)	7 (13)
Bilateral	20 (57)	41 (79)
Depression preoperative, n (%)	2 (6)	3 (6)
		Missing: 1
Anxiety preoperative, n (%)	1 (3)	2 (4)
	Missing: 1	Missing: 1
Surgery related factors		
Follow-up duration in years, median [IQR]	5.3 [2.4-7.1]	3.5 [1.5-6.1]
Localization cochlear implant vs tinnitus, n (%)		
cochlear implant contralateral to tinnitus side	9 (26)	4 (8)
cochlear implant ipsilateral to tinnitus side	6 (17)	7 (13)
unilateral cochlear implant, bilateral tinnitus	20 (57)	41 (79)
Surgical approach, n (%)		
Cochleostomy	26 (74)	36 (69)
Round window	8 (23)	12 (23)
	Missing: 1	Missing: 4

Table 1. Continued

Insertion, n (%)		
Full	34 (97)	46 (88)
Partial	1 (3)	6 (12)
Brand cochlear implant, n (%)		
Cochlear	13 (37)	25 (48)
MedEl	17 (49)	23 (44)
Advanced Bionics	5 (14)	4 (8)
Postoperative CVC in percentage score, median [IQR]	83.3 [52.0-88.0]	85.9 [78.2-94.0]
Difference in PTA threshold operated ear in dBHL, median [IQR]	25.7 [9.4-37.0] Missing: 3	16.6 [4.3-28.4] Missing: 8

IQR: interquartile range; SD: standard deviation; CVC: consonant-vowel-consonant test; PTA: pure tone average, average threshold over frequencies 0.125-8 kHz

The prevalences of prelinguality and tinnitus related comorbidity were very low in both groups and therefore these variables were not further investigated. The etiology of deafness was a variable with a lot of categories and low prevalences in many categories, therefore this variable was not further investigated. Figure 2 presents the detoriation in hearing thresholds per frequency for both groups. As the largest differences between groups were seen at the low frequencies (125-1000 Hz), only these frequencies were further investigated as potential predictors (Table 2).

Age, preoperative CVC score, tinnitus localization, localization of CI compared to tinnitus side and the difference in hearing threshold measured at 250 Hz appeared to be the most relevant predictors after univariable logistic regression analyses of all potential predictors (Table 2).

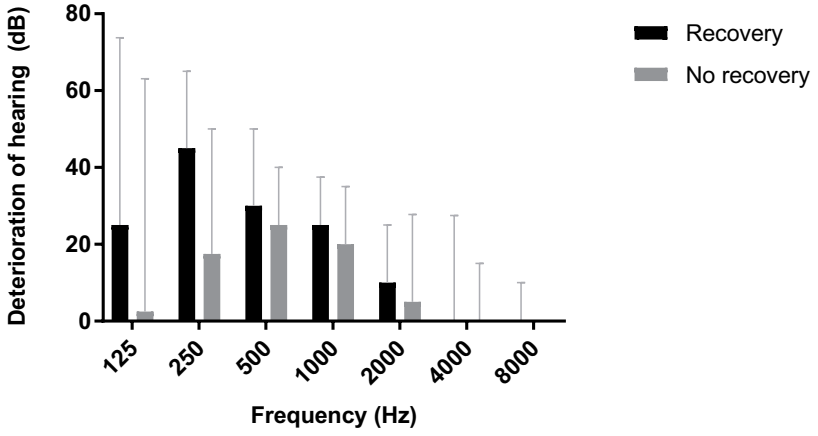

Figure 2. Deterioration of hearing in the operated ear after cochlear implantation for patients with and without tinnitus recovery. Legend: Medians with IQR are presented

Table 2. Univariable logistic regression between predictor variables and tinnitus recovery (results of pooled analyses after multiple imputation) (n=87)

Predictor	OR (95%-CI)	*p*-value
Demographics		
Age	1.033 (0.997 – 1.071)	**0.075**
Gender		
Female	REF	REF
Male	0.750 (0.317 – 1.777)	0.513
Deafness related factors		
Duration of deafness operated ear	1.004 (0.982 – 1.027)	0.738
Preoperative CVC score	0.986 (0.971 – 1.003)	**0.101**
Tinnitus related factors		
Tinnitus duration	0.964 (0.912 – 1.019)	0.193
Tinnitus severity		
Mild	REF	REF
Moderate	0.776 (0.118 – 5.112)	0.787
Severe	0.690 (0.086 – 5.573)	0.720
Localization tinnitus		
Unilateral	REF	REF
Bilateral	0.358 (0.139 – 0.919)	**0.033**
Surgery related factors		
Follow-up duration	1.100 (0.944 – 1.283)	0.223
Localization cochlear implant vs tinnitus		
cochlear implant contralateral to tinnitus side	REF	REF
cochlear implant ipsilateral to tinnitus side	0.381 (0.077 – 1.896)	0.239
unilateral cochlear implant, bilateral tinnitus	0.217 (0.059 – 0.790)	**0.021**
Surgical approach		
Cochleostomy	REF	REF
Round window	0.921 (0.329 – 2.576)	0.876
Insertion		
Partial	REF	REF
Full	4.435 (0.510 – 8.567)	0.177
Brand cochlear implant		
Cochlear	REF	REF
MedEl	1.421 (0.568 – 3.558)	0.453
Advanced Bionics	2.404 (0.550 – 0.515)	0.244
Difference hearing threshold at 125 Hz	1.005 (0.993 – 1.017)	0.444
Difference hearing threshold at 250 Hz	1.015 (0.999 – 1.031)	**0.071**
Difference hearing threshold at 500 Hz	1.006 (0.987 – 1.026)	0.533
Difference hearing threshold at 1000 Hz	1.012 (0.986 – 1.038)	0.374

OR: odds ratio; 95%-CI: 95% confidence interval; REF: reference; CVC: consonant-vowel-consonant test.
OR > 1: in favor of tinnitus recovery. *P*-values <0.157 (Akaike's criterion) are presented in bold.

Since the predictors 'tinnitus localization' and 'localization of CI compared to tinnitus' were collinear, the 'tinnitus localization' was chosen for the final analysis. After applying stepwise backward regression analysis with the remaining predictors, preoperative CVC score (OR = 0.978; 95%-CI [0.958 – 0.999]), bilateral tinnitus (OR = 0.412; 95%-CI [0.151 – 1.124]) and difference in 250 Hz (1.024, 95%-CI [1.004 – 1.044]) were the strongest predictors for tinnitus recovery (Table 3). Backward regression analysis in the original dataset without missing data revealed similar results (Table 3).

Model performance

The Hosmer and Lemeshow test for goodness of fit was not significant in all the imputed datasets with a *p*-value range between 0.121 and 0.705. Figure 3 shows the calibration curve of the predicted and observed probabilities of tinnitus recovery. The median AUC was 0.722 [IQR: 0.703-0.729].

In the original dataset with missing data the Hosmer and Lemeshow test was also not significant with a *p*-value of 0.383 and the AUC was 0.711 (95%-CI [0.595-0.826]).

Internal validation

The mean slope shrinkage factor after bootstrapping in all the imputed datasets was 0.779 (SE:0.007). This led to adjusted ORs for all the predictors (Table 3). The median AUC of the model decreased to 0.696 [IQR: 0.667-0.700].

Table 3. Multivariable logistic regression model for the prediction of tinnitus recovery following unilateral cochlear implantation (in the pooled dataset and in the original dataset as sensitivity analysis)

	Pooled dataset (15 multiple imputed sets) (n=87)			**Original dataset (complete case) (n=76)**		
Predictor	**OR (adjusted OR)**	**95%-CI**	***p*-value**	**OR**	**95%-CI**	***p*-value**
Preoperative CVC score	0.978 (0.983)	0.958 – 0.999	0.038	0.978	0.957 – 0.999	0.042
Bilateral tinnitus preoperative	0.412 (0.501)	0.151 – 1.124	0.083	0.490	0.171 – 1.402	0.184
Difference audiometry 250 Hz	1.024 (1.019)	1.004 – 1.044	0.017	1.024	1.005 – 1.044	0.013

OR: odds ratio; Adjusted OR: OR corrected for overoptimism after internal validation; 95%-CI: 95% confidence interval; CVC: consonant-vowel-consonant test; Hz: hertz
OR > 1: in favor of tinnitus recovery
Prediction rule of the pooled dataset after internal validation: linear predictor = 0,247-(0,017*preoperative CVC score)-(0,691*bilateral tinnitus)+(0,019*difference in hearing threshold at 250 Hz)

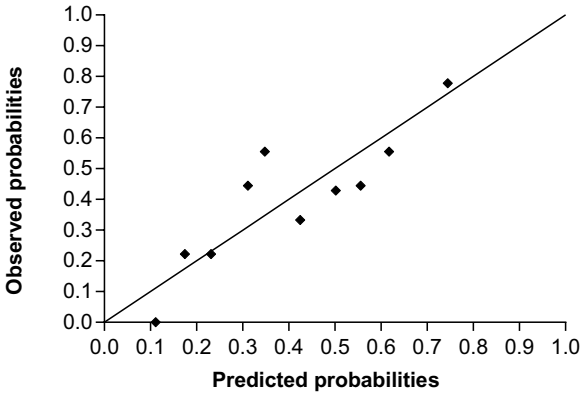

Figure 3. The frequencies of observed outcomes for tenths of predicted probabilities. Legend: results from the first imputed dataset.

DISCUSSION

Key findings

The current study used retrospective data to identify predictors for tinnitus recovery following unilateral cochlear implantation. Recovery of tinnitus was more common in patients with a lower preoperative CVC score, unilateral localization of tinnitus and larger deterioration of residual hearing at 250 Hz.

Comparison with literature

In the relatively small study population (n=40) of Kim et al. a higher preoperative THI score (indicating more severe tinnitus) predicted a larger change in THI score postoperatively[11]. In the current study, preoperative tinnitus severity was not indicated as a predictor for tinnitus recovery. An explanation for these contradictive results could be the measurement of tinnitus severity in the current study which was retrospectively measured with a multiple choice question instead of a validated tinnitus severity questionnaire. The retrospective design could have led to recall bias and therefore underestimation or overestimation of the preoperative tinnitus severity in the patients with tinnitus recovery. Also, the percentage of missings in preoperative tinnitus severity was high in the recovery group in the current study, which could have led to biased results.

A lower final BDI score (indicating less severe depression) was another predictor reported by Kim et al[11]. This finding corresponds with previous literature on the correlation between tinnitus severity and depression[7,16]. The current study did not investigate depression severity. Only the presence of depression was measured. Due to the low prevalence of depression however, the current study does not allow conclusions regarding the predictive value of this variable.

Strengths and weaknesses of this study

To our knowledge this is the first study with the primary aim to develop and internally validate a multivariable prediction model for tinnitus recovery following unilateral cochlear implantation. A wide range of clinically useful possible predictors was investigated. Another strength of our study is the internal validation of the prediction model using bootstrapping techniques. Also, missing data were handled using multiple imputation.

A limitation of this study is the retrospective study design, which could have resulted in recall bias by the relatively long follow-up period. We tried to minimize recall bias by using the prospectively measured data concerning preoperative tinnitus outcome. However, information concerning possible predictors was retrospectively collected. The long recall interval could probably have resulted in an underestimation or overestimation of the tinnitus duration and tinnitus severity. This could have resulted in an underestimation or overestimation of the predictive values of these predictors. Furthermore, patients were not asked about the exact time of the tinnitus recovery, because we assumed this would be unreliable due to the long interval. This withheld us from drawing conclusions about the time course of recovery following cochlear implantation. Also, the follow-up duration was different in both study groups, however univariable regression analysis showed this was not a significant predictor for tinnitus recovery.

Another possible limitation of this study is the selection of the included patients. Only 137 of 322 eligible patients (43%) were included. Non-response bias could have occurred. We tried to minimize this bias by sending a reminder to the patients who did not respond after the first invitation. We were not able to determine differences between responders and non-responders.

Furthermore, we were not able to determine the exact hearing threshold per frequency with the current audiometry. Therefore, a cutoff value of 130 dBHL for all frequencies was used when a tone was not heard by the patient. It is questionable whether 130 dBHL is the correct cutoff value to use and whether it is correct to use the same cutoff value for all frequencies.

Another limitation of this study is the relatively small sample size. According to the EPV criterion, we could perform a backward logistic regression analysis with a maximum of 3 variables. With the use of 4 predictors in the initial prediction model, the limit of 3 was exceeded. A recent study however, concluded that the evidence for the maximum of 10 EPV is weak and since the final model in the current study is stable, we think the exceedance did not influence the quality of the model[22]. Moreover, the list of potential predictors was relatively long and therefore we used univariable screening of predictors to identify the most important predictors. This approach could have led to the missing of a predictor that was not significant univariably, but would be significant in the multivariable analysis.

Although we investigated a long list of potential predictors, it is likely that some potentially relevant factors were missed or not available in the current study, data related to coding strategies and rehabilitation for example.

Interpretation of predictor findings and implications

We found that tinnitus recovery is higher in patients with a lower preoperative CVC score, unilateral tinnitus and larger deterioration of residual hearing at 250 Hz. In future, these findings could contribute to a better preoperative counseling of CI candidates with tinnitus and possibly lead to adjustments in structure preservation surgical techniques in order to increase the chance of tinnitus recovery.

It is hypothesized that the reduction of tinnitus after cochlear implantation is caused by the restoration of auditory input with the CI[23,24]. Another hypothesis for the reduction of tinnitus after cochlear implantation is acoustic masking. These hypotheses could explain the higher odds of tinnitus recovery in patients with unilateral tinnitus compared to patients with bilateral tinnitus, who will have stronger restoration of the pathway or masking in one of the two tinnitus ears. However, univariable logistic regression analysis showed that there was no significant higher odds on tinnitus recovery for patients with unilateral tinnitus who were implanted in the ipsilateral ear compared to patients with bilateral tinnitus. This finding is contradictive to the above listed hypotheses. A previous study already showed that unilateral cochlear implantation can reduce tinnitus in the ipsilateral, contralateral and both ears in patients with bilateral tinnitus, indicating the difficulties in tinnitus mechanisms[25].

Our study showed that deterioration of residual hearing at 250 Hz is positive for tinnitus recovery after surgery. For hearing performance however, contradictive results are found: preservation of residual hearing leads to better hearing outcomes after surgery[26]. Advances in structure preservation surgical techniques and minimal invasive electrodes during the past years have led to reduction of cochlear trauma and thereby hearing preservation in patients[26,27]. However, for the future our finding implies that adjustments are needed in structure preservation surgical techniques in CI candidates with severe tinnitus in order to increase the chance of tinnitus recovery.

The performance of the prediction model developed in this retrospective study is promising. The discrimination was reasonable as determined by an AUC of 0.696. The prediction model uses simple clinical parameters as predictors, which makes the model clinically applicable. However, before clinical use of a prediction model an AUC>0.75 is advised[28]. In order to increase the performance of the current prediction model, we would recommend to conduct a larger prospective study to develop and internally and externally validate a prediction model for tinnitus recovery following unilateral cochlear implantation.

CONCLUSION

A lower preoperative CVC score, unilateral tinnitus and larger deterioration of residual hearing at 250 Hz were positive predictors for tinnitus recovery after unilateral cochlear implantation. The performance of the prediction model developed in this retrospective study is promising. However, before clinical use of the model, the conduction of a larger prospective study is recommended.

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Chapter 1.4

Tinnitus after simultaneous and sequential bilateral cochlear implantation

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ABSTRACT

Importance
There is an ongoing global discussion on whether or not bilateral cochlear implantation should be standard care for bilateral deafness. Contrary to unilateral cochlear implantation however, little is known about the effect of bilateral cochlear implantation on tinnitus.

Objective
To investigate tinnitus outcomes one year after bilateral cochlear implantation. Secondarily, to compare tinnitus outcomes between simultaneous and sequential bilateral cochlear implantation and to investigate long-term follow-up (3 years).

Study Design
This study is a secondary analysis as part of a multicenter randomized controlled trial.

Methods
Thirty-eight postlingually deafened adults were included in the original trial, in which the presence of tinnitus was not an inclusion criterion. All participants received cochlear implants (CIs) because of profound hearing loss. Nineteen participants received bilateral CIs simultaneously and 19 participants received bilateral CIs sequentially with an inter-implant interval of 2 years. The prevalence and severity of tinnitus before and after simultaneous and sequential bilateral cochlear implantation were measured preoperatively and each year after implantation with the Tinnitus Handicap Inventory (THI) and Tinnitus Questionnaire (TQ).

Results
The prevalence of preoperative tinnitus was 42% (16/38). One year after bilateral implantation, there was a median difference of -8 (inter-quartile range (IQR): -28 to 4) in THI score and -9 (IQR: -17 to -9) in TQ score in the participants with preoperative tinnitus. Induction of tinnitus occurred in five participants, all in the simultaneous group, in the year after bilateral implantation. Although the preoperative and also the postoperative median THI and TQ scores were higher in the simultaneous group, the median difference scores were equal in both groups. In the simultaneous group, tinnitus scores fluctuated in the 3 years after implantation. In the sequential group, four patients had an additional benefit of the second CI: a total suppression of tinnitus compared with their unilateral situation.

Conclusion
While bilateral cochlear implantation can have a positive effect on preoperative tinnitus complaints, the induction of (temporary or permanent) tinnitus was also reported.

INTRODUCTION

Tinnitus is a common symptom in patients with profound sensorineural hearing loss (SNHL). Currently, standard clinical care for adult patients with bilateral profound SNHL in the Netherlands is unilateral cochlear implantation. Prevalence rates of preoperative tinnitus in cochlear implant (CI) patients range from 66% to 86%[1]. Although cochlear implantation is indicated for the hearing loss, a suppression of tinnitus is often reported as a beneficial side effect[2].

Several hypotheses exist about the etiology of tinnitus. It is thought that maladaptive plasticity in the auditory nervous system can result in tinnitus[3]. One hypothesis is that lack of peripheral auditory input leads to an overactivity of the central auditory system, which manifests as the perception of tinnitus[3,4]. Following this hypothesis, restoring the peripheral auditory input (with a CI) could lead to a decrease of tinnitus perception.

A recent systematic review showed a decrease in mean tinnitus burden after cochlear implantation in all 10 included studies[2]. On individual level, the majority of patients with preoperative tinnitus benefited from cochlear implantation (suppression rates between 8 and 45%, decrease rates between 25 and 72%); however, some patients experienced an increase in tinnitus (0-25%). In addition, newly induced tinnitus after cochlear implantation is reported (rates varying between 0 and 20%)[2,5,6]. Cochlear implantation as a treatment for invalidating tinnitus in patients with unilateral hearing loss is still part of debate in the literature, however short-term as well as long-term studies show promising results[7–10].

There is an ongoing global discussion on whether or not bilateral cochlear implantation should be standard care for bilateral deafness. Contrary to unilateral cochlear implantation however, only a few studies reported on the effect of bilateral cochlear implantation on tinnitus[11–13]. Our study group previously investigated tinnitus burden 1 year after unilateral compared with simultaneous bilateral cochlear implantation[13]. No statistically significant differences were found between the two study groups. In a study by Summerfield et al.[11] 24 unilateral CI users received a second CI with a median inter-implant interval of 2.7 years (inter-quartile range (IQR): 1.7 years). Remarkably, the mean tinnitus scores in the whole study group increased after receiving the second CI. In 7 of the 16 patients who reported tinnitus preoperatively, the tinnitus worsened after receiving the second CI. Also, in four of the eight patients without preoperative tinnitus, newly induced tinnitus occurred after receiving the second CI. In a retrospective study by Olze et al.[12] 40 sequentially bilaterally implanted patients, with a mean inter-implant interval of 3.6 years (range: 0.35-15.9 years) were evaluated. The tinnitus scores of the 28 patients with preoperative tinnitus decreased after the first CI and even further after the second CI. None of the 12 patients without preoperative tinnitus developed tinnitus postoperatively.

As the results of the above-mentioned studies are contradictive, no firm conclusions can be drawn about the additional effect of a second CI on tinnitus. Therefore, the aim of the current study was to investigate the tinnitus outcomes 1 year after bilateral cochlear implantation. Secondarily, the tinnitus outcomes in simultaneously and sequentially bilaterally implanted patients were compared. Furthermore, the long-term (3 years) tinnitus outcomes of both study groups were investigated.

MATERIALS AND METHODS

Ethical considerations

This study was approved by the Human Ethics Committees of all participating centers (NL2466001808), and was registered in the Dutch Trial Register (NTR1722). Written informed consent was obtained from all participants.

Study design

Data for the current study were collected as a secondary outcome measure as part of a multicenter randomized controlled trial (RCT). The aim of this RCT was comparing simultaneous bilateral cochlear implantation (simultaneous group) to sequential bilateral cochlear implantation with an inter-implant period of 2 years (sequential group) in adult participants with severe to profound bilateral postlingual SNHL[14,15].

Participants were evaluated before implantation and each year after implantation (Figure 1). This study reports the tinnitus outcomes 1 year following bilateral cochlear implantation, which is 1 year after bilateral implantation in the simultaneous group and 3 years after initial implantation in the sequential group. A comparison between the tinnitus outcomes in both study groups 1 year after bilateral cochlear implantation and the long-term tinnitus outcomes (3 years) are also reported.

Intervention

After giving informed consent, participants were randomly allocated to receive bilateral CIs simultaneously or sequentially with an inter-implant interval of 2 years. All participants were implanted with Advanced Bionics HiRes90K (Advanced Bionics, Sylmar, CA, USA) CIs and were provided with Harmony processors.

Tinnitus evaluation

All participants completed the Tinnitus Handicap Inventory (THI) and the Tinnitus Questionnaire (TQ) at each evaluation. Both questionnaires are internationally validated and broadly used.

