TINNITUS HETERO-GENEITY

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Tinnitus Heterogeneity

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The printing of this thesis was financially supported by: Allergy Therapeutics, ChipSoft, Daleco Pharma, DOS Medical, EmiD, Makker Hoortoestellen, MediTop, Specsavers, Stichting ORLU.

The research was partly funded by an unrestricted research grant from Cochlear Ltd. to the Department of Otorhinolaryngology and Head & Neck Surgery.

ISBN: 978-94-6419-863-8

Cover design: Ilse Modder | www.ilsemodder.nl
Lay-out: Ilse Modder | www.ilsemodder.nl
Printing: Gildeprint Drukkerijen | www.gildeprint.nl

Tinnitus Heterogeneity

Tinnitus Heterogeniteit
(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de
Universiteit Utrecht
op gezag van de
rector magnificus, prof.dr. H.R.B.M. Kummeling,
ingevolge het besluit van het college voor promoties
in het openbaar te verdedigen op

donderdag 9 november 2023 des middags te 4.15 uur

door

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geboren op 5 november 1992
te 's-Gravenhage

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General Introduction and Thesis Outline

General Introduction

Preface

Tinnitus is a heterogeneous disease. (1) Among other reasons, this heterogeneity complicates tinnitus research and consequently the clinical care of tinnitus patients. In this thesis we aim to explore this heterogeneity. To understand the relevance of this thesis, this first chapter introduces the concept of tinnitus, as well as it's epidemiology, theories on pathophysiology and psychological models, and treatment options.

Historic perspective

Many historic figures are suspected to have experienced tinnitus. Ludwig Beethoven is one of them. He is known to have complained to his physician about hearing loss and a buzzing in the ears. (2) Tinnitus has also been described by different civilizations. For example, papyrus recordings have shown that the ancient Egyptians have treated ''bewitched ears''. (2,3) Also, in historic eastern India people believed tinnitus was caused by little animals captured in their ear, which was treated by fumigation. Lastly in the renaissance period, holes have been drilled in ears, to let the "captured wind" escape. In short, tinnitus has been an object of research and a health care problem since ancient history. (3)

Tinnitus heterogeneity

Tinnitus originates from the Latin word 'tinnire', which can be translated to 'to ring'. (4) However, tinnitus encompasses any type of sound from ringing, to zooming, to buzzing. Sometimes people describe to hear an orchestra playing in their ear. (5) Tinnitus is often described as the hearing of a sound in absence of an external stimulus. (4) We can grossly divide tinnitus into subjective and objective tinnitus. In subjective tinnitus the sound cannot be objectified by others. It is a phantom sound, or the perception of a meaningless sound. In contrary, objective tinnitus can be objectified. Objective tinnitus originates from an acoustic source within the body. (4) In this thesis subjective tinnitus will be referred to as tinnitus.

There are numerous variations when it comes to tinnitus. Differences can for example be found in location, number of sounds and loudness of the sound(s). There can be temporal differences (acute versus chronic) and variations in the nature of the sound. Also, many comorbidities are associated with tinnitus. Hearing loss, temporomandibular joint disorders, and higher age are common risk factors. Comorbidities such as anxiety, depression, sleep- and concentration problems have often been described. (1)

All these factors can be of influence on the psychological reaction to the tinnitus perception, or the associated suffering. This associated suffering can also be referred

to as tinnitus distress, severity or burden, but the underlying idea describes the impact of the tinnitus on a person's daily life. While some might not experience any disease burden, others might visit several health care professionals, while for some the burden is so high that they might consider suicide or euthanasia. Quality of life is severely reduced in 1-2% of the patients with tinnitus. (6,7) Hopelessness, negative thinking, exhaustion and a feeling of being overwhelmed are also often reported. (5)

Tinnitus prevalence

A distinction between the experience of tinnitus and its associated suffering is of importance for targeting treatment as well as research activities. Numbers of tinnitus prevalence vary between 5.1 and 42.7%, while they differ between 3% and 30.9% for bothersome tinnitus. (8) The annual incidence of tinnitus is estimated at 1%. (9) As calculated by Jarach et al., this results into 740 million people to experience tinnitus globally and more than 120 million people worldwide to have a severe form of tinnitus. (9) Prevalence numbers increase to 23% for people who are 65 years or older and experience hearing loss. Moreover, in those with severe hearing loss, up to 67% experience tinnitus. (9–11)

Tinnitus can be compared to diseases which are known to be the leading causes of years lived with a disability in terms of prevalence numbers. These are hearing loss, migraine, lower back pain and neck pain. (12) It is therefore no surprise that tinnitus related health care expenses are serious. The expense of treating tinnitus alone is estimated to be 1.9 billion euros in the Netherlands, 750 million pounds per year in Great Britain, and 660 dollars per patient per year in the United States. (13–15)

Tinnitus definition

One of the reasons the prevalence numbers vary so greatly, is because of a lack of a uniform, and widely accepted definition. (12) This definition can include a combination of different time components like frequency and duration. Different results will rise from a question that inquires after the experience of tinnitus for an indefinite amount of time in the last 12 months, or the experience for tinnitus for at least three hours a day in the last year. In a recent paper the minimum time criterion for tinnitus disorder was set at a duration of at least 5 minutes a day on the majority of days. (16)

Another temporal issue with tinnitus is it chronicity. When does tinnitus change from acute to chronic? One could argue that acute tinnitus can be seen as a secondary symptom to a primary problem, such as noise induced hearing loss. While chronic tinnitus should be seen as a primary disorder. Different researchers typically adhere to a time-period between three to six months. Based on the similarities of tinnitus to chronic pain, some propose the cut-off to be at three months, as is done for chronic pain. (16)

Tinnitus assessment

Due to the subjective nature of tinnitus, measuring a patient's tinnitus has its difficulties. The heterogeneity in tinnitus assessment complicates tinnitus research due to an inability to compare study outcomes. We cannot objectify non-pulsatile tinnitus. However, we can approach a persons experienced tinnitus with matching tests. The patient is asked to listen to different sounds, with varying pitch and loudness, and asked to compare them to their perceived sound. (17)

Another way to assess tinnitus is with questionnaires. Among others one can assess tinnitus characteristics and tinnitus' related suffering. The Tinnitus Sample Case History Questionnaire (TSCHQ) was created to uniformly assess tinnitus characteristics in tinnitus patients. (18) The TSCHQ was updated in 2019. (18,19) In the 2019 European School for Interdisciplinary Tinnitus Research Screening Questionnaire (ESIT-SQ), a general section was added that could be answered by those without tinnitus as-well. (19)

Associated suffering, or the impact of tinnitus on daily life can be assessed with one-item-questions (Do you suffer from your tinnitus?) to multi-item questionnaires. These multi-item questionnaires include the Tinnitus Functional Index (TFI), the Tinnitus Questionnaire (TQ) and the Tinnitus Handicap Inventory (THI). (20–23) Each questionnaire consists of several questions (the TFI has 25 questions), that focus on different domains that can be affected by having tinnitus (24) These include the emotional and auditory components. Each multi-item questionnaire will eventually form a score that indicates a level of suffering in the patient. Because different questionnaires include different questions that focus on different domains, one cannot compare scores directly. (24)

Another issue with the assessment of tinnitus, is the question of what to assess? (25,26) In clinical trials many different outcome measures are described. This can be explained by the debate in what outcome the most important is for patients, researchers and clinicians. (26) For example, how does one assess treatment effect? Is it diminishing the loudness of the tinnitus, the impact the tinnitus has on daily life? Or ameliorating issues with concentration? Or even complete muffling of the sound(s)?

Treatment

There are many different treatment options for tinnitus. (27) They can grossly be divided in three major domains: sound therapies, psychological therapies and drug therapy. (26) However, only one therapy, cognitive behavioral therapy (CBT), has been proven effective in reducing tinnitus distress. (28)

The lack of evidence-based treatments can partly be explained by methodological difficulties concerning tinnitus research. (12) The heterogeneity of patients, and thus participants in studies, might be responsible for the large variability in outcomes of clinical trials.