The THI is a questionnaire regarding tinnitus handicap in daily life. The questionnaire comprises a 12-item functional subscale, an 8-item emotional subscale and a 5-item catastrophic subscale. The three answer options are “yes”, “sometimes” and “no”, with scores of 4, 2 and 0 respectively[16]. The total score of this questionnaire represents the severity of the tinnitus: slight (0-16), mild (18-36), moderate (38-56), severe (58-76) or catastrophic (78-100)[16,17].

The TQ consists of 52 questions on emotional and cognitive distress, intrusiveness, auditory perceptual difficulties, sleep disturbance and somatic complaints. The answer options are “true”, “partly true” and “not true”, and correspond to scores of 2, 1 and 0. Forty out of these 52 questions are used to compute the total TQ score[18].

The questionnaires are available in Dutch and a higher score indicates a higher burden of tinnitus.

Sample size

Tinnitus burden was a secondary outcome of the original RCT[14,15]. The sample size of this RCT was based on the primary outcome, which was the speech-intelligibility-in-noise. For the current study, the sample size needed to detect statistically significant changes in tinnitus scores after cochlear implantation appeared to be at least 24 participants with preoperative tinnitus. As the presence of tinnitus was not an inclusion criterion of the RCT, the proportion of participants with preoperative tinnitus (n=16) was lower than 24. The chance of detecting a true effect is therefore reduced and therefore we decided to only perform a descriptive analysis of the results.

Statistical methods

Tinnitus questionnaire scores were calculated for all participants preoperatively and each year postoperatively. In case of >10% missing data, meaning more than two questions on the THI and more than four questions on the TQ, participants would be excluded from analysis. The THI and TQ were analyzed separately since they have different clinimetric properties and measure tinnitus burden in a different way. Of the THI, the total score was calculated by the sum of all 25 questions. Of the TQ, the total score was calculated by the sum of 40 out of the 52 questions as stated by the manual[18]. A participant was considered to have tinnitus when they reached a score higher than zero on either of the questionnaires.

Changes in tinnitus scores were calculated by the subtraction of the preoperative tinnitus score from the postoperative score. Participants were divided into several categories based on their individual tinnitus complaints and evolution over time. Relevant differences in questionnaire scores are called the minimal important changes (MICs)[19,20]. If the score after implantation decreased more than the MIC, a participant was considered to have decreased tinnitus. If the score after implantation increased more than the MIC, a participant was considered to have increased tinnitus. If the difference in score was smaller than the MIC, a participant was considered to have stable tinnitus. If the postoperative score decreased to zero, a participant was considered to have a total suppression of tinnitus. For the THI, the MIC was defined as a difference of seven points between the preoperative and postoperative THI score by the study of Zeman et al[19]. This difference applies for a decrease as well as an increase in score. For the TQ, there are two different MIC scores detected by the study of Adamchic et al.[20]. Improvement was defined as a decrease of five points or more in TQ score after implantation. The MIC for deterioration was defined as an increase of one point or more in TQ score after implantation[20].

None of the results were normally distributed, therefore we reported medians and IQRs. All data were analyzed using SPSS for Windows version 21.0.

RESULTS

Recruitment and baseline characteristics

Between December 2009 and September 2012, 38 participants were included in this study. Nineteen participants were allocated to the simultaneous group and 19 participants to the sequential group[14,15,21]. Table 1 shows the baseline characteristics.

Table 1. Baseline characteristics

	Simultaneous group	Sequential group
Number of participants	19	19
Male, number (%)	8 (42)	11 (58)
Age at inclusion, years, median [IQR]	52 [36-63]	54 [43-64]
Duration severe hearing loss right ear, years, medians [IQR]	16 [11-25]	17 [9-33]
Duration severe hearing loss left ear, years, median [IQR]	16 [11-25]	18 [9-35]
PTA right ear, decibels, median [IQR]	106 [89-119]	106 [94-111]
PTA left ear, decibels, median [IQR]	108 [89-120]	108 [93-114]
Hearing aid use before CI, number/total	19/19	15/19
Tinnitus prevalence, number/total	9/19	7/19
Preoperative THI score, median [IQR]	22 [8-37]	8 [2-18]
Preoperative TQ score, median [IQR]	20 [12-27]	7 [0-24]

IQR: interquartile range; PTA: pure tone average over 1, 2 and 4 kHz, CI: cochlear implant

Loss to follow-up and missing data

In the sequential group, three participants did not receive their second CI due to withdrawal from the study for personal reasons (n=2) and central deafness due to rhesus antagonism that was missed at inclusion (n=1) (Figure 1). Therefore, the 2- and/or 3-year THI and TQ results of these patients were missing. In one other patient the 3-year TQ results were missing.

TINNITUS OUTCOMES 1 YEAR AFTER BILATERAL COCHLEAR IMPLANTATION

Participants with preoperative tinnitus

Sixteen of 38 participants (42%) experienced tinnitus before cochlear implantation according to the THI or TQ or both, of which 9 patients (47%) in the simultaneous group and 7 patients (37%) in the sequential group. The preoperative and postoperative tinnitus scores of all participants with preoperative tinnitus are shown in Table 2 and Figure 2.

The median preoperative THI score was 13 (IQR: 4-27) for all participants with preoperative tinnitus. In the simultaneous group the median preoperative THI score was 22 (IQR: 8-37) compared with 8 (IQR: 2-18) in the sequential group. The median preoperative TQ score was 17 (IQR: 6-24) for all participants with preoperative tinnitus. In the simultaneous group the median TQ score was 20 (IQR: 12-27) compared with 7 (IQR: 0-24) in the sequential group (Table 2).

One year after bilateral implantation the median difference in THI score was -8 (IQR: -28 to 4) and the median difference in TQ score was -9 (IQR: -17 to -9) for all participants with preoperative tinnitus.

One year after bilateral implantation the tinnitus had totally disappeared in 4 out of 16 participants and decreased in 6 out of 16 participants with preoperative tinnitus according to both the THI and TQ. In four participants there was disagreement between the THI and

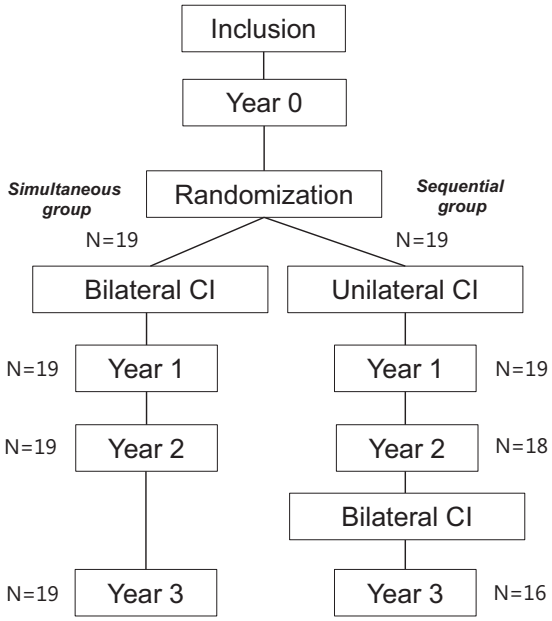

Figure 1. Flowchart of the study design

TQ (see Table 2). Two of the participants with preoperative tinnitus in the sequential group did not receive a second CI and were therefore unavailable for follow-up.

Although the preoperative and also the postoperative median THI and TQ scores were higher in the simultaneous group, the median difference scores were equal in both groups (Table 2).

Induction of tinnitus

As Table 3 and Figure 2 show, 1 year after bilateral cochlear implantation, five participants (participant 17-21) had newly induced tinnitus, all in the simultaneous group. The median THI score was 30 (IQR: 13-45) and TQ score was 20 (IQR: 8-42).

LONG-TERM RESULTS SIMULTANEOUS GROUP

Participants with preoperative tinnitus

The upper part of Figure 2 shows the progression in tinnitus scores in the nine participants with preoperative tinnitus in the 3 years after simultaneous bilateral cochlear implantation. Compared with the preoperative score, 3 years after simultaneous bilateral cochlear implantation the tinnitus had disappeared in two out of nine participants (participant 1 and 4), decreased in two out of nine (participant 2 and 3) and stabilized in one out of nine

(participant 9) participants according to both the THI and TQ. In four participants, there was disagreement between the THI and TQ.

Induction of tinnitus

As mentioned before, five participants reported a newly induced tinnitus in the first year after implantation. In two of these participants, the tinnitus was reported to be temporary (see Table 3). Two years after simultaneous bilateral implantation, one participant reported newly induced tinnitus, which had disappeared after 3 years.

Table 2. Tinnitus scores in participants with preoperative tinnitus

		THI score					TQ score				
Participant	**Group**	**Pre**	**1-yr**	**2-yr**	**3-yr**	**Δ1 yr BiCI**	**Pre**	**1-yr**	**2-yr**	**3-yr**	**Δ1 yr BiCI**
1	sim	4	0	0	0	total ↓	8	0	0	0	total ↓
2	sim	22	14	14	12	↓	24	11	13	11	↓
3	sim	22	2	0	4	↓	20	3	1	1	↓
4	sim	28	0	0	0	total ↓	41	4	2	0	↓
5	sim	46	28	30	52	↓	30	18	26	34	↓
6	sim	14	18	18	18	=	17	26	29	29	↑
7	sim	0	0	0	0	no tinnitus	1	0	0	2	total ↓
8	sim	48	22	28	28	↓	16	9	18	13	↓
9	sim	12	12	4	12	=	23	15	10	21	↓
10	seq	32	6	10	8	↓	33	7	10	7	↓
11	seq	2	0	0	0	total ↓	7	7	1	0	total ↓
12	seq	18	0	8	0	total ↓	6	8	17	0	total ↓
13	seq	8	6	4	6	=	17	21	7	8	↓
14	seq	10	4	0	2	↓	24	5	8	7	↓
15	seq	2	2	missing	missing	missing	0	4	missing	missing	missing
16	seq	4	0	0	missing	missing	0	0	0	missing	missing
Median [IQR]	total	13 [4-27]	3 [0-14]	4 [0-14]	5 [0-14]	-8* [-28 to 4]	17 [6-24]	7 [3-14]	8 [1-17]	7 [0-15]	-8.5* [-17 to -9]
Median [IQR]	sim	22 [8-37]	12 [0-20]	4 [0-23]	12 [0-23]	-8* [-23 to 0]	20 [12-27]	9 [2-17]	10 [1-22]	11 [1-25]	-8* [-15 to -4]
Median [IQR]	seq	8 [2-18]	2 [0-6]	2 [0-9]	2 [0-7]	-8* [-21 to -2]	7 [0-24]	7 [4-8]	7.5 [1-2]	7 [0-1]	-9* [-22 to -7]

THI: Tinnitus Handicap Inventory; TQ: Tinnitus Questionnaire; pre: preoperative; 1-yr: follow-up year 1; 2-yr: follow-up year 2; 3-yr: follow-up year 3; sim: simultaneous group; seq: sequential group. Δ1 yr BiCI: change in tinnitus one year after bilateral cochlear implantation (follow-up year 1 simultaneous group, follow-up year 3 sequential group). Total ↓: total suppression; ↓: decrease; =: stable; ↑: increase. A score of 0 indicated "no tinnitus". *: median difference score = tinnitus score one year after bilateral cochlear implantation minus preoperative score.

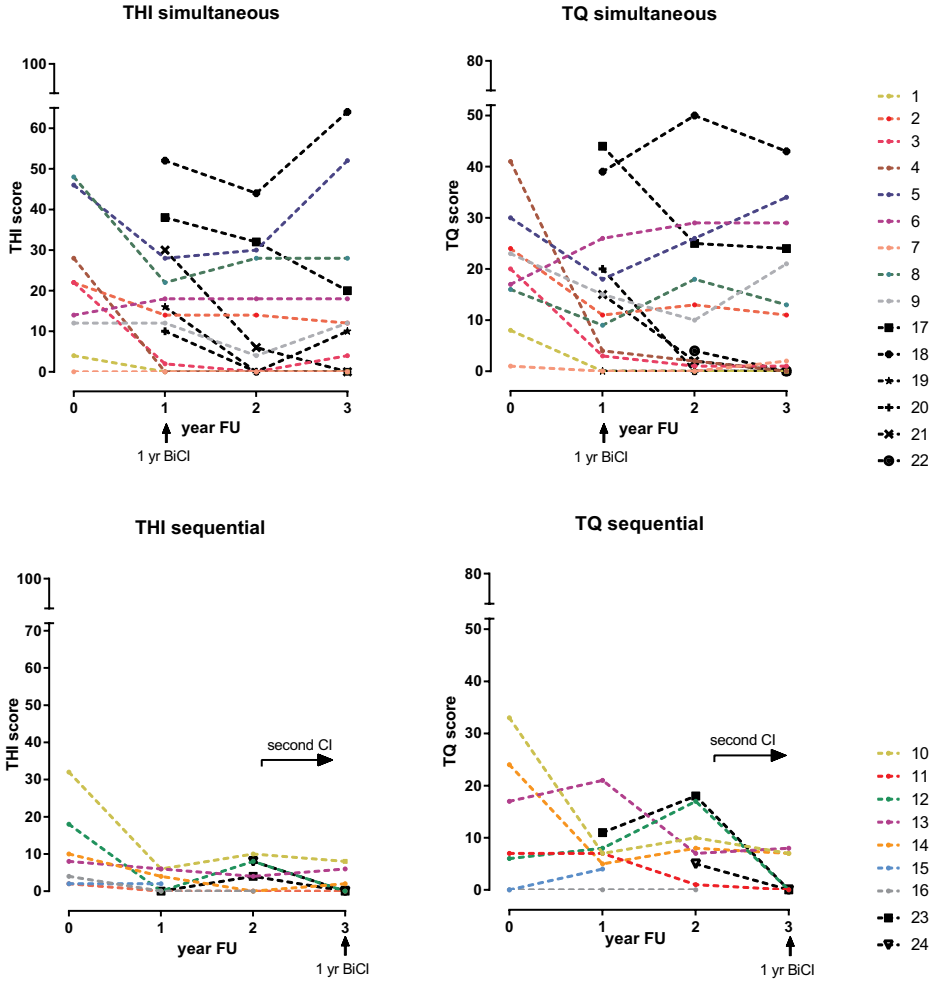

Figure 2. Tinnitus scores and its evolution over time. Legend: The upper graphs show the simultaneous implanted participants, the lower graphs show the sequential implanted participants. The left graphs show the THI scores and the right graphs show the TQ scores. Each colored line represents an individual participant with preoperative tinnitus. Each black line represents an individual participant with induced tinnitus.

LONG-TERM RESULTS SEQUENTIAL GROUP

Participants with preoperative tinnitus

The bottom part of Figure 2 shows the progression in tinnitus scores in the seven participants with preoperative tinnitus in the 2 years after unilateral implantation and in the first year after bilateral implantation. The tinnitus results 1 year after sequential bilateral implantation are described before. Compared with the unilateral situation, the tinnitus had disappeared

in two participants (participant 11 and 12). The tinnitus in participant 10 was stable after receiving the second CI. In two participants there was disagreement between the THI and TQ (participant 13 and 14) and two participants were unavailable for follow-up.

Induction of tinnitus

In the two years after unilateral implantation, two participants had newly induced tinnitus. The tinnitus disappeared in both participants after sequential bilateral cochlear implantation.

Table 3. Tinnitus scores in participants with newly induced tinnitus

		THI score				TQ score			
Participant	**Group**	**Pre**	**1-yr**	**2-yr**	**3-yr**	**Pre**	**1-yr**	**2-yr**	**3-yr**
17	sim	0	38	32	20	0	44	25	24
18	sim	0	52	44	64	0	39	50	43
19	sim	0	16	0	10	0	0	0	0
20	sim	0	10	0	0	0	20	0	0
21	sim	0	30	6	0	0	15	2	0
22	sim	0	0	8	0	0	0	4	0
23	seq	0	0	4	0	0	11	18	0
24	seq	0	0	8	0	0	0	5	0

THI: Tinnitus Handicap Inventory; TQ: Tinnitus Questionnaire; pre: preoperative; 1-yr: follow-up year 1; 2-yr: follow-up year 2; 3-yr: follow-up year 3; sim: simultaneous group; seq: sequential group. A score of 0 indicated "no tinnitus".

DISCUSSION

Key findings

In this study we investigated the prevalence and severity of tinnitus before and after simultaneous and sequential bilateral cochlear implantation. We found a relatively low prevalence (42%) and severity of preoperative tinnitus. One year after bilateral implantation there was a median difference of -8 (IQR: -28 to 4) in THI score and -9 (IQR: -17 to -9) in TQ score in the participants with preoperative tinnitus. Induction of tinnitus occurred in five participants, all in the simultaneous group, in the year after bilateral implantation. Although the preoperative and also the postoperative median THI and TQ scores were higher in the simultaneous group, the median decreases in tinnitus scores were equal after simultaneous and sequential bilateral implantation.

In the simultaneous group, tinnitus scores fluctuated in the 3 years after implantation. Total suppression or decrease of tinnitus burden occurred in four out of nine participants. In the sequential group, low median preoperative tinnitus scores were reported and the tinnitus had disappeared or decreased in four out of seven participants after a 3-year follow-

up period. Two participants did not receive a second CI and were therefore unavailable for follow-up. Four participants had an additional benefit of the second CI: a total suppression of tinnitus compared with their unilateral situation.

Comparison with literature

The preoperative tinnitus burden we found in our study is lower than described in literature[2]. Both the prevalence of tinnitus and the tinnitus burden scores preoperatively were fairly low. On the other hand, the tinnitus induction rate we found was fairly high[2,5,6]. We presume the low preoperative and high postoperative prevalence of tinnitus is due to a change of the participants' focus on hearing and all contributing factors. Therefore, it is likely that a participant did not notice the tinnitus before cochlear implantation, but by the increased attention and focus on hearing after implantation the tinnitus appeared and seemed to be newly induced. The onset of new tinnitus could also be independent of the cochlear implantation itself.

Literature on the effect of sequential bilateral cochlear implantation on tinnitus is scarce and the combination of studies that exist showed inconclusive results. Olze et al.[12] found a beneficial effect of the second CI: a further decrease of tinnitus scores in the participants with preoperative tinnitus (n=28). However, Summerfield et al.[11] found a negative effect of the second CI: increase of tinnitus scores in the whole study group (n=24), due to increased tinnitus in 7 of 16 participants with preoperative tinnitus and newly induced tinnitus in 4 of 8 participants without preoperative tinnitus. A possible reason for the discrepancy between these two studies is the difference in tinnitus outcome measurements: Olze et al. used the TQ and Summerfield et al. used a questionnaire concerning tinnitus annoyance[11,12]. In our study, four participants had an additional positive effect of the second CI on their tinnitus burden. The previous studies as well as the current study are studies with a small sample size. Therefore, no firm conclusions can be drawn. To our knowledge, no previous studies on simultaneous bilateral implantation and tinnitus are published.

Strengths and limitations

As the design of this study is an RCT, all data were prospectively collected at fixed moments and the same validated questionnaires were used in all participants to measure tinnitus burden. Besides, this is the first study which reports on the effect of simultaneous and sequential bilateral cochlear implantation on tinnitus and therefore this study provides additional evidence to the scarce knowledge.

A limitation of our study is the small sample size, which led to a low statistical power. Therefore, only descriptive analyses of the data were performed. However, it is important to report all outcome measures of an RCT and this study adds knowledge to this field with only two previous studies whose results are contradictive.

Another drawback is the lack of some participant characteristics concerning tinnitus, such as the type of tinnitus, the laterality of tinnitus and the average and maximum loudness of tinnitus. Also, we did not have information concerning psychological burden of the patients (e.g. anxiety and depression), which is known to affect tinnitus and the overall outcome

after cochlear implantation[22]. Besides, we assumed the patients suffered from subjective tinnitus; however, we did not specifically evaluate the possibility of somatic modulation, for example. Moreover, we did not have information concerning differences in tinnitus burden with the CI switched 'on' and 'off' and information concerning the exact time the CI has been worn was also lacking. Another limitation is the difference in preoperative tinnitus severity between the two study groups. This could have resulted in biased postoperative tinnitus outcomes. Tinnitus was a secondary outcome measure in the current study and not the primary complaint of the participants, neither the indication for cochlear implantation. Within the current study, no other tinnitus treatment or personalized medicine was offered to the patients[23].

Furthermore, the measurement of tinnitus is difficult, since it is a subjective symptom and consensus on which questionnaire should be used in a clinical trial is lacking[24]. In addition, as holds for the majority of questionnaires, both of the used questionnaires are not validated to measure the effectiveness of an intervention[25]. For this reason, the Tinnitus Functional Index was developed in 2012 (which was after the start of the current study)[26]. For the THI and TQ, however, the clinically relevant change in scores before and after treatment has been investigated by one study for each questionnaire[19,20]. We used the MIC scores reported in these studies, but it may be questioned whether these MIC scores are representative as for both the THI and TQ, only one study examined these scores. Since there are multiple methods to obtain the MIC and a standard method is lacking, it is plausible that a MIC detected with different methods can vary widely[27]. Besides, it is questionable whether these MIC scores are also usable in CI patients as the MIC scores are determined in groups of chronic tinnitus patients. A previous study in chronic tinnitus patients showed a mean THI score of 45 (SD: 23) and TQ score of 40 (SD: 17), both scores are much higher than the preoperative scores we found in the current study[28]. This indicates that CI patients with tinnitus may differ from chronic tinnitus patients in terms of tinnitus scores and severity and therefore it is possible that also the MIC scores of the THI and TQ differ in CI patients. The relatively low preoperative tinnitus scores in our study population could also have led to floor effects, which means that it is more difficult to detect improvement.

Future research with larger sample sizes on simultaneous and sequential bilateral cochlear implantation is needed to advance our understanding of the effects of bilateral cochlear implantation on tinnitus. The development or validation of a tinnitus questionnaire to measure treatment effects in CI patients is also needed.

CONCLUSION

The present study provides additional evidence to the scarce knowledge on the effect of bilateral cochlear implantation on tinnitus. In general, bilateral cochlear implantation had a positive effect on preoperative tinnitus complaints. The induction of (temporary or permanent) tinnitus was also reported and this should always be taken into account when counseling a patient.

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Conflicts of interest and source of funding
RF reported receiving nonrestricted grants from Advanced Bionics and being sponsored by a neurotological stipendium from the Heinsius Houbolt Foundation. JF reported receiving nonrestricted grants from Advanced Bionics and MedEl. WG reported receiving nonrestricted grants from Advanced Bionics, MedEl, Oticon, and Cochlear. No other disclosures were reported. For this study, all centers received the second cochlear implant from Advanced Bionics®. Advanced Bionics® in part sponsored this study. This company did not have any influence on the data collection, data analysis, data interpretation or study design.

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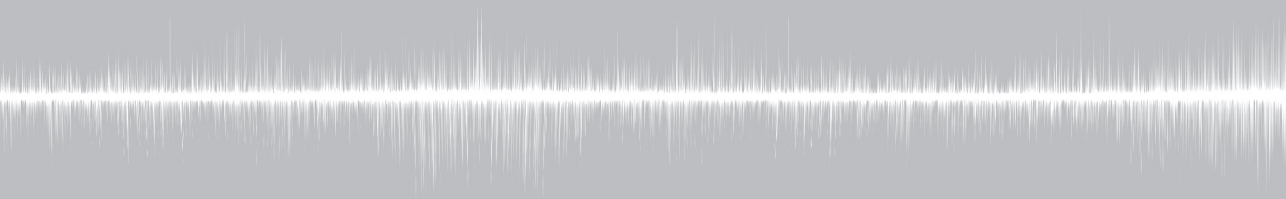

Part two

Instruments and outcomes in cochlear implantation

Chapter 2.1

Agreement between health utility instruments in cochlear implantation

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ABSTRACT

Objectives
The objectives of our study were threefold: to compare health utility scores measured with different health utility instruments in adult patients with bilateral deafness, to compare the change in health utility scores after unilateral or bilateral cochlear implantation using the different health utility instruments and to assess which health utility instrument would be the most appropriate for future studies on cochlear implantation.

Design
A prospective study.

Setting
The data for this article were collected as part of a multicenter randomized controlled trial in the Netherlands on the benefits of simultaneous bilateral cochlear implantation compared to unilateral cochlear implantation.

Participants
The study included 38 adult patients with severe to profound bilateral post-lingual sensorineural hearing loss.

Main outcome measures
Participants completed various quality of life questionnaires (the EuroQol five-dimensional questionnaire (EQ-5D), the Health Utilities Index mark 3 (HUI3), a visual analogue scale (VAS) for general quality of life and a VAS for hearing) preoperatively, and one and two years postoperatively. The general health utility instruments (EQ-5D, HUI3 and VAS general) were compared.

Results
The EQ-5D, HUI3 and VAS general utility scores differed significantly. The intraclass correlation coefficients showed poor to no agreement between these instruments. A gain in health utility after cochlear implantation was found with the HUI3 and VAS general. The highest gain in health utility was found with the HUI3.

Conclusions
A health utility score depends on the health utility instrument that is used in a specific patient population. We recommend using the HUI3 in future studies on cochlear implantation.

INTRODUCTION

In health care, the cost-effectiveness of a therapy is important. An often used method to evaluate cost-effectiveness is a cost-utility analysis (CUA). This method is recommended by the National Institute for Health and Care Excellence of England.[1] In a CUA, the result of a therapy is valued in quality-adjusted life years (QALYs).[2] A QALY is the product of quality of life (QoL) and quantity of life.[3]

Health-related quality of life (HRQoL) is expressed as a health utility score: a number between 0 and 1, in which 0 corresponds to death and 1 to a state of perfect health (sometimes a negative score is possible, which corresponds to a state worse than death).[3] A variety of instruments is used to measure health utility. Direct methods are the standard gamble (SG), time trade-off (TTO) and visual analogue scale (VAS).[3] Indirect questionnaire-based measures are, for example, the Health Utilities Index mark 3 (HUI3), the EuroQol five-dimensional questionnaire (EQ-5D), the 15-dimensional (15-D) measure and the six-dimensional health state short form (SF-6D) derived from Short Form 38 health survey (SF-36).[2,4–7] All these different health utility instruments can be used to measure QoL in a CUA. However, these instruments lack agreement and are therefore incomparable.[7–10] This incomparability is problematic as the choice of health utility instrument determines the outcome of a cost-effectiveness analysis evaluated with a CUA.[4,7–10]

Differences in outcomes of health utility instruments in cochlear implantation were shown in a recent scenario-based study[11]. The HUI3, EQ-5D, VAS and TTO were compared in four subgroups: postlingually deaf patients eligible for cochlear implantation, unilateral cochlear implant (CI) users, bilateral CI users and professionals. The health utility scores and utility gains measured with the different instruments varied widely. The HUI3 was the questionnaire of choice according to this study, because this instrument was least likely to overestimate the cost utility of a second CI.[11] Another recently published study found no agreement between the HUI3 and SF-36 in a cohort of 81 unilateral CI recipients[12].

To our knowledge, there are no real-life, prospective studies comparing the EQ-5D, HUI3, VAS for general QoL and VAS for hearing in unilateral and bilateral CI patients. The objectives of our study were threefold: to compare health utility scores measured with the EQ-5D, HUI3, VAS for general QoL and VAS for hearing in adult patients with bilateral deafness, to compare the change in these health utility scores after unilateral or bilateral cochlear implantation and to assess which health utility instrument would be the most appropriate for future studies on cochlear implantation.

MATERIAL AND METHODS

Ethical considerations

Approval for this study was obtained by the Human Ethics Committees of all participating centers (NL2466001808), and this trial was registered in the Dutch Trial Register (NTR1722). Written informed consent was obtained from all participants.

Study design and participants

This was a prospective study of 38 patients with severe to profound bilateral post-lingual sensorineural hearing loss. The data were collected as part of a multicenter randomized controlled trial on the benefits of simultaneous bilateral cochlear implantation compared to unilateral cochlear implantation. Evaluations took place preoperatively, and one and two years postoperatively. For most of the analyses, we did not distinguish unilateral from bilateral CI patients because the aim was to assess the agreement between health utility instruments.

Health utility instruments

Health utility was measured using QoL questionnaires. Preoperatively, and one and two years postoperatively, we asked the participants to complete the following questionnaires.

EQ-5D

The EQ-5D contains a thermometer indicating general health state and five dimensions of HRQoL: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has three levels: no problems, some problems and extreme problems. The result of this questionnaire is a single index value for health status. In the Dutch scoring function for the EQ-5D, utility scores range from -0.33 to 1.00.[6,13]

HUI3

The HUI3 consists of eight elements of health status: vision, hearing, speech, ambulation, dexterity, emotion, cognition and pain. Each dimension has up to six levels. From the answers, a multi-attribute health status is calculated, which results in a utility score between -0.36 and 1.00.[7]

VAS general

The VAS general contains a thermometer with a scale from 0 to 100. Participants were asked to mark their general QoL from 0 (really bad) to 100 (perfect). These scores were then converted to values between 0 and 1: divided by 100.

VAS hearing

The VAS hearing contains a thermometer with a scale from 0 to 100. Participants were asked to mark their hearing from 0 (deaf) to 100 (perfect hearing). These scores were then converted to values between 0 and 1: dividing by 100.

Of the above-mentioned questionnaires, only the scores of the EQ-5D, HUI3 and VAS general can be used as a general health utility score.

Statistical analyses

Health utility scores were computed preoperatively, one and two years postoperatively for each patient. None of the health utility outcomes were normally distributed, and therefore, we reported medians and used non-parametric tests for the analyses.

In this article, the VAS hearing was used to give an overview of a patients' subjective hearing performance before and after cochlear implantation. The VAS hearing was excluded from the analyses on agreement because it is not a general health utility instrument which can be used for a CUA.

Agreement between health utility instruments

The Wilcoxon signed-rank test was used to examine possible differences in median preoperative EQ-5D, HUI3 and VAS general health utility scores.

Bland Altman plots were created for all the combinations of general health utility instruments in the preoperative setting. This is a method to assess the agreement between different instruments[14,15]. We plotted the difference in score between two instruments (Y-axis) against the mean score (X-axis) for each subject. Three horizontal lines were added to the plot: the mean difference in score, +1.96 SD and -1.96 SD.[16] The agreement between the two instruments was examined by evaluating the spread of the scores on the Y-axis. The mean difference in score is close to zero, and the spread is small when there is good agreement between instruments.

The intraclass correlation coefficient (ICC) was calculated for all the combinations of general health utility instruments in the preoperative setting. An ICC ranges between 0.00 and 1.00, and a value closer to 1.00 represents a stronger agreement. As a general guideline, an ICC higher than 0.75 implies a good agreement and lower than 0.75 implies a poor to moderate agreement between the instruments.[16] The ICC was based on a two-way mixed model single measure, for all the combinations of health utility instruments. For the above-mentioned analyses, we did not distinguish unilateral from bilateral CI patients.

Agreement between health utility instruments: sensitivity analysis

We performed a sensitivity analysis to show several different scenarios. The statistical tests for the agreement between health utility instruments (Wilcoxon signed rank test and ICC) were therefore not only performed in the preoperative data, but also in the one- and two-year follow-up data.

Change in health utility scores after implantation

We calculated the median change in EQ-5D, HUI3, VAS general and VAS hearing scores one and two years after cochlear implantation. The Wilcoxon signed-rank test was used to examine possible differences in these change scores. This test was also used to compare the median postoperative score from each instrument with the preoperative score. Above-mentioned analyses were performed on data from the whole group (n = 38) and for the unilateral and bilateral group separately. The Mann–Whitney U-test was used to examine possible differences between the unilateral and bilateral group in EQ-5D, HUI3 and VAS general health utility scores.

All data were analyzed using SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp, and a P-value <0.05 was considered statistically significant.[17]

RESULTS

Subjects

Thirty-eight patients with severe to profound bilateral postlingual sensorineural hearing loss were included in this study. The median age at implantation was 53 years [18–70]. Start of severe hearing loss was at a median age of 31 [3–63].

Health utility scores

Figure 1 shows the health utility scores per patient in preoperative and postoperative settings. All patients completed their preoperative and one year postoperative measurements. The two-year results were missing for one subject because she decided to withdraw from the study for personal reasons.

Agreement between health utility instruments

Median health utility scores are presented in Table 1. The median preoperative EQ-5D score was 1.00, the median HUI3 score 0.55 and the median VAS general score 0.75. All these scores differed significantly from each other (Wilcoxon signed-rank test, $P < 0.001$ for all combinations). The median preoperative VAS hearing score was 0.10.

The Bland Altman plots for all the combinations of general health utility instruments in the preoperative setting are presented in Fig. 2. These plots show wide limits of agreement, which indicates that there is poor agreement and suggests that the instruments cannot be used interchangeably.

The ICCs were low for all the combinations of general health utility instruments in the preoperative setting (ICC: 0.05–0.26) (Table 2).

Agreement between health utility instruments: sensitivity analysis

Median EQ-5D, HUI3 and VAS general scores one year after implantation differed significantly from each other (Wilcoxon signed-rank test, $P < 0.001$ for all combinations). The ICCs for all the combinations of general health utility instruments one year postoperative showed poor agreement with a highest ICC of 0.45 (HUI3 versus VAS general) (Table 2).

Two years after implantation, the median EQ-5D, HUI3 and VAS general differed significantly as well (Wilcoxon signed-rank test, $P < 0.001$ for all combinations). The ICCs showed poor agreement between instruments (ICCs: 0.19–0.31) (Table 2).

Change in health utility scores after cochlear implantation

The median changes in EQ-5D, HUI3, VAS general and VAS hearing scores one and two years after implantation are described in Table 1 for the whole study group. The median change in general health utility score was highest when measured with the HUI3 (1 year:+0.17; 2 years:+0.19). The HUI3 and VAS general scores improved significantly after cochlear implantation. There was no difference between the preoperative and postoperative EQ-5D scores. The specific VAS hearing scores improved significantly after implantation (1 year: +0.60; 2 years:+0.57). The change in EQ-5D scores after implantation differed significantly

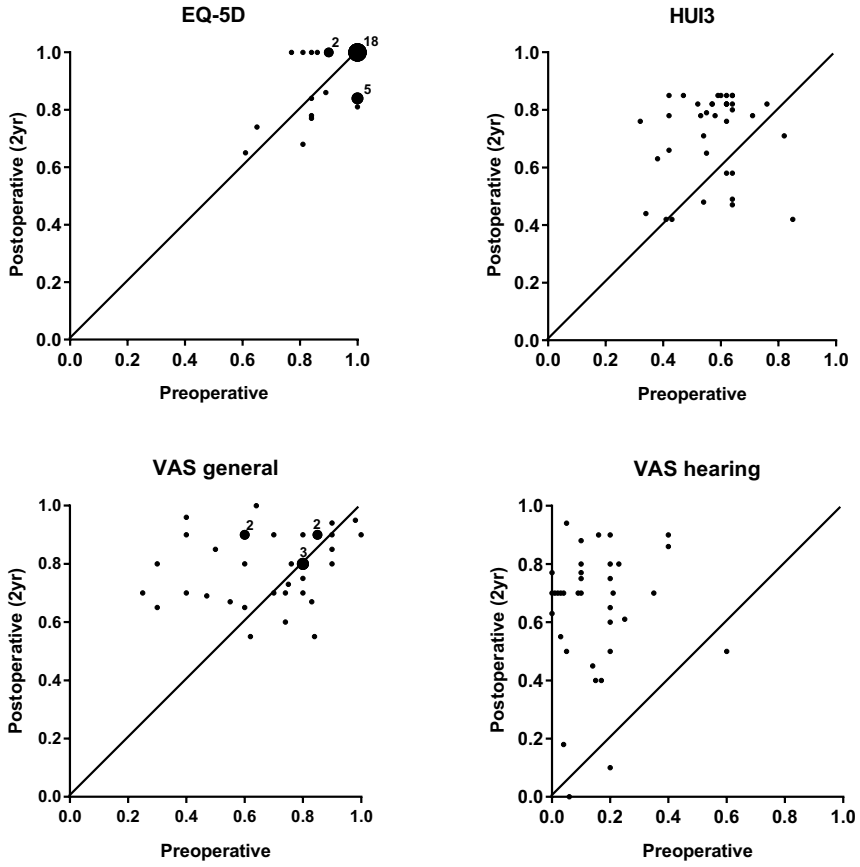


Figure 1. Health utility evaluation plot. Health utility scores per patient preoperative (x-axis) versus two years after implantation (y-axis), per health utility instrument. Each dot represents an individual patient. The larger dots represent more than one patient (the number represents the number of patients per score). The line represents the situation in which the health utility score was equal before and after implantation. All patients above this line improved, and all patients beneath this line scored worse after implantation.

from the change in HUI3 and VAS general scores. The change in HUI3 and VAS general scores did not differ significantly from each other.

The median EQ-5D, HUI3 and VAS general scores did not differ significantly between the unilateral and bilateral group. Both groups showed significant improvements in HUI3 scores after implantation. Although the VAS general scores improved after implantation in both groups, only the unilateral group showed statistically significant improvement. Neither of the groups showed differences in EQ-5D scores after implantation.

Table 1. Health utility scores

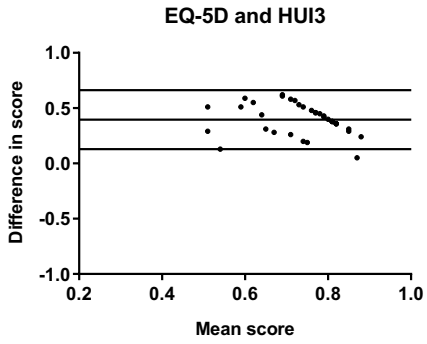
Health utility instrument	Preoperative score	One year postoperative score	Change after one year	Statistics (*p*-value)*	Two years postoperative score	Change after two years	Statistics (*p*-value)**
EQ-5D	1.00 [0.61 – 1.00]	1.00 [0.30 –1.00]	0.00 [-0.47 – 0.16]	NS	1.00 [0.65 – 1.00]	0.00 [-0.20 – 0.23]	NS
HUI3	0.55 [0.26 – 0.85]	0.78 [0.22 – 0.85]	+0.17 [-0.25 – 0.51]	<0.001	0.77 [0.42 – 0.85]	+0.19 [-0.43 – 0.46]	<0.001
VAS general	0.75 [0.25 –1.00]	0.80 [0.45 – 0.99]	+0.05 [-0.25 – 0.54]	0.027	0.80 [0.55 – 1.00]	+0.04 [-0.29 – 0.56]	0.012
VAS hearing	0.10 [0.00 – 0.60]	0.70 [0.20 – 0.90]	+0.60 [0.03 – 0.85]	<0.001	0.70 [0.00 – 0.94]	+0.57 [-0.10 – 0.89]	<0.001

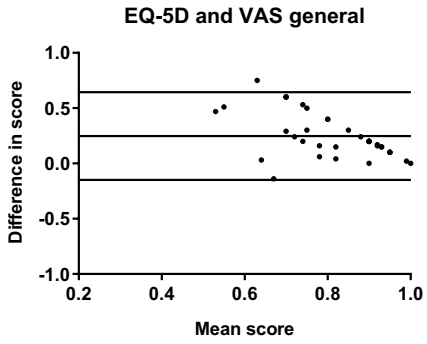
Median [range]
*Statistics: one year postoperative score compared to preoperative score, Wilcoxon signed rank test
** Statistics: two year postoperative score compared to preoperative score, Wilcoxon signed rank test
NS: not significant

Table 2. Agreement between health utility instruments

	ICC	95% confidence interval	Statistics (*p*-value)
Preoperative			
EQ-5D versus HUI3	0.05	-0.04 – 0.22	0.014
EQ-5D versus VAS general	0.08	-0.09 – 0.29	NS
HUI3 versus VAS general	0.26	-0.05 – 0.53	0.012
One year after implantation			
EQ-5D versus HUI3	0.27	-0.10 – 0.60	<0.001
EQ-5D versus VAS general	0.43	-0.08 – 0.73	<0.001
HUI3 versus VAS general	0.45	0.13 – 0.68	<0.001
Two years after implantation			
EQ-5D versus HUI3	0.19	-0.09 – 0.50	0.001
EQ-5D versus VAS general	0.28	-0.09 – 0.60	0.001
HUI3 versus VAS general	0.31	-0.05 – 0.57	0.011

ICC: intraclass correlation coefficient; NS: not significant





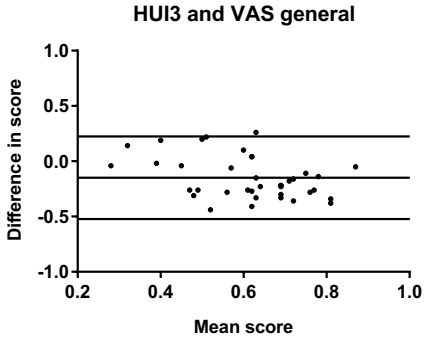


Figure 2. Bland Altman plots for agreement of health utility scores between different combinations of instruments. The individual difference between two questionnaires (y-axis) is plotted against the mean score (x-axis) for each patient. The three horizontal lines represent the mean difference, the mean difference +1.96 SD and the mean difference -1.96 SD.

DISCUSSION

Synopsis of key findings

In this study, we compared different general health utility instruments (EQ-5D, HUI3, VAS general) in a group of 38 adults with post-lingual sensorineural hearing loss who received either one or two CIs. We found poor to no agreement between these instruments. The HUI3 and VAS general scores improved significantly after cochlear implantation. The EQ-5D scores did not differ after implantation. Our finding that there is disagreement between health utility instruments is consistent with previous studies on health utility instruments in cochlear implantation.[11,12]

Strengths and limitations of the study

The major strength of our study is that we used real-life, prospectively collected data. This in contrast to one of the previous studies, where a scenario-based method was used.[11] Another strength is that we performed more extensive statistical analyses than other studies in this field to thoroughly assess the agreement between the various health utility instruments.[11,12] We performed multiple analyses (Wilcoxon signed-rank test, ICC, Bland Altman plots) and a sensitivity analysis.

A possible limitation is that the primary outcome of the original trial, which this study is part of, was to evaluate the speech in noise hearing results of unilateral compared to simultaneous bilateral implantation and not to investigate the different health utility instruments. The sample size calculation was based on that primary outcome.

Clinical applicability of the study

From the three general health utility instruments we used in our study, hearing is a specific element of interest in only one of them (HUI3). The presence of this specific element can explain the lower preoperative HUI3 scores and the higher gain in HUI3 scores after implantation compared to the other instruments in our population of hearing impaired patients. The finding that health utility scores from various instruments differ in a specific patient population is important for future research. The choice for a health utility instrument is crucial and directly affects the results of a study. In particular, in case of a cost-effectiveness study, evaluated with a CUA, the results will strongly depend on the choice of health utility instrument.[4,7–10]

Our study showed that there was no change in EQ-5D utility scores after cochlear implantation. However, the HUI3 and VAS general scores improved after implantation. Therefore, to measure change in QoL after cochlear implantation, the EQ-5D may not be a suitable instrument. The HUI3 and VAS general appear to be more appropriate to measure changes in QoL after cochlear implantation.