Currently, the recommend care for tinnitus has a stepped-care approach. With the stepped care approach, the intensity of treatment is increased each step. The stepped-care method of tinnitus starts with a consult at the general practitioner, if they notice a bothersome tinnitus, patients are referred to either an otorhinolaryngologist or an audiologist. Apart from physical assessment, patients are provided with education on tinnitus and hearing loss. If necessary, treatment can be intensified to psycho-education. As a final step CBT can be offered. (27)

Pathophysiology

The pathophysiological mechanisms of tinnitus remain unclear. Pathophysiological models can help understand tinnitus, tinnitus heterogeneity and help the research for effective therapies. Currently, there are several hypotheses.

The first hypothesis states that the sensory deprivation of hearing loss causes an increased activity in the central auditory system in response to a lack of peripheral input. (6) A second hypothesis is neural synchrony. The tonotopy in the auditory cortex is hindered by hearing loss. This might cause certain neurons to adapt to the tuning property of neighboring neurons. (4) Still, these does not explain the percept completely. For example, hearing loss is one of tinnitus main risk factors. However, not all people with tinnitus suffer from hearing loss. Also, tinnitus can still exist when the cochlea is surpassed and the auditory nerve is cut. (29) This suggests that not only the periphery is involved in tinnitus, but that central mechanisms are part of the problem. (4,6) MRI studies show that not only auditory areas are involved, but they also find increased neuronal activity in the limbic system and the cerebellum. It is therefore believed that tinnitus does not originate from one place, but that multiple systems (such as memory, emotion, attentions and stress) are also involved. (6,30)

Psychological models

Apart from pathophysiological models to understand the concept of tinnitus, psychological models have been created in order to understand the impact of tinnitus.

One of the psychological models is the neurophysiologic model by Jastreboff. (31–33) In the model the authors argue that the auditory system is not the primary system of interest in treatment of clinically relevant tinnitus. The first step in developing clinically relevant tinnitus starts in the generation of neuronal activity (e.g., in

the cochlea or auditory nerve). This is detected in subcortical auditory centers and later precepted and evaluated in cortical areas. Next, the limbic systems and automatic nervous system are sustainedly activated. The limbic systems consists of the hippocampus, amygdala and hypothalamus and is responsible for emotional associations. (31–33)

In the habitual model, the authors argue that high arousal levels or stress decrease the brain's ability to filter and ignore tinnitus. They described a reciprocal feedback loop where the focus on tinnitus might increase arousal and further diminish habituation. (34)

A more recent model is the cognitive behavioral model of tinnitus. (35) It was developed in 2014. The model argues that after the tinnitus has been detected, there is a certain selective attention and monitoring, which leads to a distorted perception and negative automatic thoughts. These in turn cause arousal and distress and a conscious process leading to more selective attention and monitoring. Beliefs and safety behaviour are thought to influence the automatic negative thoughts. (35)

An alternative cognitive behavioral model for tinnitus is the fear avoidance model. (36) The model argues that the tinnitus percept is misinterpreted as harmful. With a persistence of the sound, fear responses are created, which result in heightened awareness, avoidance and disability. The model also explains that when a person has a positive or neutral evaluation of the tinnitus, there is no or a low fear response. Leading to less distress. In conclusion the model argues that acceptance of the tinnitus labels the sound as benign, and no fear response is created. If a person avoids the percept the tinnitus can become distressing. (36)

Valorization and aim of this thesis

In summary, tinnitus heterogeneity can be described in several domains; the perception of the tinnitus, risk factors and related comorbidities, and tinnitus distress. But also, in tinnitus definition and the assessment of tinnitus. Tinnitus research has for a long time been primarily focused on clinical trials assessing the effect of treatment options on tinnitus related outcomes (e.g., distress, loudness, acceptance), as well as research on understanding tinnitus with different pathophysiological models. (37) Nonetheless, a cure for tinnitus remains to be found. One of the explanations of the absence of a cure for tinnitus, is limited interest and research funding in comparison to other chronic neurological or neuropsychiatric disorders. For example, compared to tinnitus there were 27 times more trials registered for depression therapies in 2017. Also, scientific output on depression was 30.5 times larger than for tinnitus in 2017. (12)

The heterogeneity of the condition presents a methodological challenge for developing an effective tinnitus treatment. It limits the effectiveness of clinical trials, which emphasizes the importance of addressing it. The concept of heterogeneity in tinnitus research, and in this thesis, is broad. First, as described before there is a large heterogeneity in tinnitus definition. Second, heterogeneity plays a role in the outcome measures of clinical trials of tinnitus therapies. Thirdly, clinical trials on tinnitus therapies describe a large range in outcome. This indicates a non-heterogeneous study population. In recent years different attempts have been taken to subtype tinnitus patients into certain sub-groups or profile patients based on symptom distribution on a continuous scale. (38–43) However, none of these efforts have led to a clear distinction between these subtypes or profiles.

In short, tinnitus heterogeneity is a concept that can be explained in different manners. Nonetheless, within all facets it is clear that the progress of tinnitus research in finding a cure for tinnitus is hindered by heterogeneity. In this thesis we will therefore focus on exploring tinnitus heterogeneity in different aspects.

Thesis Outline

Different aspects of tinnitus heterogeneity will be addressed and explored in this thesis. In **chapter 2** we explore the issue of heterogeneity in tinnitus outcome measures. In this chapter we describe a study in which we assessed what tinnitus patients consider the most important outcome measures in tinnitus therapy by means of a Discrete Choice Experiment (DCE). In **chapter 3** the question of tinnitus prevalence and the difficulties with tinnitus definition are addressed. We explore the differences in prevalence with different tinnitus definitions and cut-offs. In **chapter 4** we describe the differences in people with tinnitus that seek or have sought help for their tinnitus compared to people with tinnitus that do not. In **chapter 5** we elaborate on the differences between these two groups. In this chapter we focus on the difference in primary health care usage of people with tinnitus and people without tinnitus. In the final three chapters we focus on exploring heterogeneity with prediction. In **chapter 6** we analyze associations between various variables (demographic, tinnitus specific, audiological, general- and mental health) with the impact of on daily life. In **chapter 7** we describe a systematic review on tinnitus prediction models on the experience of tinnitus and the impact of tinnitus in daily life. This chapter functions as an introduction for **chapter 8.** In the penultimate chapter we describe the development and internal validation of a prediction model on tinnitus experience. Finally in **chapter 9** we discuss and interpret the results of the previous chapters. We also provide perspectives for future research.

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CHAPTER 2

What Tinnitus Therapy Outcome Measures are important for Patients? – A Discrete Choice Experiment

Frontiers in Neurology. 2021 May 25;12:668880

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Abstract

Introduction
The therapeutic rationale varies among tinnitus therapies. A recent study identified which outcome measures should be used for different types of interventions. What patients consider the most important outcome measure in tinnitus therapy is unclear.

Objectives
To study the preference of the tinnitus patient for different outcome measures in tinnitus therapy.

Methods
A discrete choice experiment was conducted. Participants were provided with two alternatives per choice set (nine choice sets total). Each choice-set consisted of four attributes (tinnitus loudness, tinnitus acceptance, quality of sleep and concentration). With a difference in one of three levels (increased, similar or decreased after treatment) between the alternatives. Results were analyzed with a mixed logit model. Preference heterogeneity was explored with covariates, correlating attributes and a latent class analysis.

Results
One hundred and twenty-seven participants took part. In the mixed logit models we found that the choice for a tinnitus therapy was significantly affected by all levels of the outcomes, except for a similar level in concentration and tinnitus acceptance. Tinnitus loudness was considered the most important outcome measure relative to the other attributes. Preference heterogeneity was not explained by correlating attributes. The latent class analysis identified two classes. The first class was similar to the mixed logit analysis, except for a non-significance of similar quality of sleep and tinnitus acceptance. The second class showed a statistical significant preference only for increased tinnitus acceptance and similar quality of sleep.