Our study showed that there were no differences in general health utility scores between unilaterally and bilaterally implanted patients. Both groups showed significant improvements in HUI3 scores after implantation; however, only the unilateral group showed statistically significant improvement in VAS general score. The bilaterally implanted patients showed

improvement in VAS general scores, but these were not statistically significant, probably due to the small sample size.

Based on our results, the HUI3 detects the most health utility gain after implantation. Therefore, we recommend using the HUI3 health utility instrument in future studies on cochlear implantation. Previous studies on cochlear implantation which used the HUI3 agree with our findings[18,19].

CONCLUSIONS

Health utility scores from various health utility instruments (EQ-5D, HUI3, VAS general) differed significantly in our population of adults with severe to profound bilateral postlingual sensorineural hearing loss before and after cochlear implantation. We found poor to no agreement between these different health utility instruments. We recommend using the HUI3 in future studies on cochlear implantation.

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Conflict of interest
Wilko Grolman receives non-restrictive grants from Advanced Bionics, MedEl, Oticon and Cochlear. For this study, all centres received the second cochlear implants from Advanced Bionics.

Source of financial support or funding
This study is sponsored by Advanced Bionics. The sponsor collaborated with us on the study design. They did not have any influence on the data collection, data analysis or data interpretation.

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Chapter 2.2

Correlation between subjective and objective hearing tests after unilateral and bilateral cochlear implantation

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ABSTRACT

Background

There are many methods for assessing hearing performance after cochlear implantation. Standard evaluations often encompass objective hearing tests only, while patients' subjective experiences gain importance in today's healthcare. The aim of the current study was to analyze the correlation between subjective (self-reported questionnaires) and objective (speech perception and localization) hearing test results in adult cochlear implant (CI) users. Secondary, the correlation between subjective and objective hearing tests was compared between bilateral and unilateral CI patients.

Methods

Data for this study were prospectively collected as part of a multicenter randomized controlled trial. Thirty-eight postlingually deafened adult patients were randomly allocated to receive either unilateral (*n*=19) or bilateral (*n*=19) cochlear implantation. We used data gathered after one year of follow-up. We studied the correlation between objectively measured speech perception and localization skills on the one hand and related domains of the Speech, Spatial and Qualities of Hearing Scale (SSQ) and Nijmegen Cochlear Implant Questionnaire (NCIQ) on the other hand. We also compared these correlations between unilateral and bilateral CI users.

Results

We found significant weak to moderate negative correlations between the subjective test results (speech domain of the SSQ and the advanced speech perception domain of the NCIQ) and the related objective speech perception in noise test results (*r*=-0.33 to -0.48). A significant moderate correlation was found between the subjective test results (spatial domain of the SSQ) and the related objective localization test results (r=0.59). The correlations in the group of bilateral CI patients (*r*=-0.28 to -0.54) did not differ significantly from the correlations in the group of unilateral CI patients (*r*=0.15 to -0.40).

Conclusions

Current objective tests do not fully reflect subjective everyday listening situations. This study elucidates the importance and necessity of questionnaires in the evaluation of cochlear implantation. Therefore, it is advised to evaluate both objective and subjective tests in CI patients on a regular basis.

BACKGROUND

Cochlear implantation is a successful treatment for severe to profound sensorineural hearing loss. Although unilateral cochlear implantation still is the standard treatment in most countries, an increasing amount of patients worldwide is being implanted bilaterally in order to improve (spatial) hearing skills and speech understanding in noise[1,2].

The eligibility criteria for cochlear implantation are constantly changing and the quality and possibilities of cochlear implants (CIs) are growing[3]. In this world of new developments, assessing hearing performance after cochlear implantation is vital. There are various methods to do this. In many CI centers, evaluations encompass objective hearing tests only. Clinically applied speech perception and localization tests are robust and reliable, but time-consuming and it is questionable if these test conditions fully represent everyday listening situations. Subjective tests (self-reported questionnaires) are easy to administer and a large set of data can be gathered in a short period of time. Also, in today's healthcare, a patients' subjective experiences gain importance[4,5]. For example, when the cost-effectiveness of a treatment is analyzed, health related quality of life questionnaires are often used to measure the effectiveness[6,7]. However, questions can be misinterpreted and missing values easily occur when patients do not fill out (parts of) the questionnaires.

Literature has shown that there are often discrepancies between subjective and objective hearing test results[8–13]. Previous studies were mainly about the correlation between subjective and objective speech perception tests. The amount of literature on correlations between subjective and objective localization tests is limited[10].

There is an ongoing global discussion on whether or not bilateral cochlear implantation should be standard care for bilateral deafness[1,2]. The current literature on correlations between subjective and objective tests however, only includes unilateral and bimodal CI users. Correlations between tests might be different for unilateral and bilateral CI users, due to differences in test sensitivity or differences in indicating their own performance. Therefore, the latter is worth investigating.

The current study is a subanalysis of a previous published study on the comparison of bilateral and unilateral cochlear implantation in adult patients with bilateral postlingual deafness[14]. One year after implantation, bilaterally implanted patients performed significantly better on part of the subjective (Speech, Spatial and Qualities of Hearing Scale (SSQ) and the visual analogue scale (VAS) on hearing) and objective (speech perception in noise when noise came from different directions and localization of sounds) tests[14].

The first objective of the current study was to investigate the correlations between subjective and objective speech perception and localization tests in adult CI patients. Secondary, the correlations between subjective and objective speech perception and localization tests were compared between bilateral and unilateral CI patients.

METHODS

Study design and participants

The current study will present the results of a secondary analysis of data collected as part of a multicentre randomized controlled trial on the benefits of simultaneous bilateral cochlear implantation compared to unilateral cochlear implantation in adults with severe to profound bilateral postlingual sensorineural hearing loss[14]. Between December 2009 and September 2012, 38 adult patients were included in this study. After giving informed consent, patients were randomly allocated to receive CIs bilaterally or unilaterally. All patients were implanted with Advanced Bionics HiRes90K (Advanced Bionics, Sylmar, California) CIs and used Harmony processors.

In this paper, we will present the correlation between subjective and objective hearing tests measured one year after implantation. Detailed descriptions of the study methods and the main study results have been reported previously[14,15].

Subjective hearing outcomes

Subjective benefits in everyday listening situations were assessed with the following questionnaires:

1. Speech, Spatial and Qualities of Hearing Scale (SSQ). This questionnaire consists of three domains of questions. Participants were asked to rate their hearing capabilities on a 0-100 scale (0= not capable at all, 100=perfectly capable). The SSQ1 comprises questions on speech understanding in silence, in background noise, in resonating environments and on the telephone. The SSQ2 comprises questions on spatial hearing; identifying directions of sounds and distance approximation, and the SSQ3 encompasses questions on the quality of hearing[16]. The final subdomain score is computed by the mean of all items on that subdomain, resulting in a range of scores from 0 to 100. A higher score reflects a greater ability.[16]
2. Nijmegen Cochlear Implant Questionnaire (NCIQ). This questionnaire contains six subdomains of hearing that are rated categorically (1-5 (never-always) and "not applicable"). The subdomains are 1. Basic sound perception, 2. Advanced sound perception (in difficult daily listening situations or background noise), 3. Speech production, 4. Self-esteem, 5. Activity limitations, 6. Social interaction[17]. The answer categories must first be transformed (1=0, 2=25, 3=50, 4=75 and 5=100). Afterwards, the final subdomain score is computed by adding together all the item scores and dividing by the number of completed items, resulting in a range of scores from 0 to 100. A higher score reflects a greater ability.[17]

Objective hearing outcomes

Speech perception in noise and sound localization tests were conducted with the Dutch version of the AB-York crescent of sound. The test battery included the Utrecht Sentence Test with Adaptive Randomized Roving levels (U-STARR), the speech-intelligibility test with spatially separated sources (SISSS), and a sound localization test[15].

1. With the U-STARR, sentences were presented in noise, both coming from straight ahead. The sentences were presented at 65, 70 or 75 dB SPL (randomly selected), in noise with an adaptive level. The outcome was the signal-to-noise ratio (SNR) average of the last sixteen sentences, which is the speech reception threshold in noise (SRTn)[15].
2. For the SISSS, the same procedure was used as for the U-STARR. The only difference was that the sentences were presented from 60° to the left (-60° azimuth) or to the right (+60° azimuth) of the subject and the noise was presented from 60° at the opposite side[15].

   A SRTn of 30 dB was considered relative silence and therefore, 30 dB was used as cutoff value on the U-STARR and SISSS.
3. For the sound localization test, a phrase 'Hello what's this?' was randomly presented from loudspeakers at 0°, ±15°, ±30° and ±60° angles, about 30 times per condition. Again, the phrase was randomly presented at 60, 65, or 70 dB SPL. The result of this test was the percentage of correct responses[15]. In the current article, the average of all three conditions was used as the localization score.

In the unilateral group, patients were encouraged to use a contralateral hearing aid (HA). The scores on the objective tests in their daily hearing situation (only CI or CI+HA) were used for the analyses. When sounds come from different directions, patients usually have a "best performing situation" and a "worst performing situation". A patient's "best performing situation" occurs when sound is presented to the best hearing ear and noise to the worst hearing ear. In the unilateral group, the best hearing ear is the implanted ear. In the bilateral group, patients usually also have one ear with which they hear (slightly) better than with the other. We defined the "best performing situation" and "worst performing situation" for each patient[14].

Statistical analysis

None of the subjective and objective test results were normally distributed. Therefore, medians, interquartile ranges (IQR) and non-parametric tests were used.

In order to get insight in the relation between the subjective and objective tests, scatter plots of individual patient scores were created with the subjective test score on the x-axis and the related objective test score on the y-axis.

We used Spearman correlation tests to quantify the relationship between subjective and objective test results. We studied the relation between the U-STARR and SISSS scores (objective) and the first domain of the SSQ (SSQ1) and the advanced sound perception domain of the NCIQ (subjective). These tests all represent advanced sound perception skills. The second domain of the SSQ (SSQ2) contains questions on sound localization, thus, we studied the relation between the SSQ2 and the objective sound localization test.

The correlations between subjective and objective tests were analyzed for the whole study group (n=38), and for the bilateral and unilateral CI patients separately. We used the Fisher's z transformation to analyze if there was a statistical significant difference between the correlations in the bilateral and unilateral CI group.

A correlation of <0.19 is considered very weak, 0.20-0.39 weak, 0.40-0.59 moderate, 0.60-0.79 strong, >0.80 very strong (for positive as well as negative values)[18]. For the speech in noise tests (U-STARR and SISSS), a low result indicates good performance, while for the localization tests and subjective tests, a high score indicates good performance. For this reason, when speech in noise results are compared with subjective outcomes, correlations are often negative. All data were analyzed using SPSS 22.0. The critical significance levels of the *p*-values were adjusted for multiple comparisons using the Benjamini-Hochberg false discovery rate method[19].

RESULTS

Details of the study population are presented in Table 1. Fifteen patients in the bilateral CI group used HAs before implantation, compared to 19 patients in the unilateral group (*p:* 0.04)[14]. All other baseline characteristics did not differ significantly. One year after cochlear implantation, 14 out of 19 patients in the unilateral group still used a contralateral HA.

Correlation between subjective and objective speech perception tests

Figure 1 presents scatter plots of the individual patient scores on the subjective (SSQ1 and the advanced speech perception domain of the NCIQ) and objective speech perception tests (U-STARR and SISSS). The correlations between all these subjective and objective speech perception tests were weak to moderate, but significant (Table 2). The weakest correlation was found for the 'SSQ1' and 'SISSS worst performing situation' (r=-0.33, p=0.046) and the

Table 1. Baseline characteristics

	Bilateral	**Unilateral**
Number of participants	19	19
Male number (%)	8 (42)	11 (58)
Age at inclusion years, median [IQR]	52 [36-63]	54 [43-64]
Duration severe hearing loss right ear years, medians [IQR]	16 [11-25]	17 [9-33]
Duration severe hearing loss left ear years, median [IQR]	16 [11-25]	18 [9-35]
PTA right ear decibels, median [IQR]	106 [89-119]	106 [94-111]
PTA left ear decibels, median [IQR]	108 [89-120]	108 [93-114]
Hearing aid use before CI number/total	19/19	15/19

PTA: pure tone average at 1, 2 and 4 kHz

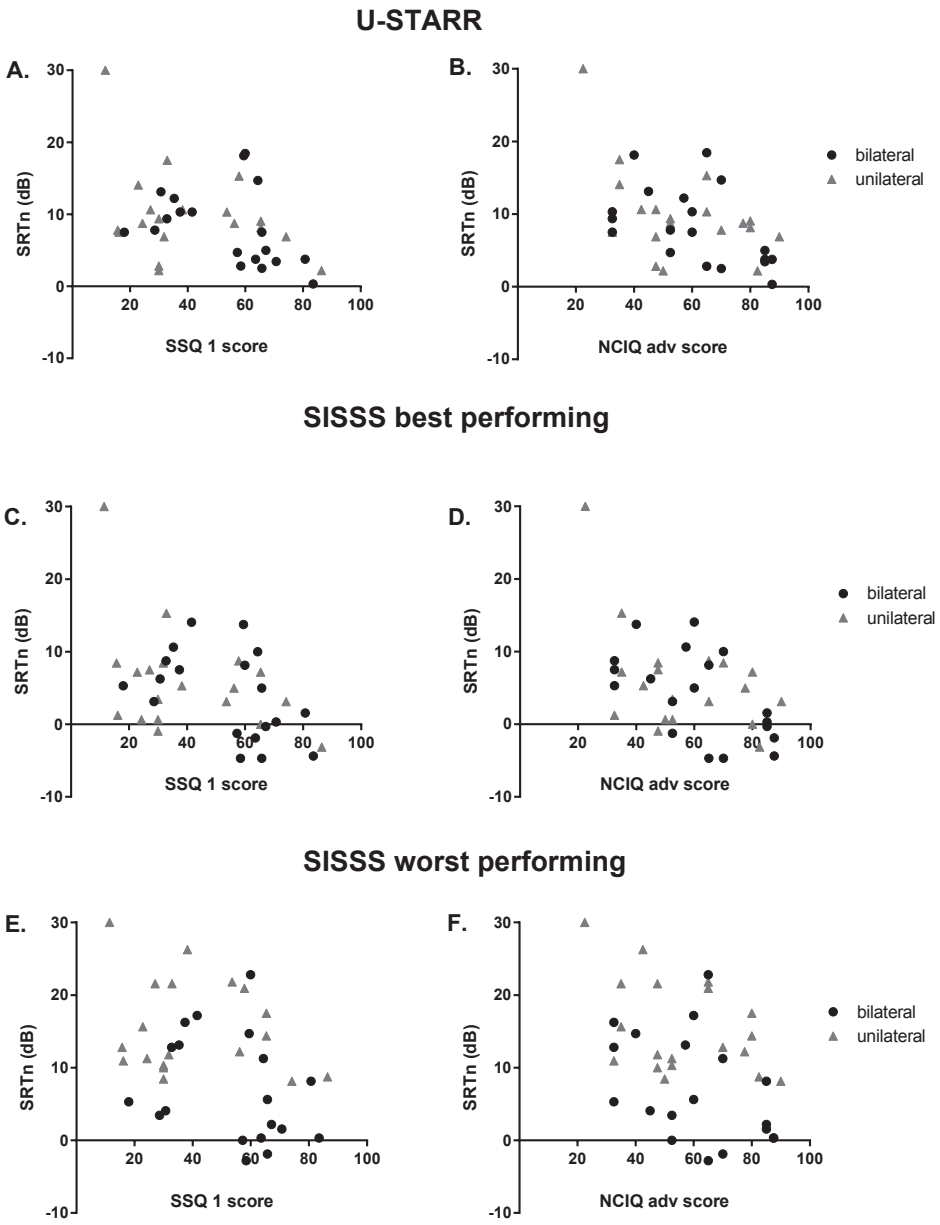

Figure 1. Correlation between subjective and objective speech perception results. Legend: Scatter plots of individual subjective and objective speech perception results. The correlation between the speech domain of the SSQ and the U-STARR (a). The correlation between the advanced speech perception domain of the NCIQ and the U-STARR (b). The correlation between the speech domain of the SSQ and the SISSS in the best (c) and worst (e) performing situation. The correlation between the advanced speech perception domain of the NCIQ and the SISSS in the best (d) and worst (f) performing situation

strongest correlation for the 'NCIQ advanced speech perception' and 'SISSS best performing situation' (r=-0.48, p=0.002). The 'NCIQ advanced speech perception domain' correlated better with the different objective speech perception tests (r between -0.39 and -0.48 corresponding moderate correlations) than the SSQ1 (r between -0.33 and -0.39, corresponding with weak correlations).

Correlation between subjective and objective localization tests

Figure 2 presents a scatter plot for the individual patient scores on the subjective (SSQ2) and objective localization test. A significant moderate correlation was found between the SSQ2 and localization test (r=0.59, p=0.0001) (lower part of Table 2).

When we corrected for multiple testing using the Benjamini-Hochberg false discovery rate method, all p-values of the correlation coefficients were lower than the for multiple testing corrected significance level, resulting in all significant correlations (Table 2).

Table 2. Correlation between subjective and objective hearing tests. Results for all cochlear implant patients (n=38)

	U-STARR		
	Spearman *r*	***p*-value**	**Corrected significance level***
SSQ 1 (Speech in silence and noise)	-0.36	**0.028**	0.0429
NCIQ advanced speech perception	-0.47	**0.003**	0.0214
	SISSS Best performing situation		
	Spearman *r*	***p*-value***	**Corrected significance level***
SSQ 1 (Speech in silence and noise)	-0.39	**0.016**	0.0286
NCIQ advanced speech perception	-0.48	**0.002**	0.0143
	SISSS Worst performing situation		
	Spearman *r*	***p*-value***	**Corrected significance level***
SSQ 1 (Speech in silence and noise)	-0.33	**0.046**	0.05
NCIQ advanced speech perception	-0.39	**0.016**	0.0357
	Localization		
	Spearman *r*	***p*-value***	**Corrected significance level***
SSQ 2 (Spatial hearing)	0.59	**0.0001**	0.0071

r: <0.19 = very weak, *r*: 0.20-0.39 = weak, *r* 0.40-0.59 = moderate, r 0.60-0.79 = strong, *r* >0.80 = very strong. U-STARR = Utrecht- Sentence Test with Adaptive Randomised Roving levels, SSQ = Speech, Spatial and Qualities hearing scale. NCIQ = Nijmegen CI Questionnaire, SISSS = speech-intelligibility test with spatially separated sources (SISSS).
*The for multiple testing corrected significance level with the Benjamini-Hochberg false discovery rate method.

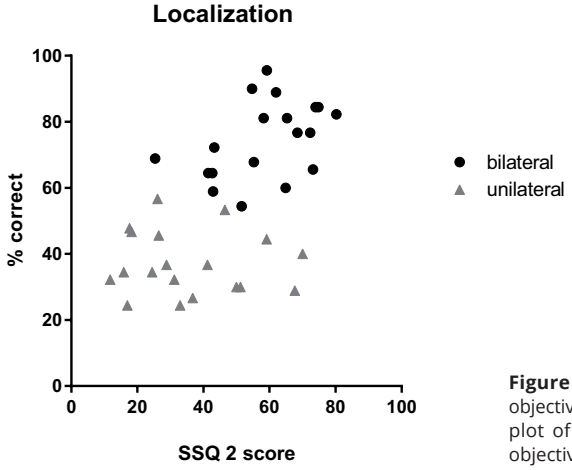

Figure 2. Correlation between subjective and objective sound localization results. Legend: Scatter plot of the spatial domain of the SSQ and the objective localization test.

Comparison of correlations between bilateral and unilateral CI patients

As presented in Table 3, the correlations between all subjective and objective hearing tests ranged between -0.28 and -0.55 (weak to moderate) in the bilateral CI group, compared to a range of -0.15 to -0.43 (very weak to moderate) in the unilateral CI group. The correlation coefficients in the bilateral group did not differ significantly from the correlation coefficients in the unilateral group, after correction for multiple testing using the Benjamini-Hochberg false discovery rate method (Table 3).

DISCUSSION

Key findings

In this study, we found significant correlations between subjective and objective hearing test results in adult CI users. The strongest correlation was found between the spatial domain of the SSQ and the objective localization test (r=0.59, a moderate correlation). The other correlations, between subjective and objective speech perception in noise test results, were weak to moderate. There could be several reasons for the lack of strong correlations between subjective and objective results. Perhaps the questionnaires and objective tests do not represent the same hearing skills. Another reason could be that the patients' views of their own hearing skills did not match their actual hearing capabilities. Therefore, it seems important to evaluate both subjectively and objectively measured hearing skills after cochlear implantation.

When we compared the outcomes of the unilateral and bilateral CI group, all correlations in the bilateral CI group were stronger than in the unilateral group, although none of the correlations differed statistically significant from each other. We cannot rule out that the latter is the result of the small sample size: 19 patients in each group.