Conclusion
Based on this study, tinnitus patients consider loudness the most important outcome measure. However, there is a variance in preference as indicated by the latent class analysis. This study underlines the importance of research into tinnitus heterogeneity. Next, this study highlights the need for research into tinnitus therapies that focus on diminishing tinnitus loudness.

Introduction

Tinnitus is an experience of sound in the absence of an external stimulus.(1) Because of variations in the definitions of tinnitus and differences in the studied population, the reported prevalence numbers vary between 5.1 and 42.7%(2). A cure for tinnitus does not exist at this moment. Treatment is therefore focused on symptom reduction. The European tinnitus guideline recommends Cognitive Behavioral Therapy (CBT) or sound therapies. However, many more treatment options are available, such as, but not limited to, pharmacological therapy, Transcranial Magnetic Stimulation (TMS) and complementary therapies.(1,3)

Tinnitus is a heterogeneous condition due to differences in experienced distress, localization and nature of the sound. Also, many different comorbidities are associated with tinnitus, such as anxiety, depression, and sleep- or concentration problems. (1,4,5) Tinnitus might also have a negative influence on quality of life. Since many different domains can be affected, measuring the impact of tinnitus on daily life and outcomes of treatments focused at these domains is complicated.(6)

In 2018 a Delphi study was conducted to explore the core outcome domains for clinical trials in tinnitus interventions.(6,7) After setting definitions of the different potential core outcome measures, agreement was reached among five different types of stakeholders (patients, healthcare professionals, researchers, commercial representatives, funders) to identify nine different outcome measures as most important per different intervention groups.(6,8) For sound therapies tinnitus intrusiveness, ability to ignore, concentration, quality of sleep and sense of control were selected as the core outcome measurements. For psychological based interventions these were intrusiveness, tinnitus acceptance, mood, negative thoughts and beliefs, and sense of control. Finally, for pharmacological based interventions the most important outcome domains were intrusiveness and tinnitus loudness.(7) This study highlights the differences in therapeutic approach necessitating different outcomes to be measured. However, this does not tell us what outcome measure is of the most importance for the patient when they seek treatment for tinnitus, and consequently what outcome measure carries the most importance for them?

A discrete choice experiment (DCE) is a quantitative method to elicit preferences from participants. In a DCE, participants are presented with a series of scenarios. Participants are forced to choose between a set of alternatives. This enables us to analyze the most important outcomes for patients who are in need of tinnitus therapy. DCE's are an increasingly popular experiment to asses patient preference in health care.(9) For example, it has been previously used to explore preference in colorectal-

cancer screening, breast cancer treatment and basal cell carcinoma treatments.(10–12) In this study we aim to analyze the preference of patients for outcome measures in tinnitus therapy with a DCE.

Methods

In a discrete choice experiment (DCE) participants are asked to choose between two or more alternatives within a choice set. Each choice set consists of a set of attributes with different levels. The attributes remain similar while the levels vary over the number of choice sets. The attributes and their corresponding levels are a key element of a DCE.

In this study, tinnitus participants were required to choose between two (hypothetical) tinnitus therapies (alternatives) (treatment A and treatment B). The tinnitus participants were presented with nine different choice sets, each consisted of four attributes with three corresponding levels. An example of a choice-set as used in this DCE is presented in table 1.

The development of this DCE consisted of different stages in chronological order: a focus group to select the most suitable outcomes for inclusion in this DCE, the DCE design, data collection and data analysis.

Table 1 Example of a Choice Set

The attributes (tinnitus loudness, concentration, quality of sleep and acceptation) can have the following levels:
- Increased after treatment compared to before treatment (Increase)
- Similar relative to before the start of treatment (Similar)
- Decreased relative to before the start of treatment (Decrease)

If both treatments were offered to you, which one would you choose?

	Option A	Option B
Tinnitus Loudness	Decrease	Similar
Concentration	Similar	Increase
Quality of sleep	Similar	Increase
Tinnitus acceptance	Increase	Similar
	□ Option A	□ Option B

Defining attributes and levels

Focus groups

For the first step two focus groups with nine participants were organized in July 2019. The focus groups were guided by an interviewer (MR). The aim of the focus group was to gain information on the most important attributes and corresponding levels in order to create a DCE. Participants were instructed to discuss the nine outcomes of the previously conducted Delphi study on concept. The nine outcome measures were tinnitus intrusiveness, ability to ignore, concentration, quality of sleep, sense of

control, tinnitus acceptance, mood, negative thoughts and beliefs, tinnitus loudness as defined by the COMIT'ID initiative (supplementary file).(7,8) The participants of the focus groups had to discuss which of these outcome measures were deemed most suitable to be included in the choice experiment of our study.(7) Therefore, these items were introduced verbally to the focus groups, without providing the definitions. They were also explained the concept of the levels, and asked to discuss which were the most suitable. In order to be sure that every participant was actively included in the discussion, we asked an independent researcher (LM) to observe the nonverbal communication of the participants. The observations of non-verbal communication by the independent researcher did not result in extra information about the outcomes of the focus groups. The participants were also asked to rate the nine outcome measures on a 5-point Likert-scale (1 totally not important to 5 very important) and list their five most important ones.

The outcomes of the focus group were discussed in the research group (AL, IS and MR). The results of the focus group were discussed and interpreted to set the final attributes and levels. To end up with a feasible DCE four attributes with different levels were included in the DCE. The five most popular attributes of the focus groups were the attributes tinnitus loudness, concentration, quality of sleep, tinnitus acceptance and tinnitus intrusiveness. After careful deliberation, we decided against including tinnitus intrusiveness, since there is no direct translation of the word in Dutch. Next, the construct of the word tinnitus intrusiveness is difficult and debatable.(7) Also, in the focus group we noticed that participants had different understandings of the word intrusiveness. This resulted in the final set of attributes; tinnitus loudness, concentration, quality of sleep and tinnitus acceptance.. The corresponding levels were similar for all attributes: increased after treatment compared to before treatment, similar relative to before the start of treatment, decreased relative to before the start of treatment. Both the attributes and levels were not formally defined in our study. Participants were not provided with a formal definition of the concept. Therefore participants relied upon their own interpretation.

DCE design

In the next stage, the DCE was created. With four attributes including three levels each, 81 (3^4) different choice sets can theoretically be created. Since it is not feasible to ask participants to fill out 81 different choice sets, we developed a fractional factorial Bayesian efficient design in Ngene version 1.2.1. 2018. Bayesian efficient designs maximize the information that can be obtained from the choice data and the accuracy of estimate choice model parameters. (13,14)

Thirty-six choice sets, blocked into four versions with each nine different choice sets

were created. Participants were randomized in one of four blocks.

An efficient design functions optimally when utility weights or priors of attributes are added to the design. We therefore first conducted a pilot study (n = 30) to deduct priors. These priors were subsequently used to update the final design.

Questionnaire

Based on above described methodology a questionnaire was developed for participants. The questionnaire consisted of an instruction for the choice-experiment, the choice-sets of the choice experiment, as well as additional questions. The additional questions were used for the baseline characteristics and covariate analysis. They included three questions regarding health literacy, as this could influence outcome of the DCE. Besides this, questions regarding tinnitus characteristics and the impact of tinnitus on daily life (distress) were asked. The questions regarding tinnitus characteristics were based on the tinnitus sample case history questionnaire (TSCHQ) and the ESIT questionnaire. (15)

The impact of tinnitus on daily life was measured with the Tinnitus Functional Index (TFI).(16) The TFI is a 25-item questionnaire using 11 point Likert scale questions. The outcome is a score from 0 (not a problem) – 100 (a very big problem). The questionnaire consists of eight subscales; intrusiveness, sense of control, cognition, sleep, hearing, relaxation, quality of life and emotions. In this study we used the validated 2014 Dutch translation of the TFI, with a high reliability as expressed in a Cronbach's alpha of 0.91. (17)

Recruitment, logistics and ethics

For all steps of the study participants were eligible if they were 18 years or older and sought help or planned to seek help for their tinnitus. For the focus groups participants were recruited from the tinnitus outpatient clinic of the otorhinolaryngology department of the UMC Utrecht by the consulted otologist, from patients visiting a regional audiological clinic and by an announcement on the website of the Dutch tinnitus patients association (*Stichting Hoormij*). These people received information about the study and were subsequently invited to one of two focus groups that took place in the UMC Utrecht. Informed consent was given to use the data collected from the focus groups.