Table 3. Correlation between subjective and objective hearing tests. Results for bilateral (n=19) and unilateral patients (n=19) separately

	U-STARR				
	Bilateral		**Unilateral**		***p*-value comparison correlation***
	Spearman *r*	***p*-value***	**Spearman *r***	***p*-value***	
SSQ 1 (Speech in silence and noise)	-0.50	0.031	-0.21	0.379	0.342
NCIQ advanced sound perception	-0.55	0.014	-0.43	0.067	0.653
	SISSS best performing situation				
	Bilateral		**Unilateral**		***p*-value comparison correlation***
	Spearman *r*	***p*-value***	**Spearman *r***	***p*-value***	
SSQ 1 (Speech in silence and noise)	-0.44	0.057	-0.29	0.230	0.624
NCIQ advanced sound perception	-0.54	0.016	-0.38	0.109	0.562
	SISSS worst performing situation				
	Bilateral		**Unilateral**		***p*-value comparison correlation***
	Spearman *r*	***p*-value***	**Spearman *r***	***p*-value***	
SSQ 1 (Speech in silence and noise)	-0.28	0.247	-0.15	0.544	0.697
NCIQ advanced sound perception	-0.43	0.067	-0.38	0.110	0.865
	Localization				
	Bilateral		**Unilateral**		***p*-value comparison correlation***
	Spearman *r*	***p*-value***	**Spearman *r***	***p*-value***	
SSQ 2 (Spatial hearing)	0.47	0.042	-0.22	0.929	0.038

r: <0.19 = very weak, *r* 0.20-0.39 = weak, *r* 0.40-0.59 = moderate, *r* 0.60-0.79 = strong, *r* >0.80 = very strong. U-STARR = Utrecht- Sentence Test with Adaptive Randomised Roving levels, SSQ = Speech, Spatial and Qualities hearing scale. NCIQ = Nijmegen CI Questionnaire, SISSS = speech-intelligibility test with spatially separated sources (SISSS).
*After correction for multiple testing with the Benjamini-Hochberg false discovery rate procedure, none of the test results yielded significant results.

Comparison with the literature

A recently published meta-analysis reviewed the correlation between different types of (subjective) hearing-specific and CI-specific questionnaires and (objective) speech perception scores in CI patients[8]. Thirteen studies were included. These studies showed low correlations between hearing-specific and CI-specific questionnaires on the one hand and objective

speech perception scores on the other hand[8]. The pooled correlation between CI-specific questionnaire scores (for example NCIQ) and speech perception in noise was weak (r=0.26, p:0.0064). Other studies, not included in the meta-analysis, also found predominantly weak to moderate correlations between subjective and objective speech perception tests[9–13]. In a study of Hirschfelder et al. subjective and objective hearing tests were compared in 56 unilateral CI users[11]. They found significant weak to moderate (r=0.28-0.56) correlations between the NCIQ total score, the NCIQ advanced sound perception, the NCIQ speech production domains and both objective speech perception tests (Freiburger monosyllable test in quiet and Hochmair, Schulz, Mozer (HSM) sentence test in noise). Damen et al. studied 69 postlingually deafened adult patients (59 unilaterally implanted and 10 non-implanted) and found significant correlations between the NCIQ total score and two Dutch standardized speech perception tests in quiet (the Antwerp-Nijmegen syllable (r=0.48) and the NVA phoneme test (r=0.32))[9].

In a study of Brendel et al. the Everyday Listening Questionnaire (ELQ) 2 was significantly correlated to objective speech perception tests (Monosyllables, HSM in quiet and HSM in noise), but the strength of the correlations was not mentioned[12]. To date, only one study included objective spatial hearing tests[10]. Heo et al. reviewed the correlation between all domains of the SSQ and objective speech perception and localization tests in 14 unilateral CI recipients with a contralateral HA[10]. The spatial domain of the SSQ was significantly correlated with the environmental sound localization (r=0.57) and perception (r=0.55) scores. The quality domain was significantly correlated with all perception scores (r=0.54-0.66)[10]. To our knowledge, there is no previous literature on the differences in correlations between bilateral and unilateral CI patients.

A drawback of some of the previous studies is the lack of clear hypotheses. That has resulted in the presentation of multiple random correlations between objective test scores and questionnaire scores without clear clinical relevance. Also, the authors did not correct for multiple testing. Nevertheless, our findings are in agreement with the previous literature, and our study methodologically fills the gaps of previously mentioned studies. We chose to study only clinically relevant relations by combining (parts of the) subjective tests with corresponding objective tests. To minimize the chance of finding incidental results we corrected for multiple testing. Another strength of our study is the use of prospectively collected data. All participants had completed the questionnaires one year after implantation and had performed the objective tests within the same week. None of the participants were lost to follow-up and we did not have any missing data. Also, to our knowledge our study is the first to investigate correlations between subjective and objective test results in bilateral CI patients. A weakness of the study is the small sample size. This might be the reason why we found some insignificant results after correcting for multiple testing.

CONCLUSION

In this study, correlations between subjective and objective speech perception and spatial hearing tests were weak to moderate, but significant, in adult CI patients. The correlation between subjective and objective hearing tests seemed not different for bilateral compared to unilateral CI patients. This study elucidates the importance and necessity of questionnaires in the evaluation of cochlear implantation. Also it shows that patients may experience their own hearing performance differently than objective tests would suggest. Therefore, it is advised to use both objective and subjective tests in cochlear implant patients on a regular basis.

Competing interests
Wilko Grolman receives non-restrictive grants from Advanced Bionics, MedEl, Oticon and Cochlear. All other authors report no competing interests.

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Chapter 2.3

Longitudinal analyses of subjective outcome measures after simultaneous versus sequential bilateral cochlear implantation - results of a randomized controlled trial

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Another version of this manuscript is submitted as a part of a larger manuscript:

A multicenter randomized controlled trial on simultaneous versus sequential bilateral cochlear implantation – long term longitudinal analyses of objective and subjective measures and complications

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ABSTRACT

Objective

The primary aim of this study was to longitudinally compare the subjective outcomes of simultaneous bilateral cochlear implantation (simBiCI) to sequential BiCI (seqBiCI) in adults with severe to profound postlingual sensorineural hearing loss.

Design

This study was a multicenter randomized controlled trial (RCT) with a 4 year follow-up period. Participants were allocated to receive bilateral cochlear implants (CIs) simultaneously (simBiCI group) or sequentially with an inter-implant interval of 2 years (UCI/seqBiCI group). Subjective outcome measures encompassed questionnaires on 1. quality of life (QoL): the EuroQol five-dimensional questionnaire (EQ-5D), the Health Utilities Index mark 3 (HUI3), a Visual Analogue Scale (VAS) on general health, and the Time Trade-off (TTO); 2. quality of hearing (QoH): the VAS on hearing, the Speech, Spatial and Qualities of Hearing Scale (SSQ) and the Nijmegen Cochlear Implant Questionnaire (NCIQ); and 3. tinnitus: Tinnitus Handicap Inventory (THI) and Tinnitus Questionnaire (TQ). All outcome measures were analyzed longitudinally using a linear or logistic regression analysis with an autoregressive residual covariance matrix (generalized estimating equations type).

Results

Nineteen participants were randomly allocated to the simBiCI group and 19 participants to the UCI/seqBiCI group. Three participants in the UCI/seqBiCI group decided not to proceed with their second implantation and were therefore unavailable for follow-up. Only in one of the four QoL questionnaires (the TTO), a significantly lower utility score over time was seen in the UCI/seqBiCI group compared to the simBiCI group. All subdomains of the SSQ and the social interaction domain of the NCIQ were also significantly lower over time in the UCI/seqBiCI group. These differences were most likely caused by the lower performance in the unilateral situation in the UCI/seqBiCI group, as all of the outcomes in this group improved after receiving the second CI. Furthermore, no longitudinal differences were seen in tinnitus burden prevalence between groups.

Conclusion

This RCT showed that the most evident differences over time between UCI/seqBiCI and simBiCI were seen on the QoH outcomes (representing subjective outcomes regarding speech perception in noise and localization) which was caused by the lower performance in the unilateral situation of this group.

INTRODUCTION

Since decades, unilateral cochlear implantation (UCI) is standard clinical care for adult patients with bilateral severe to profound sensorineural hearing loss (SNHL) in the Netherlands[1]. Patients with unilateral hearing, however, experience difficulties in speech perception in noise and sound localization[1], due to the lack of three binaural effects: 1) binaural summation effect, 2) squelch effect, and 3) head shadow effect[2]. Various studies already showed significant benefits for bilateral cochlear implantation (BiCI) over UCI regarding speech perception in noise, localization and several patient reported outcomes[1,3–5].

There is an ongoing global discussion on whether or not BiCI should be standard clinical care for adult patients with bilateral severe to profound SNHL and whether these patients should receive their bilateral cochlear implants (CIs) simultaneously or sequentially. One major point of this discussion, is the cost-effectiveness of BiCI compared with UCI and simultaneous BiCI (simBiCI) compared with sequential BiCI (seqBiCI). Cost-effectiveness of treatments has become an important topic in today's healthcare. An often-used method to evaluate cost-effectiveness is a cost-utility analysis[6]. In these analyses, the outcomes of self-reported health-related quality of life (QoL) instruments are leading. Therefore, QoL outcomes have become important instruments in the current healthcare system. Other patient reported outcomes gain in importance as well, because the healthcare system is moving towards a more patient centered system[7–9]. Patient reported outcome measures (PROMs) capture patients' subjective experience of illness, impairment and disability[10], further in this paper called 'subjective outcomes'. These outcomes in the evaluation of cochlear implantation include QoL, quality of hearing (QoH) and tinnitus.

To date, studies analyzing long-term outcomes after BiCI with longitudinal data analyses are lacking. Moreover, to our knowledge studies evaluating subjective outcomes after simBiCI compared with seqBiCI in adult patients are lacking as well, except from the previous articles from our research group. These previous studies cross-sectionally reported on the subjective (and objective) results of our randomized controlled trial (RCT) concerning simBiCI compared with seqBiCI with a two-year inter-implant interval, after 1 year of BiCI experience[11,12]. Subjective outcomes evaluated in this RCT were self-reported questionnaires on QoL, QoH and tinnitus.

The aim of the current study was to analyze the (4 years) subjective outcomes longitudinally after simBiCI compared with seqBiCI in adult patients with bilateral severe to profound SNHL.

METHODS

Ethics approval

This study was approved by the Human Ethics Committees of the Academic Medical Center Amsterdam and all participating centers (University Medical Centers of Utrecht, Maastricht, Nijmegen, Leiden and Groningen) (NL2466001808), registered in the Dutch Trial Register (NTR1722) and conducted according to the Declaration of Helsinki. Written informed consent was obtained from all participants.

Study design and participants

This RCT evaluates the longitudinal (4 years) subjective outcomes after simBiCI compared with seqBiCI in adults with severe to profound SNHL.

Between December 2009 and September 2012, all patients eligible for cochlear implantation in the five collaborating centers were discussed and inclusion and exclusion criteria were verified for each patient[3,11,13]. The inclusion criteria were: (1) age between 18 and 70 years old; (2) postlingual onset of SNHL; (3) pure-tone average (PTA) ≥ 70 dB in both ears; (4) duration of severe to profound SNHL of <20 years in each ear and a difference in duration of deafness between both ears of <10 years; (5) marginal benefit of hearing aids (HAs), defined as an aided consonant vowel consonant (CVC) phoneme score of ≤50% at 65 dB sound pressure level (SPL); (6) Dutch as native language; (7) willingness and ability to participate in all scheduled procedures; (8) general health allowing general anesthesia for the duration of potential simBiCI; (9) Dutch health insurance coverage; and (10) agreement to be implanted with Advanced Bionics implants. The exclusion criteria were: (1) previous CI; (2) abnormal cochlear anatomy; and (3) chronic ear infections[3,11,13].

Intervention

After giving written informed consent and undergoing baseline evaluations, patients were randomly allocated to simBiCI (simBiCI group) or seqBiCI with an inter-implant interval of 2 years (UCI/seqBiCI group). All patients were implanted with Advanced Bionics HiRes90K implants (Advanced Bionics, Sylmar, CA, USA) and used Harmony processors.

Subjective outcomes

All outcome measures, unless otherwise mentioned below, were evaluated at baseline, and after 1, 2, 3, and 4 years of follow-up (Figure 1).

QoL outcomes

The QoL questionnaires included the EuroQol five-dimensional questionnaire (EQ-5D), the Health Utilities Index mark 3 (HUI3), a Visual Analogue Scale (VAS) on general health, and the Time Trade-off (TTO)[14–17]. The EQ-5D contains a thermometer indicating general health state and five dimensions of QoL: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has three levels: no problems, some problems, extreme problems. The result is a single index value for health status: a utility scores ranging from -0.33 to 1.00[6,14,17]. The HUI3 consists of eight elements of health status: vision, hearing, speech, ambulation, dexterity, emotion, cognition and pain. Each dimension has up to six levels. The result is a utility score between -0.36 and 1.00.[6,15] The VAS general contains a thermometer with a scale from 0 to 100. Participants were asked to mark their general QoL from 0 (really bad) to 100 (perfect). These scores were then converted to values between 0 and 1: dividing by 100.[6] The TTO is a direct method for the measurement of health status. Participants were asked whether they were willing to trade expected life years for perfect hearing. The utility score was calculated as: utility=(life expectancy – number of years a participant would trade)/ life expectancy. The TTO was not evaluated at baseline. For all QoL outcomes, a higher score reflects better QoL.

QoH outcomes

The QoH questionnaires included the VAS on hearing, the Speech, Spatial and Qualities of Hearing Scale (SSQ) and the Nijmegen Cochlear Implant Questionnaire (NCIQ)[18,19]. The VAS hearing contains a thermometer with a scale from 0 to 100. Participants were asked to mark their hearing from 0 (deaf) to 100 (perfect hearing). These scores were then converted to values between 0 and 1: dividing by 100[6]. The SSQ consists of three domains of questions. Participants were asked to rate their hearing capabilities on a 0-100 scale (0= not capable at all, 100=perfectly capable). The SSQ1 comprises questions on speech understanding in silence, in background noise, in resonating environments and on the telephone. The SSQ2 comprises questions on spatial hearing; identifying directions of sounds and distance approximation, and the SSQ3 encompasses questions on the quality of hearing[18]. The final subdomain score is computed by the mean of all items on that subdomain, resulting in a range of scores from 0 to 10[7,18]. The NCIQ contains six subdomains of hearing that are rated categorically (1-5 (never-always) and "not applicable"). The subdomains are 1. Basic sound perception, 2. Advanced sound perception (in difficult daily listening situations or background noise), 3. Speech production, 4. Self-esteem, 5. Activity limitations, 6. Social interaction[19].

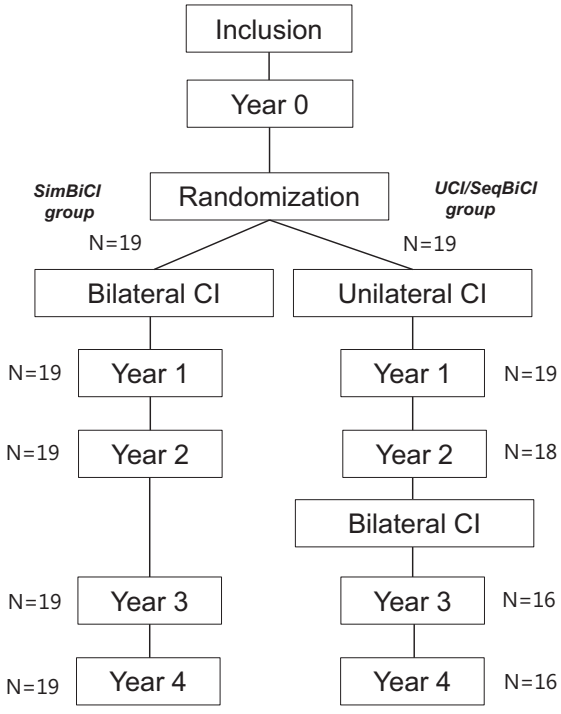

Figure 1. Flowchart of the study. Legend: simBiCI: simultaneous bilateral cochlear implantation; UCI/seqBiCI: unilateral cochlear implantation/sequential bilateral cochlear implantation ; CI: cochlear implant.

The answer categories must first be transformed (1=0, 2=25, 3=50, 4=75 and 5=100). Afterwards, the final subdomain score is computed by adding together all the item scores and dividing by the number of completed items, resulting in a range of scores from 0 to 100. A higher score reflects a greater ability.[7,19] As this questionnaire is specifically designed for the evaluation after cochlear implantation, this questionnaire was not administered at baseline. For all QoH outcomes, a higher score reflects a greater ability.

Tinnitus outcomes

The tinnitus questionnaires included the Tinnitus Handicap Inventory (THI) and Tinnitus Questionnaire (TQ)[20,21]. The THI is a questionnaire regarding tinnitus handicap in daily life. The questionnaire comprises a 12-item functional subscale, an 8-item emotional subscale and a 5-item catastrophic subscale[12,20,22]. The TQ consists of 52 questions on emotional and cognitive distress, intrusiveness, auditory perceptual difficulties, sleep disturbance and somatic complaints[21]. Both tinnitus questionnaires were administered to all participants, but could only be completed when a participant experienced tinnitus. For both questionnaires, a higher score reflects a higher tinnitus severity.

Sample size calculation

The sample size of this RCT was based on the primary outcome, which was the objectively measured speech perception in noise. Fourteen participants in each group were needed to detect a clinically relevant difference of 3 dB between groups on the speech perception in noise from straight ahead test with a standard deviation of 3 dB, an alpha of 0.05 and a power of 80%. Five additional subjects were included per group to compensate for any expected loss to follow-up[3,4,11].

Missing data and loss to follow-up

In case participants were loss to follow-up, analyses were performed with and without these missing cases as a sensitivity analysis.

Statistical methods

Prior to analysis, all data were double-checked by two researchers independently. Patient characteristics were presented as counts, percentages, and medians with interquartile ranges (IQRs).

All outcome measures were analyzed longitudinally (follow-up points 1, 2, 3 and 4 years) via a linear regression analysis with an autoregressive residual covariance matrix (generalized estimating equations type, using a maximum likelihood estimation method). The tinnitus outcomes were analyzed longitudinally via a logistic regression analysis with an autoregressive residual covariance matrix (generalized estimating equations type), as we dichotomized the outcome: the presence of tinnitus burden (yes or no). A participant was considered to experience tinnitus burden when a score higher than 0 was reached on either of the questionnaires. We chose this method instead of a linear regression analysis with THI and TQ scores, because participants who did not suffer from tinnitus did not complete

the questionnaires and therefore, the THI and TQ scores of these patients were 'missing'.

All of the models included time (as a categorical variable), group (simBiCI versus UCI/seqBiCI), the interaction between time and group (in order to study whether the course of scores differed between the groups) and baseline score of the particular outcome (to adjust for a possible baseline differences). For the TTO and NCIQ, there were no baseline scores, and therefore the baseline VAS health respectively VAS hearing scores were used. HA use at baseline was the only variable which differed statistically significantly between both groups[3], and for that reason, we added this variable to all models in order to verify whether it was a possible confounder. Residuals of the final linear models were checked for normality and showed a normal distribution. To visualize the course of all subjective outcomes for both study groups, we created graphs for all outcome measures, presenting mean outcome values with standard deviations (SDs).

A *p*-value <0.05 was considered statistically significant. The regression models were generated in SPSS version 22.0 whereas the residue analyses were performed in SAS version 9.4.

RESULTS

Participants

Between December 2009 and September 2012, 38 participants were included in this study. Nineteen participants were allocated to simBiCI and 19 participants to UCI/seqBiCI[3,4,11]. Table 1 shows the baseline characteristics. As previously mentioned, the groups were similar at baseline, except for the number of participants using a HA (19 vs 15).

Missing data and loss to follow-up

During the second and third year of follow-up, two participants in the UCI/seqBiCI withdrew for personal reasons. Another participant was excluded from the UCI/seqBiCI group because of poor performance with the first implant. This participant appeared to have a hearing loss due to rhesus antagonism and was expected not to benefit from a second CI because of this central cause of deafness (Figure 1)[3,4,11].

At year 3 the results of the VAS health and hearing were missing in one participant in the simBiCI group and the TTO was missing for another participant in this group. At year 4 the EQ-5D was missing for one participant in the simBiCI group and TTO was missing for another participant in this group.

QoL outcomes

Figure 2. shows the QoL outcomes preoperatively and during 4 years of follow-up for both study groups. The EQ-5D, HUI3 and VAS general health scores did not differ significantly between the UCI/seqBiCI and simBiCI group over time (Appendix 1). Also the course of these scores did not differ between groups and for both groups the EQ-5D, HUI3 and VAS general scores remained stable over the 4 years of follow-up.

Table 1. Baseline characteristics

	SimBiCI	UCI/seqBiCI
Male, number (%)	8 (42)	11 (58)
Age at inclusion, years, median [IQR]	52 [36-63]	54 [43-64]
Duration severe hearing loss right ear, years, medians [IQR]	16 [11-25]	17 [9-33]
Duration severe hearing loss left ear, years, median [IQR]	16 [11-25]	18 [9-35]
PTA right ear, dB, median [IQR]	106 [89-119]	106 [94-111]
PTA left ear, dB, median [IQR]	108 [89-120]	108 [93-114]
Hearing aid use before CI, number/total	19/19	15/19
Treatment Hospital		
Utrecht	8	11
Maastricht	5	4
Nijmegen	3	2
Leiden	2	1
Groningen	1	1
Cause of deafness		
Hereditary	9	7
Unknown and progressive	6	9
Sudden Deafness	2	0
Head trauma	1	0
Meningitis	0	2
Rhesus Antagonism	0	1
Sound exposure	1	0

Sim: simultaneous; BiCI: bilateral cochlear implantation; UCI: unilateral cochlear implantation; seq: sequential; IQR: interquartile range; PTA: pure tone average over 1, 2 and 4 kilohertz; dB: decibels; CI: cochlear implant

The TTO score was significantly lower in the UCI/seqBiCI group compared with the simBiCI group over time (-0.078 [-0.140 - -0.017], p=0.017). However, a significant improvement was seen in the UCI/seqBiCI group after receiving CI2 (year 3 vs year 1: 0.084 [0.003- 0.165], *p*=0.017). HA use was a significant confounder for the HUI3 only.

QoH outcomes

Figure 3 shows the QoH outcomes preoperatively and during 4 years of follow-up for both study group. The VAS hearing scores differed significantly between the UCI/seqBiCI and simBiCI group over time (-0.12 [-0.24 - -0.01], *p*=0.036) (Appendix 2). The course of these scores did not differ between groups. Although not significantly, the scores in the UCI/seqBiCI group improved after receiving CI2.

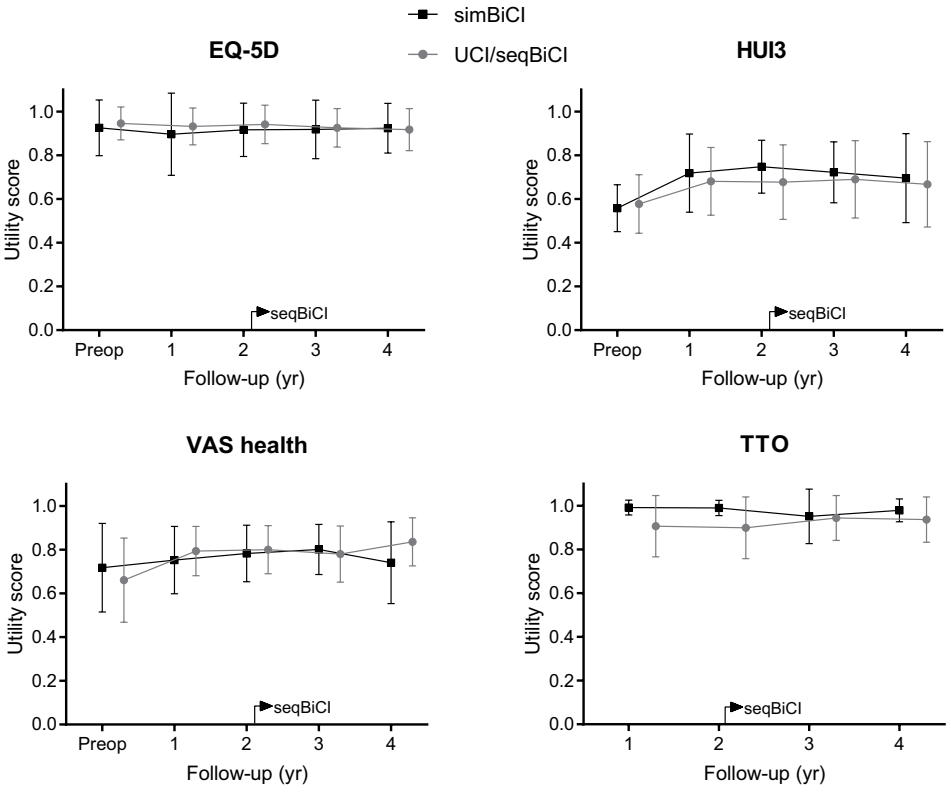

Figure 2. Quality of life outcomes. Mean scores with SD are presented. EQ-5D: Dutch EuroQol-5D; HUI3: Health Utilities Index 3; VAS: Visual analogue scale; TTO: Time trade off; yr: year; CI: cochlear implant; SimBiCI = simultaneous bilateral cochlear implantation; UCI/seqBiCI = unilateral cochlear implantation/sequential bilateral cochlear implantation group. To improve readability, the results of both groups are presented interleaved, yet follow-up moments were similar in both groups.

The SSQ1, SSQ2 and SSQ3 scores were significantly lower in the UCI/seqBiCI group compared with the simBiCI group over time (most evident for SSQ2: -2.32 [-3.38 - -1.26], *p*=<0.001). A significant improvement was seen in the UCI/seqBiCI group after receiving CI2 for the SSQ1 (year 4 vs year 1: 0.75 [0.10 – 1.41], *p*=0.025) and the SSQ 2 and 3 (years 3 and 4 vs year 1, for example year 3 vs year 1 for SSQ2: 1.82 [0.60 – 3.04], *p*=0.004). In the simBiCI group, all SSQ scores remained stable in the 4 years of follow-up.

From all NCIQ domain scores, only the social interaction score was significantly lower in the UCI/seqBiCI group compared with the simBiCI group over time (-9.26 [-18.20 - -0.33], *p*=.042). Significant increases in basic sound perception, self-esteem, activity and social interaction scores were seen in the UCI/seqBiCI group after receiving CI2 (year 4 vs year 1, most evident for basic sound perception: 12.22 [4.27 – 20.17], *p*=.003). In the simBiCI group, all NCIQ scores remained stable in the 4 years of follow-up.

Tinnitus outcomes

Figure 4 shows the prevalence of tinnitus burden preoperatively and during 4 years of follow-up for both study groups. The prevalence of tinnitus burden, corrected for baseline prevalence, did not differ significantly between the UCI/seqBiCI and simBiCI group over time. Also the course of tinnitus burden did not differ between groups and for both groups the presence of tinnitus burden remained stable in the 4 years of follow-up (Appendix 3).

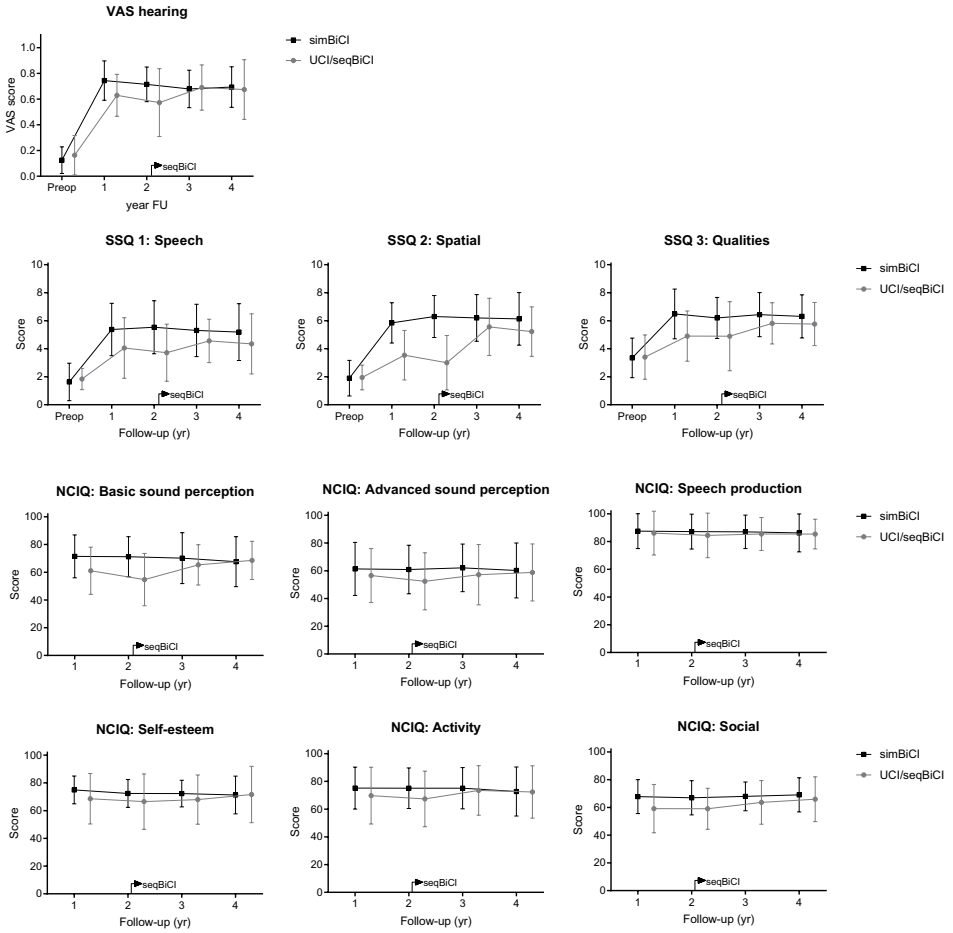

Figure 3. Quality of hearing outcomes. Mean scores with SD are presented. VAS: visual analogue scale; SSQ: Speech, Spatial and Qualities Hearing Scale; NCIQ: Nijmegen Cochlear Implant Questionnaire; yr: year; CI: cochlear implant; SimBiCI = simultaneous bilateral cochlear implantation; UCI/seqBiCI = unilateral cochlear implantation/sequential bilateral cochlear implantation group. To improve readability, the results of both groups are presented interleaved, yet follow-up moments were similar in both groups.

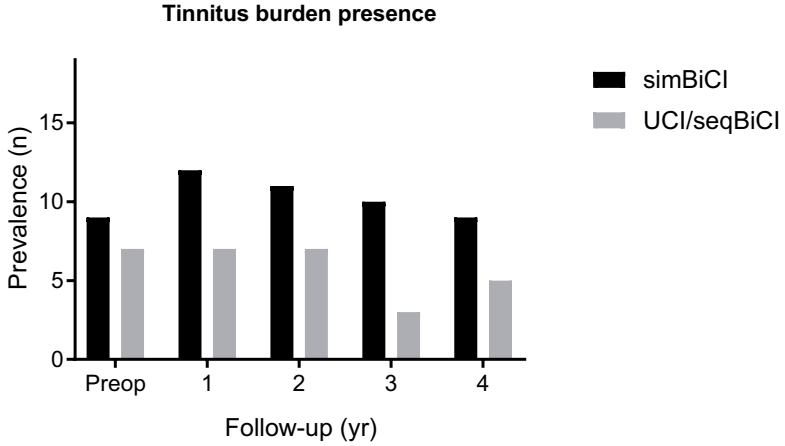

Figure 4. Tinnitus outcomes. The number of participants with the presence of tinnitus burden is presented. The presence of tinnitus burden is defined as a score higher than 0 on either one of the tinnitus questionnaires. SimBiCI =simultaneous bilateral cochlear implantation; UCI/seqBiCI = unilateral cochlear implantation/sequential bilateral cochlear implantation group.

Sensitivity analysis

A sensitivity analysis of the data without participants with missing data revealed no differences regarding direction, effect sizes or significance of the results compared to the primary analysis except for the NCIQ basic sound perception: a significant overall lower NCIQ basic sound perception score was seen in the UCI/seqBiCI group (-11.61, *p:* 0.028).

DISCUSSION

Key findings

The current study evaluated the longitudinal subjective outcomes longitudinally after simBiCI compared with seqBiCI, with a 2-year inter-implant interval, in adult patients with severe to profound SNHL.

This study showed that the most evident differences over time between UCI/seqBiCI and simBiCI were seen on the QoH outcomes, especially the SSQ. Only in one out of four QoL questionnaires (the TTO), a significantly lower utility score was seen in the UCI/seqBiCI group compared to the simBiCI group over time. These differences between groups, were caused by the lower performance in the UCI/seqBiCI group in their unilateral situation, as all of these results improved after receiving the second CI. Although the prevalence of tinnitus burden seemed higher in the simBiCI group, no significant difference was seen between both groups over time.

Comparison with literature

To our knowledge, no previous studies compared simBiCI with seqBiCI, and therefore we are unable to compare our findings with literature. Corresponding to existing literature on only seqBiCI, we found that patients after seqBiCI benefited from receiving a second CI, on some of the subjective outcomes[23–26]. The lack of general QoL improvement in 3 out of 4 QoL questionnaires in our study corresponded to earlier findings from the study of Summerfield et al.[23]. That study found no significant changes on all QoL measures, EQ-5D, HUI3, VAS and Glasgow Health Status Inventory (GHSI), in 24 patients after seqBiCI. In the study of Härkonen et al.[25] different QoL instruments were used: the Glasgow Benefit Inventory (GBI) and the 15D health-related QoL questionnaire, in a small group of 15 patients to evaluate the extra benefit of the second CI. Both scores improved significantly after seqBiCI[25]. These contradictive findings illustrate the importance of the choice for QoL instruments to evaluate the effectiveness of seqBiCI. Particularly when cost-effectiveness is evaluated, the QoL results are leading. As confirmed with the current study, most general health utility instruments are not appropriate to measure changes after cochlear implantation[6,23,27]. The EQ-5D and VAS health instruments for example do not incorporate a hearing element, and are therefore not sensitive to detect change in QoL as a result of cochlear implantation[6]. Moreover, in our current study ceiling effects of EQ-5D and TTO were seen, making it even more difficult to detect improvement. Thus, the use of a QoL instrument with a hearing element in cochlear implant studies, for example the HUI3, seems appropriate[6,27]. As Figure 2 and our previous study showed: HUI3 scores improved after UCI and simBiCI when compared to the situation before implantation[6]. Nonetheless, to detect smaller differences, such as the additional effect of a second CI in the UCI/seqBiCI group or differences between simBiCI and seqBiCI, as investigated in the current study, the HUI3 is not sensitive enough. Compared to the QoL questionnaires, the QoH questionnaires used in the current study, showed a larger benefit of seqBiCI. All subdomains of the SSQ and the basic sound perception, self-esteem, activity and social interaction subdomains of the NCIQ improved significantly after receiving the second CI, which is in line with previous literature[23–26]. These findings are also in line with the known benefits of binaural hearing compared to monaural hearing: better speech perception in noise and localization abilities. The latter mentioned aspect are well represented in these QoH questionnaires.

In this study, three participants did not proceed to seqBiCI after UCI. Australian data previously suggested that not all UCI patients proceed to seqBiCI[28]. Therefore, our findings may be a realistic representation of the actual clinical population. It is plausible that patients' withdrawal is influenced by good performance with the first CI, yet conversely, bad performance with the first CI could make patients reluctant to proceed to seqBiCI.

Strengths and limitations

The major strength of the current study is the study design, which was an RCT, which provides a high level of evidence, since allocation bias is excluded. Furthermore, data was prospectively gathered at the same time points for all participants. Another strength is the

longitudinal method for data analyses (GEE). These strengths distinguish the current study from previous studies.

A possible limitation of this study is the fact that the sample size may have been too small to detect differences in secondary outcomes, since a power analysis is aimed at a primary outcome. Longitudinal analyses however, have more power compared to cross-sectional analyses because of the repeated observations at the individual level. This approach may have limited the lack of power. Three participants were lost to follow-up. This could have led to a bias in treatment effect. However, the sample size calculation incorporated loss to follow-up up to 5 participants per group. Moreover, sensitivity analyses showed comparable results to the original analyses regarding effect sizes. Another possible limitation is the use of logistic regression instead of linear regression for the tinnitus outcomes. Continuous data provides more information than dichotomous data. We only used the presence of tinnitus and not the THI and TQ scores. We had to choose this method, because participants who did not suffer from tinnitus did not complete the questionnaires and therefore, the THI and TQ scores of these patients were 'missing'. Linear regression analysis with all these 'missings' would give biased results.

CONCLUSION

In this manuscript, we evaluated the longitudinal subjective outcomes after simBiCI compared with UCI/seqBiCI in adult patients with severe to profound SNHL. Most evident differences between groups over time were seen on the QoH outcomes, especially the SSQ. These differences were most likely caused by the lower performance in this group in their unilateral situation, as all of these outcomes improved after receiving the second CI.

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Conflict of interest
JHMF receives non-restrictive grants from Advanced Bionics and MedEl. RHF receives non-restrictive grants from Advanced Bionics and is sponsored by a neurotological stipendium from the Heinsius Houbolt Foundation. WG received non-restrictive research grants from Cochlear Advanced Bionics and MedEl. All authors completed the ICMJE uniform disclosure form and declared no further competing interests.

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APPENDIX 1

Results from a linear regression analysis with an autoregressive residual covariance matrix (generalized estimating equations type) for quality of life outcomes.

	Parameter	Estimate	Standard deviation	*p*-value	Lower bound 95%-CI	Upper bound 95%- CI
EQ-5D	Treatment	0.023	0.031	0.459	-0.038	0.083
	Year 2	0.020	0.030	0.495	-0.038	0.079
	Year 3	0.023	0.028	0.425	-0.033	0.079
	Year 4	0.034	0.025	0.178	-0.016	0.083
	SeqxYear2	-0.009	0.042	0.825	-0.093	0.074
	SeqxYear3	-0.021	0.041	0.618	-0.102	0.061
	SeqxYear4	-0.038	0.036	0.296	-0.108	0.033
	EQ-5D baseline	0.688	0.097	**0.000**	0.493	0.883
HUI3	Treatment	-0.011	0.051	0.827	-0.112	0.090
	Year 2	0.030	0.045	0.504	-0.059	0.119
	Year 3	0.005	0.041	0.909	-0.077	0.086
	Year 4	-0.037	0.034	0.270	-0.104	0.030
	SeqxYear2	-0.034	0.064	0.601	-0.160	0.093
	SeqxYear3	0.012	0.060	0.836	-0.106	0.130
	SeqxYear4	0.035	0.049	0.479	-0.062	0.132
	HUI3 baseline	0.512	0.169	**0.004**	0.171	0.852
	HA use	-0.173	0.070	**0.017**	-0.314	-0.033
VAS health	Treatment	0.053	0.040	0.186	-0.026	0.132
	Year 2	0.030	0.035	0.394	-0.039	0.099
	Year 3	0.048	0.032	0.135	-0.015	0.112
	Year 4	-0.012	0.025	0.647	-0.062	0.038
	SeqxYear2	-0.021	0.050	0.672	-0.120	0.078
	SeqxYear3	-0.062	0.046	0.179	-0.154	0.029
	SeqxYear4	0.053	0.037	0.155	-0.020	0.126
	VAS health baseline	0.210	0.077	**0.009**	0.054	0.365
TTO	Treatment	-0.078	0.031	**0.013**	-0.140	-0.017
	Year 2	-0.002	0.030	0.958	-0.061	0.057
	Year 3	-0.040	0.029	0.169	-0.096	0.017
	Year 4	-0.012	0.024	0.627	-0.060	0.036
	SeqxYear2	-0.005	0.043	0.913	-0.089	0.079
	SeqxYear3	0.084	0.041	**0.043**	0.003	0.165
	SeqxYear4	0.047	0.035	0.183	-0.023	0.117
	VAS health baseline	0.124	0.053	**0.025**	0.017	0.231

Reference treatment group = simBiCI. Reference year = year 1. The final model contained the following variables: time + treatment + time x treatment + baseline score. In case there was a confounding role for hearing aid use at baseline, this variable was included in the final model as well. EQ-5D: EuroQol five-dimensional questionnaire; HUI3: the Health Utilities Index mark 3; HA: hearing aid; VAS: Visual Analogue Scale on general health; TTO: Time Trade-off; seq = unilateral cochlear implantation/sequential bilateral cochlear implantation group

APPENDIX 2

Results from a linear regression analysis with an autoregressive residual covariance matrix (generalized estimating equations type) for quality of hearing outcomes.