For the pilot DCE and final DCE participants were recruited in the October 2019 – march 2020, through an advertisement on the either the website of the Dutch tinnitus patients association *(Stichting Hoormij.nl*) or at the tinnitus outpatient clinic of the UMC Utrecht. The advertisement included a brief summary of the research project.

People who applied for study participation were informed about the study procedures by postal/digital mail. When informed consent was obtained and people fulfilled inclusion criteria, participants were included in the study. The questionnaires, including the DCE, were electronically sent to the participants digitally with Castor EDC(18). For the pilot study data was collected in November / December 2019. The final experiment was conducted in February/March 2020. If participants did not respond within one to two weeks they were sent a reminder to fill out the questionnaire. The Medical Research Ethics Committee (MREC) of the UMC Utrecht confirmed that the Medical Research Involving Human Subjects Act (WMO) does not apply to this research and an official approval of this study is therefore not required under the WMO (local number 19/690).

Sample size

We estimated a sample size based on the rule of thumb as proposed by Johnson & Orme.(19) This is performed with the following formula: N > 500c / (t × a). Where t is the number of choice tasks, a the number of alternatives and c the number of analysis cells. However, the calculation of an optimal sample size for estimating non-linear discrete choice models from DCE data is complicated as it depends on the true values of the unknown parameters estimated in choice models. (20) Lancsar & Louviere mentioned that based on empirical experience one rarely requires more than 20 respondents per questionnaire version. All information combined led to a minimum sample size requirement of 83 respondents.

Data analysis

In this paper data analysis was performed on the combination of the pilot version and the definitive version of the DCE. Descriptive variables were analyzed with SPSS version 25.0.0.2. Normality was visually assessed. Means and standard deviations (SD) were calculated, just as frequencies. Age was determined as the difference from date of birth to study year. For the pilot group this was 2019, for the final version of the DCE this was 2020.

Discrete Choice data

Data analysis was conducted with the Nlogit econometric software version 6, September 2016. Both a mixed logit and a latent class analysis was applied.(21)

Mixed Logit Model

A mixed logit model determines the average impact of the different attributes on the utility function. The utility function is expressed as:

$$U_{ij} = \beta_0 + (\beta_1 + v_{1i})*\textit{Tinnitus loudness decreased} + (\beta_2 + v_{2i})*\textit{Tinnitus loudness similar}$$

$$+ (\beta_3 + v_{3i})*\textit{QoS increased} + (\beta_4 + v_{4i})*\textit{Tinnitus acceptance similar} + (\beta_5 + v_{5i})*\textit{Tinnitus acceptance increased} + (\beta_6 + v_{6i})*\textit{Concentration similar} + (\beta_7 + v_{7i})*\textit{Concentration increased} + (\beta_8 + v_{8i})*\textit{QoS similar} + \varepsilon_{ij}$$

β_o is the constant, β_1 to β_8 are the mean attribute utility weights and v1i to v8i are errors, which describe individual variation to the utility weights. ε_{ij} is an error part.

All variables were effect coded. ''With effects coding, all nonomitted levels are coded as –1 when the omitted level is present. The coefficient on the omitted level of an effects-coded variable can be recovered as the negative sum of the coefficients on the nonomitted levels of that attribute. Therefore, effects coding yields a unique coefficient for each attribute level included in the study.''(22) p 303 Reference levels were the worst potential outcome; i.e. increased tinnitus loudness and decreased concentration, sleep quality and tinnitus acceptance. The mixed logit model allows for variation around preferences in the population. The preferences are described with a β (mean) and a standard deviation (SD) of the error term. A positive or negative sign indicates the attribute level is either preferred or not preferred.

In our model, random parameters were defined by a normal distribution using halton draws with 500 repeated simulations. At first, all attributes were defined as random parameters. Attributes without a statistically significant standard deviation were no longer defined as random parameters in the next model (with a smaller set of random parameters and the other parameters as fixed). To explore preference heterogeneity covariates (age, tinnitus distress and gender) were added as interactions to the model. Only statistically significant interactions were kept in the final model. Best model fit was based on the log likelihood function.

A ranking in relative importance was calculated by dividing the random parameter's utilities range between the worst and best level by the total sum of all parameters.

Latent class model.

To further analyze preference heterogeneity a latent class analysis (LCLOGIT) was performed with different amount of classes (two to seven). Best model fit was based upon the Aikake information criterium (AIC), the AIC/N and clinical interpretability / relevance. Since the classes are 'latent', it is not known which participants belongs to which class. However, by means of posterior probabilities we made the best estimate to which class a participants belongs.(23) This information was used to describe the classes with the baseline characteristics.

Results

There were 127 participants in our study. Thirty out of thirty (100%) participated in the pilot version. Ninety-seven of 98 participants (99%) who signed informed consent filled out the definitive version. In this study data of the pilot version and the final version are reported. The mean age of the respondents of both the pilot and final version was 62.2 years of age (SD 10.3). 54 of 127 (42.5%) participants were female and the mean TFI score was 45.2 (SD 20.1). (Table 2) Considering health literacy 106 out of 127 participants (83.5%) never needed help with reading information from the hospital or general practitioner. Ninety of 127 (70.9%) were very much certain that they filled out medical forms correctly themselves and 93 of 127 (73.2%) did not experience difficulties with written information. (Table 3)

Table 2. Baseline characteristics of study participants for total study group and split per different classes (based on table 5).

Characteristic		Total study population	Classes	
		(n = 127)	Class 1 (n = 72)	Class 2 (n = 55)
		N (%)	N (%)	N (%)
Age (years)[1]		62.2 (10.3)	62.0 (10.3)	62.5 (10.4)
Gender (female)		54 (42.5)	33 (45.8)	21 (38.2)
TFI [1]		45.2 (20.1)	46.5 (20.6)	43.5 (19.5)
TFI subscales[1]				
Intrusiveness		60.2 (22.7)	62.4 (22.7)	57.3 (22.5)
Sense of Control		61.2 (20.1)	62.9 (20.6)	58.9 (19.4)
Cognitive		36.7 (23.4)	38.8 (24.3)	33.9 (22.1)
Sleep		43.4 (31.5)	42.3 (32.4)	44.8 (30.5)
Auditory		45.5 (29.0)	42.9 (28.9)	48.8 (29.0)
Relaxation		44.2 (26.3)	45.9 (27.3)	42.0 (24.9)
Quality of Life		37.5 (26.7)	39.8 (27.5)	34.5 (25.6)
Emotional		35.6 (26.8)	39.6 (27.7)	30.4 (24.8)
Scales 1 – 10 [1]				
Acceptance		6.4 (2.2)	6.2 (2.3)	6.6 (2.0)
Loudness		6.7 (2.1)	6.5 (2.2)	6.9 (1.9)
Concentration		5.3 (2.1)	5.4 (2.1)	5.3 (2.2)
Tinnitus characteristics				
Start of tinnitus	Less than 3 months ago	0 (0.0)	0 (0.0)	0 (0.0)
	3 – 6 months ago	5 (3.9)	3 (4.2)	2 (3.6)
	6 months or longer	122 (96.1)	69 (95.8)	53 (96.4)
Pattern	Constant	114 (89.8)	64 (88.9)	50 (90.9)
	Intermittent	13 (10.2)	8 (11.1)	5 (9.1)
Number of sounds	One	67 (52.8)	41 (56.9)	26 (47.3)
	More than one	60 (47.2)	31 (43.1)	29 (52.7)
	- Amount[1]	3.0 (1.4)	3.1 (1.4)	3.1 (1.4)

Table 2. CONTINUED.