	Parameter	Estimate	Standard deviation	*p*-value	Lower bound 95%-CI	Upper bound 95%-CI
VAS hearing	Treatment	-0.122	0.057	0.**036**	-0.236	-0.008
	Year 2	-0.029	0.052	0.581	-0.132	0.074
	Year 3	-0.056	0.048	0.249	-0.152	0.040
	Year 4	-0.050	0.039	0.198	-0.127	0.027
	SeqxYear2	-0.028	0.075	0.710	-0.175	0.120
	SeqxYear3	0.128	0.070	0.069	-0.010	0.266
	SeqxYear4	0.107	0.056	0.060	-0.005	0.220
	VAS hearing baseline	0.201	0.166	0.232	-0.132	0.534
SSQ1	Treatment	-1.524	0.533	**0.006**	-2.591	-0.458
	Year 2	0.161	0.356	0.651	-0.542	0.865
	Year 3	-0.063	0.304	0.835	-0.665	0.538
	Year 4	-0.183	0.225	0.418	-0.630	0.263
	SeqxYear2	-0.409	0.508	0.423	-1.414	0.597
	SeqxYear3	0.831	0.440	0.062	-0.041	1.703
	SeqxYear4	0.750	0.330	**0.025**	0.096	1.405
	SSQ1 baseline	0.984	0.220	**0.000**	0.540	1.429
SSQ2	Treatment	-2.319	0.534	**0.000**	-3.380	-1.259
	Year 2	0.460	0.472	0.332	-0.473	1.392
	Year 3	0.357	0.426	0.403	-0.485	1.200
	Year 4	0.291	0.336	0.389	-0.376	0.959
	SeqxYear2	-0.999	0.673	0.140	-2.328	0.331
	SeqxYear3	1.824	0.617	**0.004**	0.604	3.044
	SeqxYear4	1.543	0.492	**0.002**	0.567	2.520
	SSQ2 baseline	0.421	0.190	**0.032**	0.039	0.803
SSQ3	Treatment	-1.623	0.550	**0.005**	-2.723	-0.523
	Year 2	-0.288	0.401	0.474	-1.081	0.505
	Year 3	-0.087	0.346	0.802	-0.772	0.598
	Year 4	-0.229	0.259	0.378	-0.743	0.284
	SeqxYear2	0.307	0.565	0.588	-0.811	1.425
	SeqxYear3	1.051	0.494	**0.036**	0.072	2.029
	SeqxYear4	1.205	0.374	**0.002**	0.463	1.947
	SSQ3 baseline	0.473	0.161	**0.006**	0.146	0.800
NCIQ basic	Treatment	-9.620	5.315	0.075	-20.218	0.978
	Year 2	-0.263	4.119	0.949	-8.406	7.879
	Year 3	-1.316	3.601	0.715	-8.441	5.810
	Year 4	-3.863	2.737	0.161	-9.292	1.565
	SeqxYear2	-5.513	5.881	0.350	-17.139	6.112
	SeqxYear3	6.352	5.216	0.226	-3.970	16.673
	SeqxYear4	12.222	4.009	**0.003**	4.273	20.171
	VAS hearing baseline	-19.889	17.165	0.253	-54.545	14.767

Appendix 2 Continued

	Parameter	Estimate	Standard deviation	*p*-value	Lower bound 95% - CI	Upper bound 95% - CI
NCIQ advanced	Treatment	-3.523	6.426	0.586	-16.391	9.345
	Year 2	-0.376	4.049	0.926	-8.383	7.631
	Year 3	0.764	3.456	0.825	-6.076	7.605
	Year 4	-1.034	2.558	0.687	-6.106	4.038
	SeqxYear2	-3.124	5.787	0.590	-14.569	8.322
	SeqxYear3	2.485	5.006	0.621	-7.425	12.394
	SeqxYear4	5.969	3.747	0.114	-1.460	13.398
	VAS hearing baseline	7.293	21.821	0.740	-36.823	51.410
	Hearing aid use	-7.025	9.622	0.470	-26.485	12.436
NCIQ speech	Treatment	0.680	4.581	0.883	-8.497	9.857
	Year 2	-0.340	2.785	0.903	-5.848	5.168
	Year 3	-0.559	2.368	0.814	-5.248	4.129
	Year 4	-1.334	1.746	0.447	-4.796	2.128
	SeqxYear2	-1.014	3.981	0.799	-8.888	6.861
	SeqxYear3	-2.524	3.430	0.463	-9.316	4.267
	SeqxYear4	-1.785	2.558	0.487	-6.856	3.286
	VAS hearing baseline	-29.738	15.691	0.065	-61.456	1.980
	Hearing aid use	-4.760	6.921	0.496	-18.754	9.234
NCIQ self-esteem	Treatment	-6.806	4.844	0.165	-16.488	2.877
	Year 2	-2.602	3.346	0.438	-9.218	4.013
	Year 3	-2.635	2.873	0.361	-8.321	3.051
	Year 4	-3.684	2.140	0.088	-7.928	0.559
	SeqxYear2	0.713	4.781	0.882	-8.741	10.167
	SeqxYear3	2.618	4.161	0.530	-5.618	10.855
	SeqxYear4	7.084	3.135	**0.026**	0.869	13.299
	VAS hearing baseline	10.330	16.380	0.532	-22.770	43.429
NCIQ activity	Treatment	-6.147	5.595	0.276	-17.338	5.044
	Year 2	-0.150	3.796	0.969	-7.656	7.357
	Year 3	-0.124	3.252	0.970	-6.562	6.313
	Year 4	-2.476	2.417	0.308	-7.269	2.317
	SeqxYear2	-1.719	5.425	0.752	-12.447	9.009
	SeqxYear3	6.108	4.411	0.197	-3.217	15.433
	SeqxYear4	7.802	3.540	**0.030**	0.783	14.822
	VAS hearing baseline	18.473	19.026	0.338	-20.007	56.953
NCIQ social	Treatment	-9.264	4.471	**0.042**	-18.201	-0.327
	Year 2	-0.804	3.149	0.799	-7.031	5.423
	Year 3	0.157	2.711	0.954	-5.209	5.523
	Year 4	1.308	2.025	0.520	-2.708	5.325
	SeqxYear2	0.954	4.499	0.832	-7.943	9.850
	SeqxYear3	5.790	3.927	0.143	-1.982	13.563
	SeqxYear4	7.074	2.966	**0.019**	1.191	12.956
	VAS hearing baseline	15.457	15.016	0.310	-14.913	45.827

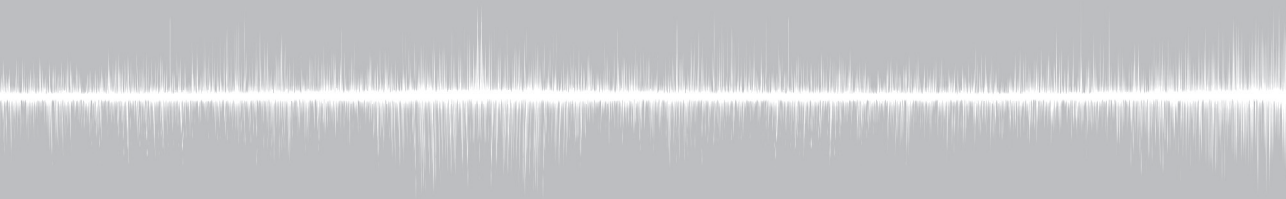
Reference treatment group = simBiCI. Reference year = year 1. The final model contained the following variables: time + treatment + time x treatment + baseline score. In case there was a confounding role for hearing aid use at baseline, this variable was included in the final model as well. VAS: Visual Analogue Scale on hearing; SSQ: Speech, Spatial and Qualities of Hearing Scale; NCIQ: Nijmegen Cochlear Implant Questionnaire; HA: hearing aid; SimBiCI = simultaneous bilateral cochlear implantation; seq = unilateral cochlear implantation/sequential bilateral cochlear implantation group

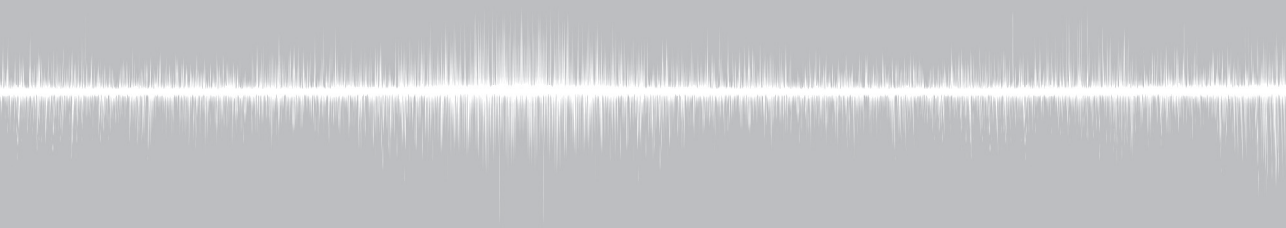
APPENDIX 3

Results from a logistic regression analysis with an autoregressive residual covariance matrix (generalized estimating equations type) for the presence of tinnitus burden.

Parameter	Estimate	Standard deviation	*p*-value	Odds ratio	Lower bound 95% - CI	Upper bound 95% - CI
Treatment	-1.110	0.7918	0.161	0.330	0.070	1.556
Year 2	-0.278	0.5155	0.590	0.758	0.276	2.080
Year 3	-0.578	0.6006	0.336	0.561	0.173	1.822
Year 4	-0.869	0.6452	0.178	0.419	0.118	1.485
SeqxYear2	0.637	0.6122	0.298	1.891	0.569	6.277
SeqxYear3	-0.833	0.8966	0.353	0.435	0.075	2.520
SeqxYear4	0.610	0.7606	0.423	1.840	0.414	8.172
Tinnitus baseline	2.404	0.7202	**0.001**	11.068	2.698	45.401

Reference treatment group = simBiCI. Reference year = year 1. The final model contained the following variables: time + treatment + time x treatment + baseline tinnitus burden presence. SimBiCI = simultaneous bilateral cochlear implantation; seq = unilateral cochlear implantation/sequential bilateral cochlear implantation group





General discussion

PART 1 COCHLEAR IMPLANTATION AND TINNITUS

The first part of this thesis evaluates the effect of cochlear implantation on tinnitus, which is often prevalent in cochlear implant (CI) candidates.

Tinnitus following unilateral cochlear implantation

Already in 1981 House and Brackmann[1] reported improvement in tinnitus after cochlear implantation. Since then, numerous studies focussed on this 'side effect' of cochlear implantation. A systematic overview of the literature regarding the effect of cochlear implantation on tinnitus in adult patients with bilateral severe to profound sensorineural hearing loss (SNHL) was given in **Chapter 1.1** of this thesis. Ten cohort studies with a moderate risk of bias were finally included for further analyses. These included studies were only reporting on unilateral cochlear implantation (UCI). A large heterogeneity between these studies and the lack of studies with a low risk of bias, withheld us from performing a meta-analysis. On group level, most studies showed an overall reduction of mean tinnitus burden questionnaire score after UCI. On patient level, most studies reported a positive effect of cochlear implantation on tinnitus (complete recovery or decrease) in the majority of the patients. However, an increase of tinnitus was also described in 0-25% of patients and even newly induced tinnitus was reported in 0-10% of patients. The results we found with our own retrospective cohort study in **Chapter 1.2** were in line with the results of the studies in the systematic review.

Tinnitus following bilateral cochlear implantation

Contrary to UCI, only a few studies reported on the effect of bilateral cochlear implantation (BiCI) on tinnitus[2,3]. According to a recent literature search, only two other studies investigated the effect of sequential BiCI (seqBiCI) on tinnitus. Olze et al.[3] found a beneficial effect of the second CI resulting in a further decrease of tinnitus scores in the participants with preoperative tinnitus (n=28). In contrast, Summerfield et al.[2] found a negative effect of the second CI: increase of tinnitus scores in the whole study group (n=24), due to increased tinnitus in 7 of 16 participants with preoperative tinnitus, and newly induced tinnitus in 4 of 8 participants without preoperative tinnitus. In **Chapter 1.4**, we found an additional benefit of seqBiCI on tinnitus in the majority of patients. This was a descriptive study presenting cross-sectional results of a multicenter randomized controlled trial (RCT) on the benefits of simultaneous BiCI (simBiCI) versus seqBiCI with an inter-implant interval of 2 years. In **Chapter 2.3** we evaluated the longitudinal (4 years) tinnitus prevalence outcomes of this RCT comparing simBiCI with seqBiCI. No significant differences in tinnitus prevalences were found between both groups over time.

Prediction of tinnitus recovery

In general, a positive effect of UCI (**Chapter 1.1** and **Chapter 1.2**) and BiCI (**Chapter 1.4**) is seen on preoperative tinnitus burden in the majority of patients. However, not all patients with preoperative tinnitus benefit from cochlear implantation regarding their tinnitus symptoms. Which CI patients with preoperative tinnitus will recover from tinnitus after

cochlear implantation and which patients not, is barely investigated. For that reason, we conducted the study in **Chapter 1.3** where we tried to identify possible predictors for tinnitus recovery following UCI. We found three significant predictors for tinnitus recovery after UCI: a lower preoperative score on a speech perception test (Consonant-Vowel-Consonant (CVC) test), unilateral localization of tinnitus and a larger deterioration of residual hearing at hearing threshold 250 Hz. This final multivariable prediction model was internally validated. To our knowledge this was the first study developing and internally validating a multivariable prediction model for tinnitus recovery following UCI. The performance of our prediction model is promising, but a larger prospective study is needed before it can be used in daily clinical practice.

Difficulties in tinnitus research

The current thesis as well as tinnitus research in general have to cope with some difficulties and limitations, which we will address in the following section.

Lack of consensus regarding tinnitus instruments

The large heterogeneity between the tinnitus studies, included in the systematic review from **Chapter 1.1** is representative for tinnitus studies in general. This heterogeneity is partly caused by the use of different instruments to measure tinnitus burden. The measurement of tinnitus is difficult, since it is a subjective symptom and consensus on which questionnaire should be used in clinical trials is lacking.[4,5] The most used instrument in the included studies was the Tinnitus Handicap Inventory (THI), which is an internationally validated questionnaire developed by Newman et al.[6] Another often-used questionnaire for the evaluation of tinnitus is the Tinnitus Questionnaire (TQ)[7]. The use of a wide range of different tinnitus instruments leads to incomparable study outcomes. Another problem in the currently used tinnitus questionnaires, is that the majority of instruments is not validated to measure the effectiveness of an intervention[8]. For this reason, the Tinnitus Functional Index (TFI) was developed, a questionnaire that is responsive to treatment-related changes[9,10]. To overcome all current shortcomings in the measurement of tinnitus, a workgroup of the TINnitus research NETwork (TINNET) is established which aims to develop standard outcome measurements for tinnitus in clinical trials and everyday clinical practice[4].

Tinnitus instruments in cochlear implant patients

Another point of discussion regarding the measurement of tinnitus is that the current tinnitus questionnaires are developed for chronic tinnitus patients and not particularly for CI candidates or CI patients. CI candidates and CI patients with tinnitus may differ from chronic tinnitus patients in, for example, terms of tinnitus burden severity. In **Chapter 1.4** we found a median THI score of 13 [IQR: 4-27] and TQ score of 17 [IQR: 6-24] in CI candidates with preoperative tinnitus. A previous study from our department in chronic tinnitus patients who were not candidates for CI, found much higher tinnitus severity scores: a mean THI score of 45 (SD: 23) and TQ score of 40 (SD: 17)[11]. The relatively low preoperative tinnitus scores in our study population could have led to floor effects, which means that it is more

difficult to detect improvement. Therefore, it can be questioned, whether the current used tinnitus instruments are also the denoted instruments to use in CI candidates or patients.

Indication for cochlear implantation

Unlike most tinnitus intervention studies, tinnitus was not part of the inclusion criteria for cochlear implantation in the studies in this thesis regarding tinnitus. In 'normal' intervention studies, the presence of the disease and sometimes a minimum severity level of the disease belong to the inclusion criteria. In the studies in this thesis however, patients received a CI because of severe to profound SNHL and not because of tinnitus. This led to a couple of limitations. The first limitation to be discussed is a low statistical power. In **Chapter 1.4**, tinnitus was a secondary outcome measure of an RCT. The sample size of this RCT was based on the primary outcome, and the presence of tinnitus was not an inclusion criterion of this RCT. Therefore, the proportion of participants with preoperative tinnitus was too low to detect statistically significant changes in this cross-sectional study and consequently, we performed a descriptive analysis of the results. In **Chapter 2.3** we performed longitudinal analyses of this RCT. Longitudinal analyses have more power compared to cross-sectional analyses because of the repeated observations at the individual level. With this approach we tried to limit the lack of power. In addition, the severity of tinnitus was also not an inclusion criterion in our studies. As stated above, the tinnitus severity in **Chapter 1.4** was therefore rather low.

When designing an optimal intervention study regarding the effect of cochlear implantation on tinnitus in patients with severe to profound SNHL, some limitations occur due to the nature of the study population. The highest level of evidence from original studies can be delivered by an RCT. Patients would be randomly allocated to a CI group or a control group. However, as UCI is the standard clinical care for patients with bilateral severe to profound SNHL, it is unethical to withhold this treatment from these patients. Therefore, it is impossible to conduct an RCT and the highest possible level of evidence includes cohort studies without control groups.

Complexity of tinnitus

Another point of discussion is the complexity of tinnitus. Many different etiological conditions may underlie tinnitus, leading to different forms. It is assumed that these forms also have different pathophysiologies and will react different on specific treatments.[12] A limitation of our (and many other) studies is, that we did not thoroughly distinguish between these different forms of tinnitus and we assumed the tinnitus was of the subjective otic type[13]. In case of objective tinnitus the sound arises from an internal physical source and it has often an identifiable cause, such as an aneurysm, arteriovenous malformation or myoclonus[14]. However, subjective tinnitus can also be caused by an underlying somatic disorder[15]. Stimulation of the somatosensory system, by movements of the jaw, temporomandibular joint, extra-ocular muscles or neck, may modulate the loudness (or sometimes pitch) of tinnitus[16,17]. If the tinnitus is linked to an underlying somatic disorder of the musculoskeletal system, this is called somatic or somatosensory tinnitus which appears to be present in a

significant percentage of tinnitus patients[13,15,16]. By a thorough anamnesis and physical examination, this type of tinnitus could be diagnosed.

Moreover, tinnitus is a multidimensional problem and it is known that the distress a patients subjectively experiences from tinnitus varies largely among patients[18]. Meikle et al.[19] concluded decades ago that the subjectively experienced tinnitus severity was not correlated with the loudness, type nor the frequency of the tinnitus[19]. This suggests that other factors than the physical characteristics of the tinnitus, influence the distress a patient subjectively experiences from tinnitus. A lot of studies investigated a wide range of possible associated factors and often contrary findings are reported. Factors associated with tinnitus severity include mood disorders like depression or anxiety, sleep disorders, personality traits, gender and age. The most investigated and reported association is the association with depression.[19–24] In the management of tinnitus, it is important to get insight in these possible contributing factors. In **Chapter 1.3**, we investigated some of these factors (age, gender, depression and anxiety) as possible predictors for tinnitus recovery following UCI. None of these factors were included in our final prediction model. The study of Kim et al.[25] however, previously found an association between a lower depression score and improvement of tinnitus following cochlear implantation. The retrospective study design from **Chapter 1.3** could have led to recall bias, which could have resulted in an underestimation of these possible predictors. Besides, anxiety and depression were self-reported by the patient and not diagnosed by a physician. A larger prospective study is needed to thoroughly investigate a wide range of factors which are possibly associated with tinnitus recovery following cochlear implantation.

For both the pathophysiology of tinnitus as the exact mechanism on how cochlear implantation influences tinnitus, a lot of theories exist, but there is still no consensus about these mechanisms. This thesis adds knowledge to the current literature, but future research is needed to give further insights into these mechanisms.

PART 2 INSTRUMENTS AND OUTCOMES IN COCHLEAR IMPLANTATION

Health utility instruments

There is an ongoing global discussion on whether or not BiCI should be standard clinical care for adult patients with bilateral severe to profound SNHL and whether these patients should receive their bilateral CIs simultaneously or sequentially. One major point of this discussion, is the cost-effectiveness of BiCI compared with UCI and simBiCI compared with seqBiCI. Cost-effectiveness of treatments has become an important topic in today's healthcare. An often-used method to evaluate cost-effectiveness is a cost-utility analysis (CUA). In these analyses, the outcomes of self-reported quality of life (QoL) instruments, in particular health utility instruments, are leading. Previous literature from various fields showed that the use of different health utility instruments can result in different utility scores[26–28]. Incomparability between these instruments is problematic as the choice of health

utility instrument will largely affect the outcome of the CUA. In **Chapter 2.1** we cross-sectionally compared different health utility instruments in a group of 38 adult patients with severe to profound SNHL who received either one or two CIs. Poor to no agreement was found between the EuroQol five-dimensional questionnaire (EQ-5D), the Health Utilities Index mark 3 (HUI3), and a VAS for general health. A gain in health utility after cochlear implantation was found with the HUI3 and VAS general only, and of these instruments, the HUI3 detected the largest gain. In **Chapter 2.3** we evaluated the longitudinal (4 years) health utility outcomes after simBiCI compared with seqBiCI. These longitudinal results also showed that most general health utility instruments are not appropriate to measure changes after cochlear implantation which was consistent with previous literature[2,29]. A possible explanation is that most health utility instruments do not incorporate a hearing element, and are therefore not sensitive to detect change in QoL as a result of cochlear implantation. Moreover, in **Chapter 2.1** and **2.3**, ceiling effects of some of the utility instruments were seen, making it even more difficult to detect improvement. Thus, the use of a QoL instrument with a hearing element in cochlear implant studies, for example the HUI3, seems appropriate and is therefore recommended[29]. HUI3 scores improved after UCI and BiCI when compared to the situation before implantation. Nonetheless, to detect smaller differences, such as the additional effect of a second CI in the seqBiCI group or differences between simBiCI and seqBiCI (**Chapter 2.3**), the HUI3 was not sensitive enough.

Quality of hearing instruments

In order to specifically measure subjective changes due to therapy in a certain field, disease-specific instruments are developed. In cochlear implantation the Speech, Spatial and Qualities of Hearing Scale (SSQ) and Nijmegen Cochlear Implant Questionnaire (NCIQ) are often used examples of measurements for disease-specific QoL, also called quality of hearing (QoH) instruments. **Chapter 2.3** showed that these instruments are better able to measure changes after cochlear implantation. Compared to the QoL questionnaires, the QoH questionnaires evaluated in this chapter, showed a larger benefit of seqBiCI for example. All subdomains of the SSQ and most subdomains of the NCIQ improved significantly after receiving the second CI, which is in line with previous literature[2,3,30,31]. These findings are also in line with the known benefits of binaural hearing compared to monaural hearing: better speech perception in noise and localization abilities. The latter mentioned aspects are well represented in these QoH questionnaires. However, at this moment, these instruments are not validated to use in a CUA.

Subjective versus objective outcomes

Not only health utility outcomes, but all patient reported outcomes gain in importance, because the healthcare system is increasingly moving towards a more patient-centered system[32,33]. Patient reported outcomes measures (PROMs) capture patients' subjective experience of illness, impairment and disability[34]. However, in the current clinical evaluation of cochlear implantation, these subjective outcomes are hardly used. The standard clinical evaluation after cochlear implantation often only encompass objective hearing tests, mostly

speech perception in silence or noise tests. **Chapter 2.2** of this thesis shows significant correlations between subjective and objective hearing test results in adult CI users. The strongest correlation was found between the spatial domain of the SSQ and the objective localization test (r=0.59, a moderate correlation). The other correlations, between subjective and objective speech perception in noise test results, were weak to moderate. There could be several reasons for the lack of strong correlations between subjective and objective results. It is likely that the questionnaires and objective tests do not represent the exact same hearing skills. The currently used objective tests in clinical evaluation do not fully reflect a patients' everyday listening situation. Another relevant topic could be that the patients' views of their own hearing skills do not match their actual hearing capabilities. Nonetheless, in the evaluation of cochlear implantation, it is important to use both subjective and objective hearing instruments.

CONCLUSIONS AND RECCOMENDATIONS

The current thesis underlines the importance of subjective outcomes in the evaluation of cochlear implantation. This is in accordance with the trend in today's healthcare, which is focused at the needs of patients and thus PROMs gain in importance. In future, subjective outcomes as tinnitus, QoL and QoH should be part of the standard clinical evaluation of the patient after cochlear implantation. We have shown that, apart from measuring these PROMS, the right choice of which instrument to use is essential. Therefore, consensus is needed on which subjective instruments regarding tinnitus, QoL and QoH should be implemented in standard clinical evaluations of cochlear implant patients.