Characteristic		Total study population	Classes	
		(n = 127)	Class 1 (n = 72)	Class 2 (n = 55)
		N (%)	N (%)	N (%)
Pulsatile	Yes	20 (15.7)	11 (15.3)	9 (16.4)
Hearing difficulties	I hear nothing	2 (1.6)	1 (1.4)	1 (1.8)
	Severe problems	42 (33.1)	21 (29.2)	21 (38.2)
	Mediocre problems	37 (29.1)	19 (26.4)	18 (32.7)
	Small problem	29 (22.8)	18 (25.0)	11 (20.0)
	No problem	17 (13.4)	13 (18.1)	4 (7.3)
Sought help		120 (94.5)	69 (95.8)	51 (92.7)
Type of help	Self-management	85 (70.8)	48 (69.6)	37 (72.5)
	Psychological treatment	67 (55.8)	41 (59.4)	26 (51.0)
	Audiological treatment	63 (52.5)	36 (52.2)	27 (52.9)
	Physiotherapy	28 (23.3)	21 (30.4)	7 (13.7)
	Psychiatric treatment	20 (16.7)	11 (15.9)	9 (17.6)
	Alternative treatment	50 (41.7)	33 (47.8)	17 (33.3)
	Other	13 (10.8)	7 (10.1)	6 (11.8)
Plans to seek help		6 (4.7)*	2 (2.8)	4 (7.3)
Type of help	Self-management	3 (50.0)	1 (50.0)	2 (50.0)
	Psychological treatment	4 (67.0)	1 (50.0)	3 (75.0)
	Audiological treatment	4 (67.0)	1 (50.0)	3 (75.0)
	Physiotherapy	1 (16.7)	0 (0.0)	1 (25.0)
	Psychiatric treatment	0 (0.0)	0 (0.0)	0 (0.0)
	Alternative treatment	2 (33.3)	1 (50.0)	1 (25.0)
	Other	1 (16.7)	0 (0.0)	1 (25.0)

[1] Mean (standard deviation). Other: - sought help: *Neuromodulation, earplugs, none (n = 5)**, doctor, ghnatologist, orthomanual therapist, supplements, EMDR, electromagnetic pulses.* - Plans to seek help: *implants*
*1 person answered both questions did you seek help or do you plan to seek help negatively. However since the participant answered positively at the question at inclusions, the data was included in the analyses. **the same was applicable for the 5 people that answered in the open area box: none. They however did answer positively at the question did you seek help

Preferences

The main results of choice experiment by the mixed logit model are presented in Table 4. The final model had a log-likelihood function of -587,77 and an adjusted pseudo R^2 of 0,258. Uniform distributions were tested, but did not improve the model. All variables presented are main effects.

Respondents showed a significant preference for a tinnitus treatment that results in a decrease (β = 2.03(1.48 – 2.58)) or similar level tinnitus loudness (β=0.31 (0.11 – 0.50)), an increase in (β = 0.88 (0.57 – 1.18)) or similar level of quality of sleep (β = 0.38 (0.20 – 0.56)), an increased (β = 0.90 (0.65 – 1.15)) or similar tinnitus acceptance (β = 0.25 (0.05-0.44)) and an increase in concentration (β = 0.51 (0.30 – 0.72)). Overall, the choice for a tinnitus therapy was significantly affected by all levels of the outcomes, except

for a similar level in concentration. In addition, all signs are in the expected direction (positive β's), confirming theoretical validity of the model.

All standard deviations of the random parameters were statistically significant, indicating preference variation among participants. To explore the heterogeneity, three covariates (age, gender and TFI score) were added to the model. A significant interaction was found with a similar level of tinnitus acceptance and the TFI of β = -0.01 (-0.02 – -0.001). Adding this interaction improved the model significantly to a LL of -584.86, with an adjusted pseudo R_2 of 0.26. The interaction changed the level of significance of the main effect of similar tinnitus acceptance from 5% to 1% (β = 0.72 (0.28-1.16)).Correlations among all different parameters were explored; the model did not improve significantly and was therefore not reported.

The relative importance of the random parameters was calculated for both the main effect model and the model with the interaction. Similar results were yielded. Tinnitus loudness was the most important outcome measure, followed by tinnitus acceptance, quality of sleep and concentration in that order.

Table 3, Health Literacy questions and outcome

Health Literacy	N (%)
How often does somebody help you with reading letters or folders from your general practitioner or the hospital?	
Never	106 (83.5)
Occasionally	18 (14.2)
Sometimes	0 (0.0)
Often	2 (1.6)
Always	1 (0.8)
How certain are you that you fill out medical forms correctly yourself?	
Very much	90 (70.9)
Quite	32 (25.2)
A little	1 (0.8)
A very little	1 (0.8)
Not at all	3 (2.4)
How often is it difficult for you to understand more about your health, because you do not completely understand written information?	
Never	93 (73.2)
Occasionally	26 (20.5)
Sometimes	7 (5.5)
Often	0 (0.0)
Always	1 (0.8)

Table 4, Result of the mixed effect model.

	Main model			Model including covariates		
Attributes and levels	**Estimate (95% CI)**	**Standard deviation (95% CI)**	**Relative Importance**	**Estimate (95% CI)**	**Standard deviation (95% CI)**	**Relative importance**
Random parameters in utility function						
Tinnitus loudness decreased[1]	2.03 (1.48-2.58)***	2.00 (1.46 – 2.53)***	0.47 (1)	2.03 (1.48 – 2.59)***	1.98 (1.46 – 2.51)***	0.44 (1)
Tinnitus loudness similar	0.31 (0.11 – 0.50)***	0.45 (0.14 – 0.76)***		0.31 (0.12 – 0.50)***	0.44 (0.14 – 0.74)***	
QoS increased	0.88 (0.57 – 1.18)***	0.95 (0.60 – 1.31)***	0.19 (3)	0.88 (0.57 – 1.19)***	0.95 (0.59 – 1.31)***	0.21 (3)
Tinnitus acceptance similar	0.25 (0.05 – 0.44)**	0.46 (0.18 – 0.74)***		0.72 (0.28 – 1.16)***	0.43 (0.14 – 0.72)***	
Tinnitus acceptance increased	0.90 (0.65 – 1.15)***	0.60 (0.32 – 0.87)***	0.22 (2)	0.90 (0.65 – 1.44)***	0.61 (0.33 – 0.88)***	0.25 (2)
Fixed parameters						
Constant	-0.12 (-0.33 – 0.08)			-0.13 (-0.33 – 0.08)		
Concentration similar	0.001 (-0.161 – 0.164)		0.11 (4)	0.001 (-0.16 – 0.16)		0.10 (4)
Concentration increased	0.51 (0.30 – 0.72)***			0.50 (0.29 – 0.71)***		
QoS similar	0.38 (0.20 – 0.56)***			0.38 (0.20 – 0.56)***		
(Interaction Tinnitus acceptance similar x TFI)				-0.01 (-0.02 – -0.002)**		
LogLikelihood	-587.77			-584.86		
Chi squared	(14) 408.9 (p = 0.000)			(15) 414.8 (p=0.000)		
Adjusted pseudo R^2	0.258			0.262		
AIC/N	1.053			1.050		

[1]effect coding: worst level can be retrieved for example increased tinnitus loudness: -1.0(2.03+0.31) =–2.39), *** significance at 1% level, ** significance at 5% level

Attribute Trade-off

By inserting parameter estimates and attribute levels in the utility function, we gain insight in how participants were willing to trade of between levels of attributes. For example, a change from decreased tinnitus loudness (β = 2.03) to similar tinnitus loudness (β = 0.31) would lead to a utility decrease of Δ -1.72, when all other attributes would remain similar. An increase in tinnitus acceptance (Δ +0.65), quality of sleep (Δ +0.50) and concentration (Δ +0.52) from the similar level would lead to a utility increase of Δ +1.67. Since 1.67 is smaller than 1.72, this utility increase does not compensate the utility decrease of tinnitus loudness.

Latent class analysis

Models were made for two to seven different classes. The choice for optimal latent class model was based on model fit and clinical interpretability. Only the model with two classes could be interpreted clinically. The model showed an AIC of 1247.4 and an AIC/N of 1.091. The first class had an estimated latent class probability of 0.57 (0.44 – 0.70), the second of 0.43 (0.30 – 0.56). The first class was similar to the mixed logit model in terms of significant parameters, except for an insignificant similar level of QoS and tinnitus acceptance in the first class (β = -0.03 (-0.33 – 0.27), -0.06 (-0.33 – 0.21). Tinnitus loudness was still considered the most important attribute relative to sleep, tinnitus acceptance and concentration in that order. In the second model statistical significance was achieved for two attributes; a similar level of QoS (β = 0.31 (0.12 – 0.50) and an increased level of tinnitus acceptance (β = 0.51(0.32 – 0.70)). Tinnitus acceptance was the most important attribute relative to sleep, concentration and tinnitus loudness in that order. (Table 5)

Table 5, Outcome of the latent class analysis, *** significance at 1% level

	Class 1		**Class 2**	
	Estimate (95% CI)	**Relative importance**	**Estimate (95% CI)**	**Relative importance**
Tinnitus loudness decreased	2.65 (1.98 – 3.31)***	0.56 (1)	-0.01 (-0.34 – 0.31)	0.02 (4)
Tinnitus loudness similar	0.48 (0.23 – 0.73)***		-0.04 (-0.23 – 0.15)	
Concentration similar	0.02 (-0.18 – 0.22)		-0.002 (-0.17 – 0,16)	
Concentration increased	0.58 (0.32 – 0.83)***	0.11 (4)	0.19 (-0.01 – 0.40)	0.16 (3)
QoS similar	-0.03 (-0.33 – 0.27)		0.31 (0.12 – 0.50)***	
QoS increased	0.95 (0.66 – 1.23)***	0.18 (2)	0.24 (-0.02 – 0.50)	0.33 (2)
Tinnitus acceptance similar	-0.06 (-0.33 – 0.21)		0.17 (-0.02 – 0.37)	
Tinnitus acceptance increased	0.76 (0.50 – 1.02)***	0.14 (3)	0.51 (0.32 – 0.70)***	0.49 (1)
Estimated latent class probabilities	0.57 (0.44 – 0.70)		0.43 (0.30 – 0.56)	
Aikakes information criterium	1247.4			
AIC/N	1.091			

The mean age was 62.0 (SD 10.3) for class 1 and 62.5 (SD 10.4) for class 2. The mean TFI score was 46.5 (SD 20.6) for class 1 and 43.5 (SD 19.5) for class 2. Class 1 had a mean of 42.3 (SD 32.4) on the TFI subscale sleep, compared to 44.8 (30.5) in class 2. Class 1 scored a mean score of 6.2 (SD 2.3) on the VAS scale for acceptance, 6.5 (SD 2.2) on loudness and 5.4 (2.1) on concentration, compared to 6.6 (SD 2.0) for acceptance, 6.9 (SD 1.9) on loudness and 5.3 (SD 2.2) for concentration in class 2. 31 of 72 (43.1%) participants in class 1 experienced more than one sound, compared to 29 of 55 (52.7%) participants of class 2.

Discussion

In this study we conducted a discrete-choice experiment to understand the preference of tinnitus patients for outcome measures in tinnitus therapy. In a mixed logit analysis we found that a decrease in tinnitus loudness was the most important outcome measure compared to the others. A change from decreased tinnitus loudness to a similar level of tinnitus loudness, could not be compensated by an increase in levels for the other three attributes (sleep, concentration and tinnitus acceptance). Preference heterogeneity was present, since all standard deviations of the random parameters were statistically significant in the mixed logit model. Preference heterogeneity could not be explained by correlating the attributes, but there was a significant model improvement with the interaction of similar level of tinnitus acceptance and the TFI. The optimal model of the latent class analysis showed two classes. The first class was very similar to the mixed logit analysis; primarily a decrease of tinnitus loudness was preferred next to an increase of the other attributes. In the second class only an increase in tinnitus acceptance or a similar level of quality of sleep was preferred. The mean TFI score of 45.2 (SD 20.1) can be interpreted as that tinnitus is considered a moderate problem by the participants according to the grading of the TFI. (16) This is in correspondence with our inclusion criteria that participants were in need or have been in need of help.

Tinnitus loudness was considered the most desirable outcome compared to the other attributes. This means that tinnitus loudness is the most desirable outcome measure for tinnitus patients in treatment relative to quality of sleep, tinnitus acceptance and concentration. Assessing tinnitus loudness however, has its difficulties. First there is no consensus of one standardized test for measuring tinnitus loudness.(24) For example, the perceptual attributes can be measured with tinnitus matching experiments. (25,26). The subjective impact of loudness can be measured with self-reported scales. (27) Discrepancies have been described between subjective and objective measures. (28,29) These discrepancies demonstrate the difficulties in the concept of tinnitus. Even though the description of the phenomenon tinnitus is straightforward, the concept of what it means for patients varies greatly. (30,31) Loudness alone does not fully explain the experienced distress and therefore, a decrease in subjective loudness does not necessarily correlate with a similar amount of decrease in tinnitus distress. This is in accordance with tinnitus distress models where tinnitus distress encompasses emotion and reaction next to the sound experience. (29,32–34) This idea is also grasped in the TFI. The total score consists of eight different domains that could all have an effect on the total impact of tinnitus on daily life.(16)

The outcomes of this study raise the question on how to reduce the tinnitus loudness.

A systematic review showed that most trials that aim to reduce tinnitus loudness are pharmacological trials.(25) A previous study on preferences on outcomes in tinnitus patients showed that 52% were very interested to take a pill if it would reduce tinnitus loudness and annoyance by half. 62% would even take a pill if the tinnitus loudness and annoyance would be completely eliminated.(35)

The latent class analysis showed that 57% of the participants considered an improvement in all attributes important. They have the strongest preference for tinnitus loudness, relative to quality of sleep, tinnitus acceptance and concentration in that order, similar to the mixed logit model. However, for 43% of the participants tinnitus acceptance and sleep were the most important outcome measures. Both classes were very similar based on the baseline characteristics. They had similar mean scores on the total TFI and the TFI subscale on sleep. The same is applicable for the VAS-scales on tinnitus acceptance, loudness and concentration. Even though the first class prefers a loudness and the second class acceptance. Differences can be found on the amount of experienced sounds; class 2 seemed to experience more sounds. One might hypothesize that a higher total amount of sounds might explain that an increase in QoS and acceptance is preferred over a decrease in loudness. However, this is not explained by the similar levels on the VAS scale for acceptance and the TFI subscale for sleep. Please note, as stated in the methods section, these are estimates of belongings to classes. Since these are ''latent'' classes, the true belonging of an individual to a class cannot be assessed.(23)

Heterogeneity in tinnitus complaints is a common issue in tinnitus research, and limits the generalizability of therapy outcomes that might focus on one aspect of this disease. (4,36) It is commonly believed that there are subtypes of tinnitus patients. (4,36) Therefore, this study stresses the need for research of finding these subtypes of tinnitus patients which could be related to the preferred outcome measure for tinnitus therapy. Next this study underlines the importance of shared decision making in the process of choosing suitable therapy.

The lack of adequate and evidence based treatments for different tinnitus patients highlights the importance of improving the methods for tinnitus research.(36) This starts with defining outcomes, defining the exact study population and patient's needs.(6,37) The heterogeneity of the condition and its patients makes it challenging to define criteria for reliable and effective treatment trials. We believe that defining the preference of patients, could function as a foundation for defining outcomes. (7) Additionally it provides insight in the heterogeneity and subtypes of patients affected by the condition. The COMiT'ID study focused on uniformity of research and developed a core outcome set for tinnitus research. The authors recommend specific

outcome measures for different intervention types. For example tinnitus loudness should be an outcome measure in drug therapies.(7) In this study we solely assessed the choices people make in a selection of outcome measures aimed at treatment, independent of intervention type. The combination of both studies could be of importance for future trials. Based on that perspective both the Delphi trial and this discrete choice experiment could be complementary to each other.(6) Next, we recommend more research into therapies that might diminish tinnitus loudness, not necessarily only drug therapies. We encourage authors to consider loudness to be assessed as an additional outcome measure to the core set in the other intervention types (sound, psychological) as recommend by the COMiT'ID.