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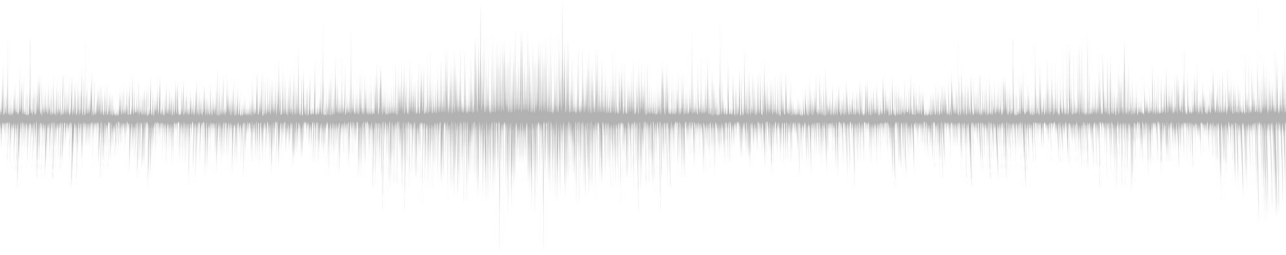
Summary



In this thesis multiple subjective (self-reported) instruments and outcomes in the evaluation of cochlear implantation are evaluated. The **General introduction** gives a short overview of the physiology of normal hearing and the pathophysiology of hearing loss. Unilateral cochlear implantation (UCI) is a standard treatment for adult patients with bilateral severe to profound sensorineural hearing loss (SNHL). Developments in the candidacy criteria for cochlear implantation, such as bilateral cochlear implantation (BiCI), are evaluated. A symptom often prevalent in patients with severe to profound SNHL is (subjective) tinnitus. After cochlear implantation, most patients experience a reduction of tinnitus complaints as a possible 'side effect'. Since tinnitus is a subjective symptom, subjective instruments (questionnaires) are used in the evaluation of tinnitus. Other subjective instruments that can be used in the evaluation of cochlear implantation are quality of life (QoL) and quality of hearing (QoH) questionnaires. In the current healthcare system, there is a growing interest in subjective outcomes.

Furthermore, the general introduction presents an outline of this thesis. In the first part, the effect of cochlear implantation on tinnitus is further investigated with multiple study designs and in different patient groups. The second part focuses mostly on other subjective instruments and outcomes in the evaluation of cochlear implantation and aims to give recommendations for future research and clinical care.

In **Chapter 1.1** we systematically reviewed the literature on the effect of cochlear implantation on tinnitus in adult patients with bilateral severe to profound SNHL. Ten cohort studies reporting on UCI were included. Large heterogeneity between studies and the lack of studies with a low risk of bias made it undesirable to pool the data in a meta-analysis and therefore a descriptive analysis was used instead. On group level, most studies showed a decrease of tinnitus after UCI. On patient level, however, increase of tinnitus and newly induced tinnitus were also reported in a minority of patients.

In **Chapter 1.2** we performed a retrospective cohort study at the Department of Otorhinolaryngology, Head and Neck Surgery from the University Medical Center Utrecht (UMCU) to evaluate our 10-year results regarding the effect of UCI on tinnitus in adult patients with bilateral severe to profound SNHL. The prevalence of preoperative tinnitus was 64%. In the majority of individual patients, cochlear implantation had a positive effect on tinnitus (complete recovery or decrease compared to the preoperative situation). However, an increase of tinnitus was also reported (10%). In the patients without tinnitus preoperatively, newly induced tinnitus occurred in 14%. In this study, we also investigated the effect of turning the cochlear implant (CI) processor 'on' on current tinnitus symptoms. When turning the CI processor 'on', significant decreases in median Visual Analogue Scale (VAS) scores for tinnitus loudness, annoyance and pitch were seen.

In **Chapter 1.3** we used partly the same database as in Chapter 1.2, to develop and internally validate a prediction model for tinnitus recovery following UCI. The outcome of the prediction model was complete recovery of tinnitus and only the data of patients with preoperative

tinnitus were used (n=87). As no previous studies on this topic exist, we investigated a large set of clinically relevant possible predictors. Three predictors for tinnitus recovery following UCI were identified: a lower preoperative score on a speech perception test (Consonant-Vowel-Consonant (CVC) test), unilateral localization of tinnitus and a larger deterioration of residual hearing at 250 Hz. After internal validation, the performance of the prediction model was reasonable. Especially for a first retrospective study the performance of this model is promising. However, a larger prospective study is needed before it can be used in daily clinical practice.

In **Chapter 1.4** we evaluated the effect of BiCI on tinnitus in adult patients with bilateral severe to profound SNHL. This was a descriptive study, which was part of a multicenter randomized controlled trial (RCT) on the benefits of simultaneous BiCI (simBiCI) versus sequential BiCI (seqBiCI) with an inter-implant interval of 2 years. Tinnitus was evaluated before and each year after cochlear implantation with two questionnaires: the Tinnitus Handicap Inventory (THI) and the Tinnitus Questionnaire (TQ). The prevalence of preoperative tinnitus was rather low compared to literature: 42%. On group level, BiCI had a positive effect on preoperative tinnitus severity scores. On patient level, however, the induction of (temporary or permanent) tinnitus was also reported in some patients without preoperative tinnitus, with a higher prevalence in the simBiCI group. Although the preoperative and also the postoperative tinnitus severity scores were higher in the simBiCI group, the effect sizes were comparable for simBiCI and seqBiCI.

In **Chapter 2.1** we evaluated the agreement between different QoL instruments or health utility instruments, that can be used in the evaluation of cochlear implantation. As part of the in Chapter 1.4 mentioned RCT, health utility was measured with the following validated instruments: the EuroQol five-dimensional questionnaire (EQ-5D), the Health Utilities Index mark 3 (HUI3), and a VAS for general health. The EQ-5D, HUI3 and VAS general utility scores differed statistically significantly and the intraclass correlation coefficients showed poor to no agreement between these instruments. A gain in health utility after cochlear implantation was found with the HUI3 and VAS general only. Based on our results, the HUI3 detects the most health utility gain after cochlear implantation. Therefore, we recommend using the HUI3 health utility instrument in future studies on cochlear implantation.

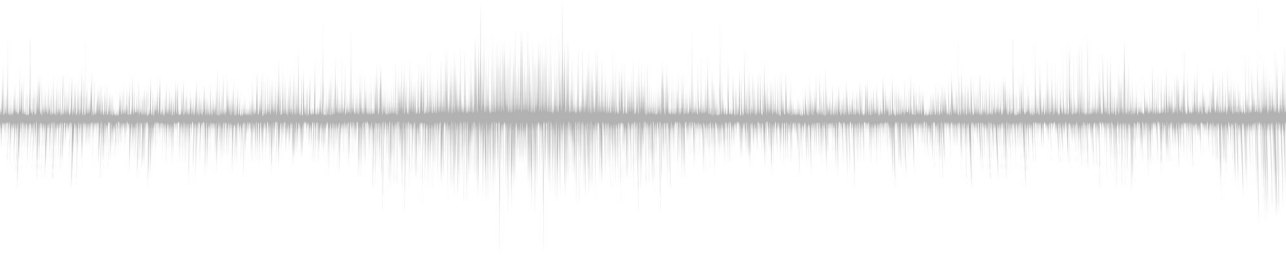
In **Chapter 2.2** we evaluated the correlation between subjective and objective hearing instruments after UCI and BiCI. As part of our previously mentioned RCT, multiple subjective and objective hearing outcomes were measured. We studied the correlation between objectively measured speech perception in noise and localization skills on the one hand and related domains of the Speech, Spatial and Qualities of Hearing Scale (SSQ) and Nijmegen Cochlear Implant Questionnaire (NCIQ) on the other hand. The use of one-year of follow-up data enabled us to also compare these correlations between bilateral and unilateral CI patients, as the patients in the seqBiCI group were only having one CI at this moment. Significant weak to moderate correlations were found between different subjective

and objective speech perception in noise tests. The highest correlation was found between the subjective and objective localization tests, but also this correlation was only of moderate strength. The correlations did not differ significantly between unilateral and bilateral CI patients. This chapter underlines the importance and necessity of questionnaires in the evaluation of cochlear implantation, as current objective tests do not fully reflect subjective everyday listening situations.

In **Chapter 2.3** we evaluated the 4 years subjective outcomes longitudinally after simBiCI compared with UCI/seqBiCI as part of the previously mentioned RCT. All QoL, QoH and tinnitus outcomes were analyzed longitudinally using a linear or logistic regression analysis with an autoregressive residual covariance matrix (generalized estimating equations type). The most evident differences over time between the UCI/seqBiCI group and the simBiCI group were seen on the QoH outcomes, especially the SSQ. Only in one out of four QoL questionnaires (the Time Trade-off (TTO)), a significantly lower utility score was seen in the UCI/seqBiCI group group compared to the simBiCI group over time. These differences between groups, were most likely caused by the lower performance in the UCI/seqBiCI group in their unilateral situation, as all of the outcomes in this group increased after receiving the second CI. No significant differences were seen between the prevalence of tinnitus in both groups over time.

In the **General discussion** we summarized the results of this thesis and discussed difficulties and limitations of the current thesis and the literature in general. This thesis underlines the importance of subjective outcomes in the evaluation of cochlear implantation, which is in accordance with the trend in today's healthcare. In future, subjective outcomes as tinnitus, QoL and QoH should therefore be part of the standard clinical evaluation after cochlear implantation. However, before these instruments can be implemented in standard clinical evaluations, consensus is needed on which instruments are best to use in this patient group.

Nederlandse samenvatting



In dit proefschrift worden meerdere subjectieve (zelf gerapporteerde) meetinstrumenten en uitkomsten geëvalueerd, die gebruikt kunnen worden in de evaluatie van cochleaire implantatie. In de **Algemene introductie** wordt een overzicht gegeven van de fysiologie van het normale gehoor en de pathofysiologie van gehoorverlies. Unilaterale cochleaire implantatie (UCI) is vaak de gekozen behandelingsmodaliteit voor bilateraal ernstig sensorineuraal gehoorverlies in volwassenen. Ontwikkelingen in de indicatiecriteria voor cochleaire implantatie, zoals bilaterale cochleaire implantatie (BiCI) worden besproken. Een vaak voorkomende klacht van patiënten met ernstig sensorineuraal gehoorverlies is (subjectieve) tinnitus. Na cochleaire implantatie wordt er in het merendeel van de patiënten een afname van tinnitus klachten gezien. Tinnitus is een subjectieve klacht en wordt daarom geëvalueerd met behulp van subjectieve meetinstrumenten (vragenlijsten). Andere subjectieve meetinstrumenten die gebruikt kunnen worden bij de evaluatie van cochleaire implantatie zijn 'kwaliteit van leven' en 'kwaliteit van horen' vragenlijsten. In de huidige gezondheidszorg bestaat er een toenemende interesse in het gebruik van subjectieve meetinstrumenten.

In het eerste gedeelte van dit proefschrift, wordt het effect van cochleaire implantatie op tinnitus verder onderzocht met behulp van meerdere studieontwerpen en in verschillende patiëntengroepen. Het tweede gedeelte richt zich grotendeels op andere subjectieve instrumenten en uitkomsten in de evaluatie van cochleaire implantatie met het doel om aanbevelingen te kunnen doen voor toekomstig onderzoek en klinische zorg.

In **Hoofdstuk 1.1** hebben we de beschikbare literatuur over het effect van cochleaire implantatie op tinnitus in volwassen patiënten met bilateraal ernstig sensorineuraal gehoorverlies, op een systematische manier beoordeeld en samengevat. Er werden tien cohortstudies geïncludeerd die allen rapporteerden over UCI. Door de grote heterogeniteit tussen de studies en de afwezigheid van lage 'risico op bias' studies, was poolen van de studies in een meta-analyse niet gewenst en waren we genoodzaakt een beschrijvende analyse uit te voeren. Op groepsniveau werd in het merendeel van de studies vermindering van tinnitus gezien na UCI. Op patiëntniveau werden verergering van tinnitus of nieuw geïnduceerde tinnitus echter ook beschreven bij een minderheid van de patiënten.

In **Hoofdstuk 1.2** beschrijven we de 10-jaars resultaten van de afdeling Keel-, Neus-, Oorheelkunde van het Universitair Medisch Centrum Utrecht (UMCU) met betrekking tot het effect van UCI op tinnitus in volwassen patiënten met bilateraal ernstig sensorineuraal gehoorverlies. De prevalentie van preoperatieve tinnitus was 64%. In het merendeel van de patiënten werd een positief effect gezien van UCI op tinnitusklachten (complete verdwijning of afname in vergelijking met de preoperatieve situatie). Er waren echter ook patiënten die een verergering van tinnitusklachten ervoeren (10%). In 14% van de patiënten die voor de operatie geen last hadden van tinnitus, was er sprake van tinnitus inductie na de operatie.

Tevens hebben we in deze studie het effect van het aan en uit zetten van de processor van het cochleair implantaat (CI) op reeds aanwezige tinnitusklachten onderzocht. Aanzetten van de CI processor leidde tot significante dalingen van de mediane Visual Analogue Scale (VAS) scores voor zowel de luidheid, verveling als de hoogte van de tinnitus.

Voor de studie in **Hoofdstuk 1.3** hebben we gedeeltelijk dezelfde database gebruikt als in hoofdstuk 1.2, om een voorspelmodel voor tinnitusherstel na UCI te ontwikkelen en intern te valideren. De uitkomst van het voorspelmodel was compleet herstel van tinnitus en alleen de data van de patiënten die preoperatief last hadden van tinnitus werden hiervoor gebruikt (n=87). Aangezien er geen eerdere studies over dit onderwerp bestaan, hebben we een breed scala aan klinisch relevante mogelijke voorspellers onderzocht. Drie voorspellers voor tinnitus herstel werden geïdentificeerd: een lagere preoperatieve spraakverstaan score, unilaterale lokalisatie van tinnitus en een groter verlies van het restgehoor na implantatie gemeten op 250 Hz. Na interne validatie, was de prestatie van het voorspelmodel redelijk. Met name voor een eerste retrospectieve studie, is de prestatie veelbelovend. Voordat we dit model in de dagelijkse klinische praktijk kunnen toepassen, is het echter noodzakelijk om een grotere prospectieve studie uit te voeren.

In **Hoofdstuk 1.4** hebben we het effect van BiCI op tinnitus in volwassen patiënten met bilateraal ernstig sensorineuraal gehoorverlies onderzocht. Dit was een beschrijvende studie die voortkwam uit een gerandomiseerde multicenter studie naar de voordelen van simultaan BiCI (simBiCI) ten opzichte van sequentieel BiCI (seqBiCI) met een inter-implant interval van 2 jaar. Vóór de implantatie en ieder jaar ná de implantatie werden tinnitusklachten geëvalueerd met behulp van twee vragenlijsten: Tinnitus Handicap Inventory (THI) en Tinnitus Questionnaire (TQ). De prevalentie van preoperatieve tinnitusklachten was relatief laag in vergelijking met de literatuur: 42%. Op groepsniveau werd een positief effect gezien van BiCI op preoperatieve tinnitus scores. Op patiëntniveau werd echter ook (tijdelijke of permanente) inductie van tinnitus beschreven in sommige patiënten die vóór de operatie geen last hadden van tinnitus, waarvan de prevalentie hoger was in de simBiCI groep. Ondanks dat de pre- en postoperatieve tinnitus scores hoger waren in de simBiCI groep, was de grootte van het effect gelijk voor simBiCI en seqBiCI.

In **Hoofdstuk 2.1** hebben we de overeenkomst tussen verschillende kwaliteit van leven instrumenten of 'health utility' instrumenten onderzocht die gebruikt kunnen worden in de evaluatie van cochleaire implantatie. Als onderdeel van de gerandomiseerde studie, eerder beschreven in hoofdstuk 1.4, werd 'health utility' gemeten met behulp van de volgende gevalideerde vragenlijsten: de EuroQol five-dimensional questionnaire (EQ-5D), de Health Utilities Index mark 3 (HUI3), en een VAS voor algemene gezondheid. De utiliteit scores van de EQ-5D, HUI3 en VAS voor algemene gezondheid verschilden significant van elkaar. De intraclass correlatiecoëfficiënten lieten slechte tot geen overeenkomst zien tussen de verschillende instrumenten. Alleen met de HUI3 en VAS werd een toegenomen utiliteit gezien na implantatie en de grootste gezondheidswinst werd gevonden met de HUI3. Om die reden bevelen we de HUI3 aan om te gebruiken in toekomstige CI studies.

In **Hoofdstuk 2.2** hebben we de correlatie tussen subjectieve en objectieve gehoorinstrumenten na UCI en BiCI onderzocht. Als onderdeel van de eerdergenoemde gerandomiseerde studie, werden meerdere subjectieve en objectieve gehooruitkomsten

gemeten. We bestudeerden de correlatie tussen objectief gemeten spraakverstaan in ruis en lokalisatie vaardigheden aan de ene kant en de Speech, Spatial and Qualities of Hearing Scale (SSQ) en Nijmegen Cochlear Implant Questionnaire (NCIQ) aan de andere kant. Het gebruik van 1-jaars follow-up data, stelde ons in staat om deze correlaties te vergelijken in bilaterale en unilaterale CI patiënten, aangezien de patiënten in de seqBiCI groep op dit moment slechts 1 CI hadden. Significante, maar zwak tot matige correlaties werden gevonden tussen de verschillende subjectieve en objectieve spraakverstaan in ruis testen. De hoogste correlatie werd gevonden tussen de subjectieve en objectieve lokalisatie testen, maar ook de sterkte van deze correlatie was slechts matig. Tussen uni- en bilaterale CI patiënten werden geen verschillen in correlaties gevonden. Dit hoofdstuk onderstreept het belang en de noodzaak van het gebruiken van vragenlijsten in de evaluatie van cochleaire implantatie, aangezien de huidige objectieve testen de dagelijkse luistersituaties van de patiënt niet volledig weerspiegelen.

In **Hoofdstuk 2.3** hebben we de 4-jaars subjectieve uitkomsten longitudinaal vergeleken tussen simBiCI en seqBiCI als onderdeel van de eerdergenoemde gerandomiseerde studie. Alle kwaliteit van leven, kwaliteit van horen en tinnitusuitkomsten werden longitudinaal geanalyseerd met behulp van lineaire of logistische regressie analyse met een autoregressive residual covariance matrix (generalized estimating equations type). Het meest evidente verschil tussen simBiCI en UCI/seqBiCI groep gemiddeld over tijd, werd gezien op de kwaliteit van horen uitkomsten, met name de SSQ. Slechts op één van de vier kwaliteit van leven vragenlijsten (de Time Trade-off (TTO)), werd gemiddeld over tijd een significant lagere utiliteit gezien in de UCI/seqBiCI groep. Deze verschillen tussen de groepen kunnen hoogstwaarschijnlijk verklaard worden door de lagere prestatie van de UCI/seqBiCI groep in hun unilaterale situatie, aangezien al deze uitkomsten verbeterden na het krijgen van het tweede CI. Met betrekking tot de prevalentie van tinnitus werden er gemiddeld over tijd geen verschillen gezien tussen de groepen.

In de **Algemene discussie** vatten we de resultaten van dit proefschrift samen en bediscussiëren we moeilijkheden en beperkingen van het huidige proefschrift en de literatuur in het algemeen. Dit proefschrift onderstreept het belang van subjectieve uitkomsten in de evaluatie van cochleaire implantatie. Dit laatste is ook in lijn met de trend in de huidige gezondheidszorg. In de toekomst, zullen subjectieve uitkomsten zoals tinnitus, kwaliteit van leven en kwaliteit van horen daarom onderdeel moeten worden van de standaard klinische evaluaties na cochleaire implantatie. Voordat deze instrumenten geïmplementeerd kunnen worden in de standaardzorg, is echter consensus nodig over welke instrumenten het best gebruikt kunnen worden in deze patiëntengroep.

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**These authors contributed equally to this publication and therefore share first authorship*

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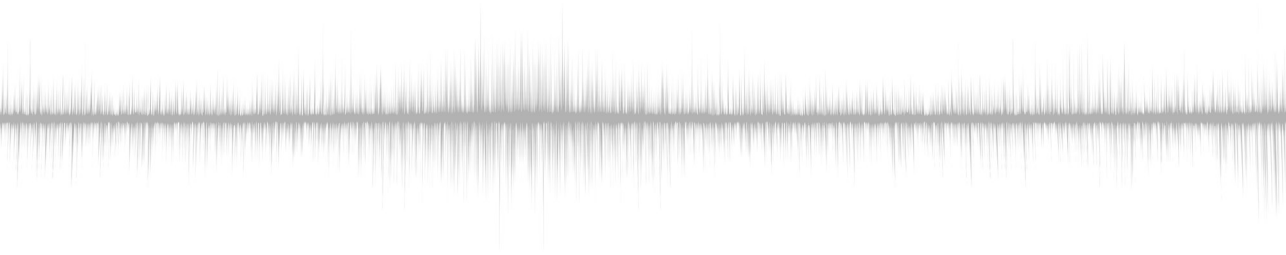
Curriculum vitae



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She started her PhD at the same department in 2015, that led to this thesis. She was supervised by prof. dr. R.J. Stokroos, prof. dr. W. Grolman and dr. I. Stegeman. During her PhD she studied Epidemiology at the department of Epidemiology and Biostatistics VU Medical Center, which she completed in 2017. In March 2018, after completing her thesis, she started working as an associate at LOGEX, a company that provides insights into the performance of health care institutions based on big data analytics.