Strengths and limitations

There are several limitations applicable to this study. The primary limitation is the lack of a formal definition of the attributes and levels. The outcome measures used in this study, were previously defined in the COMiT'ID studies as follows: "*tinnitus loudness: how loud your tinnitus sounds, quality of sleep: getting the right amount of undisturbed sleep for you that leaves you feeling refreshed and rested, tinnitus acceptance: recognizing that tinnitus is a part of your life without having a negative reaction to it, concentration: ability to keep your attention focused.*"(8)[additional file] Participants in our study were not instructed with any formal definitions. They had to rely upon their own interpretation. Participants could have had different ideas and concepts for the different attributes and levels used in this study. The second is the fact that only a small set of (four) attributes could be investigated in order to make the DCE feasible. We acknowledge that the participants might prefer other outcome measures outside of the pre-selected outcome measures of this study (e.g. the effect of tinnitus on hearing). Also, the attributes were based on a previously conducted elaborate Delphi experiment. However the selection of the outcome measures for our study was based on discussion in the focus groups and the research group.(7) Another limitation of this study was that it did not include the specific type of intervention. It might be interesting to observe what will happen if intervention type would be added as an attribute or in a labeled design. A fourth limitation is the fact that we included participants only if they planned to seek help for their tinnitus or if they had already sought help. A bias could have been introduced by participants that did not have an active wish (anymore) for help at the moment of filling out the questionnaire.

Conclusions

A discrete choice experiment was conducted in order to understand the preference of tinnitus patients in four different outcome measures (tinnitus loudness, tinnitus acceptance, quality of sleep and concentration) for tinnitus therapy. The experiment forced participants to choose the most important attribute with a specific level. A decrease in tinnitus loudness was considered the most important outcome measure compared to quality of sleep, tinnitus acceptance and concentration. The mixed logit analysis showed heterogeneity that was not explained by covariates. A statistically significant interaction was found between a similar level and tinnitus acceptance and the TFI score. A latent class analysis showed two classes. The first class was similar to results of the mixed logit analysis, the second showed a statistical significant preference only for tinnitus acceptance and quality of sleep. This study stresses the importance of researching tinnitus heterogeneity. Also, this study highlights the need for research into tinnitus therapies that might diminish tinnitus loudness.

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CHAPTER 3

Using different Cut-Offs to Define Tinnitus and assess its Prevalence - A Survey in the Dutch General Population

Frontiers in Neurology. 2021 August 11;12:69092

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Abstract

Introduction
Tinnitus prevalence numbers in the literature range between 5% and 43%, depending on the studied population and definition. It is unclear when tinnitus becomes pathologic.

Objectives
To assess the tinnitus prevalence in the Dutch general population with different cut-offs for definition.

Methods
In this cross-sectional study a questionnaire was sent to a sample (n = 2251) of the Nivel (Netherlands Institute for Health Services Research) Dutch Health Care Consumer Panel. Three questions were asked to assess the presence of tinnitus, duration, and frequency of the complaint. We classified people as having pathologic tinnitus when participants experienced it for 5 – 60 minutes (daily or almost daily or weekly), or tinnitus for >60 minutes or continuously (daily or almost daily or weekly or monthly). Tinnitus impact on daily life was measured with the Tinnitus Functional Index (TFI) and a single-item question. Answers were stratified to mid-decade years of age. Prevalence numbers were weighted by gender and age to match the Dutch population.

Results
932 of 2251 participants (41%) filled out the questionnaire. The median age was 67.0 (IQR 17). 338 of 932 (36%) experienced tinnitus for an undefined amount of time during the last year. 216 of 932 (23%) met our definition of having pathologic tinnitus (21% when weighted for age and gender). The median TFI score for all pathologic tinnitus participants was 16.6 (IQR 21.8)). 50.4% of the pathologic tinnitus participants had a TFI in the range 0 – 17, which can be interpreted as not a problem.

Conclusion
23% (unweighted) or 21% (weighted) of our sample met our definition of pathologic tinnitus, which was based on a combination of duration and frequency over the last year. The TFI score of 47.7% of the pathologic tinnitus participants is ≥ 18. This indicates that they consider the tinnitus to be at least "a small problem" (11.1% (unweighted) or 8.9% (weighted) of the total study group). This study illustrates the difficulties with defining pathologic tinnitus. In addition, it demonstrates that tinnitus prevalence numbers vary with different definitions and, consequently, stresses the importance of using a uniform definition of tinnitus.

Introduction

Till date, the prevalence of tinnitus in the general population remains uncertain. In a systematic review conducted in 2016 a wide range in tinnitus prevalence numbers were found in included studies, with numbers varying between 5.1% and 42.7% in the adult population.(1–3) The variation in numbers is mainly believed to be caused by the use of different definitions of tinnitus. The phenomenon of tinnitus is clearly described in literature as the experience of a sound, in the absence of an external stimulus(4). Still, the authors of the systematic review identified eight variations on screenings questions to identify those having tinnitus. This varied from tinnitus lasting for more than five minutes at a time or the experience of tinnitus within the last year. However, besides criteria of time elements, there are multiple components that could contribute to a definition. The authors argue that, for example, the impact of tinnitus on daily life could be part of the definition.(1) Since, the mere presence of tinnitus does not necessarily mean the individual person experiences it as pathologic or distressing.(4) At this moment there is no consensus on when tinnitus becomes so distressing that it becomes pathologic, or the individual starts, for example, to seek help.

Knowledge about the prevalence of a disease is important for the organization of healthcare and prevention of the condition.(5) Moreover, in the conceptual analysis 'Why is there no cure for tinnitus' published in 2019, several other consequences were related to the lack of more detailed knowledge about prevalence numbers such as the lack of improvement in pharmacological therapies.(6) Due to the absence of prevalence information companies are not informed about the potential market for their future product, and therefore do not develop a product for patients.(6) These issues urge the need to assess the prevalence of tinnitus in the general population by usage of a clear description of the experienced symptoms.

In order to elucidate the tinnitus prevalence we have designed this study. We wanted to assess tinnitus prevalence in a general population sample. Next, to tackle the issues of defining tinnitus we asked several questions, with different cut-offs, rather than one general screening question. Those included questions on tinnitus presence, but also on the impact of tinnitus on daily life. Our primary aim was therefore, to assess the prevalence of tinnitus in the Dutch general population with different cut-offs for its definition.

Methods

This paper was written according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement. (7)

Study design & population

This is a cross-sectional study of a cohort of people aged 18 years and older of the Dutch population. Data was prospectively collected with a questionnaire send to a sample of panel members of the Dutch Health Care Consumer panel (DHCCP) of Nivel (the Netherlands institute for health services research)(8).

The goal of the Dutch Health Care Consumer Panel is to measure, at national level, opinions on and knowledge about health care and the expectations and experiences with health care. The Consumer Panel is a so-called 'access panel'. An access panel consists of a large number of persons who have agreed to answer questions on a regular base. In addition, many background characteristics of these persons (for example age, level of education, income, self-reported general health) are known. At the time of this study (January 2020), the panel consisted of approximately 12 000 people aged 18 years and older. From the access panel samples can be drawn for every separate survey. It is not possible for people to sign up on their own initiative. The panel is renewed on regular base. Renewal is necessary to make sure that members do not develop specific knowledge of, and attention for, healthcare issues, and that no 'questionnaire fatigue' occurs. Moreover, renewal compensates for panel members who, for example, have died or moved without informing us about the new address. (8)

This study is a smaller part of a larger study on tinnitus characteristics, risk factors, and health care usage. The questionnaire sample therefore consisted of all panel members (N=2.291) of the Consumer Panel who gave permission to combine their answers of the survey with health care consumption data as registered by their general practitioner. (9) The participants of the DHCCP received a questionnaire by postal mail, and online, depending on the preference of the panel member. The postal questionnaire was sent on January 14th 2020, with one postal reminder was sent on January 30th. The online questionnaire was sent on January 16th 2020, two electronic reminders were sent on January 23rd and January 30th 2020. The questionnaire closed on February 14th 2020. No further actions were undertaken to optimize the response rate for this study specifically. In general, all panel members are kept involved by newsletters. The study report on a part of the data collected in the questionnaire.

Outcome assessment

Questionnaire

Tinnitus presence

The presence of tinnitus was assessed with three questions, based on the studies by McCormack et al., Baguley et al., and Langguth et al. and expert opinion. (1,10,11) First all participants were asked the question whether they had experienced tinnitus in the last year. Tinnitus was described as: *Tinnitus is the hearing of e.g. a beep, whistle, sissing, zoom or another sound without the actual presence of the sound in your surroundings. This can last for a very short amount of time or a whole day*. If participants responded positively (yes) on that question, they were asked two follow-up questions. The first inquired about the time related characteristics of the tinnitus (tinnitus lasting < 5 minutes, 5-60 minutes, ≥60 minutes or continuously) and the second about frequency of the experienced sound (daily or almost daily, weekly, monthly, less than once a year). To interpret the outcome, we classified people as having pathologic tinnitus when they were experiencing tinnitus for: 5 – 60 minutes (daily or almost daily or weekly), ≥60 minutes or continuously (daily or almost daily or weekly or monthly).

Impact of tinnitus

Participants that met the definition of pathologic tinnitus were asked about the impact of tinnitus on daily life measured with the Tinnitus Functional Index (TFI). (12,13) The TFI consists of 25 questions, each with an 11-point Likert scale. The TFI creates a score from 0 (not a problem) - 100 (a very big problem), that can be subdivided into five categories, namely: scores ranging between 0-17 can be interpreted as not a problem, 18-31 as a small problem, 32-53 as a moderate problem 54-72 as a big problem, and 73-100 as a very big problem.(14) Furthermore the TFI consists of eight subscales to measure the impact of tinnitus on; intrusiveness, sense of control, cognition, sleep, hearing, relaxation, quality of life, and emotions. The questionnaire was first developed in English, and validated before translation to Dutch in 2014. The Dutch translation has a high internal consistency with a Cronbach's alpha of 0.91.(13)

Subjective problem

The question: *"how big a problem is your tinnitus at this moment?"* was asked to those with pathologic tinnitus. Answer options were: "*no problem*", "*small problem*", "*reasonable problem*", "*large problem*" or "*very large problem*".

Data handling & Ethics

Data are analyzed anonymously and the privacy of the panel members is guaranteed, as is described in the privacy policy of the Dutch Health Care Consumer Panel. This complies with the General Data Protection Regulation (GDPR). According to Dutch legislation, neither obtaining informed consent nor approval by a medical ethics

committee is obligatory for conducting research through the panel (CCMO, 2020). (8) The Medical Research Ethics Committee (MREC) of the University Medical Center Utrecht (UMC Utrecht) confirmed on November 20th 2019, that the Medical Research Involving Human Subjects Act (WMO) does not apply to this study and that therefore official approval by the MREC is not required under the Human Subjects Act (MREC local protocol number 19-745).

Statistical analysis

Statistical analyses were performed with SPSS version 25.0.0.2 Normality was visually assessed. Frequencies, medians and interquartile ranges (IQR) were calculated. Prevalence data, and the subjective problem of tinnitus was stratified per mid-decade groups. Total TFI scores were calculated for those with pathologic tinnitus and stratified per mid-decade groups. TFI categories and subscales were calculated. The sample was not representative in terms of age for the Dutch population. To give a more precise estimate of the prevalence numbers we corrected the prevalence numbers of pathologic tinnitus with a weight factor by age and gender. The weight factors ranged from 0.35 to 5.72 in males, and 0.47 to 3.21 in females. The weight factors were calculated by dividing the amount of males and females per age-group (18-49, 50-64, and 65+) in the study sample with the corresponding age-groups of the Dutch general population as provided by the Dutch Central Bureau of Statistics on 1-12-2019. (15)

Results

Study population

The questionnaire was sent to 2251 panel members, of which 932 (41.1%) filled out the questionnaire. The median age of participants was 67.0 (IQR 17) years. A total of 444 (47.6%) males and 488 (52.4%) females took part.

Frequency and duration of experienced tinnitus

Table 1 shows that 338 of 932 participants (9 missing, 36.3%) experienced tinnitus in the last year. Of those 338, 81 (3 missing, 24.0%) experienced it for less than 5 minutes, 64 (3 missing, 18.9%) for 5 – 60 minutes, 41 (3 missing, 12.1%) for >60 minutes or more and 149 (3 missing, 44.1%) experienced it continuously. Answers to questions regarding the duration of the experienced sound were combined with answers to questions regarding frequency. One hundred thirty-two of 216 (61.1%) participants experienced tinnitus continuously, daily or almost daily in the last year. Forty-two of 81 (51.9%) participants experienced tinnitus less than 5 minutes every month in the last year. (Table 2)

Table 1. Duration of tinnitus experience in the last year stratified per mid-decade age groups.

Age	Experience of tinnitus[1] (n (%))	< 5 minutes (n (%))	5 – 60 minutes (n (%))	≥60 minutes or more (n (%))	Continuously (n (%))
18-24	1 ((0,3)	0 (0.0)	1 (1.6)	0 (0.0)	0 (0.0)
25-34	0 (0,0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
35-44	13 (3.8)	2 (2.5)	7 (10.9)	2 (4.9)	2 (1.3)
45-54	48 (14.2)	18 (22.2)	7 (10.9)	7 (17.1)	16 (10.7)
55-64	76 (22.5)	20 (24.7)	14 (21.9)	7 (17.1)	35 (23.5)
65-74	130 (38.5)	33 (40.7)	16 (25.0)	17 (41.5)	62 (41.6)
75+	70 (20.7)	8 (9.9)	19 (29.7)	8 (19.5)	34 (22.8)
All	338 (36,3)	81 (24.0)	64 (18.9)	41 (12.1)	149 (44.1)

[1]in the last year. 9 missing (1.0%) for experience of tinnitus, 3 missing (0.9%) for duration (< 5 minutes – continuously)

Numbers of pathological tinnitus

We defined 216 (23.2%) of the complete study population (932 participants) as having pathologic tinnitus. When weighted for age and gender this changed to 195 of 932 participants (21.0%). This resulted in 63.9% of those that experienced tinnitus in the last year (216 of 338). 52 of the 216 pathologic tinnitus participants (24.1%) were between 55 and 64 years of age. The median age of the participants with pathologic tinnitus was 66.5 years (IQR 15). One hundred twenty-four (57.4%) of the participants with pathologic tinnitus (n = 216) were male.

Table 2. Frequency of tinnitus experience in the last year stratified per duration (table 1) and mid-decade age groups in amount and percentage n (%).

Age	**<5 minutes** (n = 81, 0 missing (0%))				**5 – 60 minutes** (n = 61, 3 missing (4.7%))				**≥ 60 minutes** (n = 41, 0 missing (0%))				**Continuously** (N = 138, 11 missing (7.4%))				Pathologic Tinnitus (N= 216)
	D	W	M	Y	**D**	**W**	M	Y	**D**	**W**	**M**	Y	**D**	**W**	**M**	Y	
18-24	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	**0 (0.0)**	**0 (0.0)**	0 (0.0)	1 (20.0)	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	0 (0.0)	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	0 (0.0)	0 (0.0)
25-34	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	**0 (0.0)**	**0 (0.0)**	0 (0.0)	0 (0.0)	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	0 (0.0)	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	0 (0.0)	0 (0.0)
35-44	0 (0.0)	0 (0.0)	2 (4.8)	0 (0.0)	**2 (10.0)**	**3 (15.0)**	1 (6.3)	1 (20.0)	**2 (9.5)**	**0 (0.0)**	**0 (0.0)**	0 (0.0)	**2 (1.5)**	**0 (0.0)**	**0 (0.0)**	0 (0.0)	9 (4.2)
45-54	2 (40.0)	4 (33.3)	11 (26.2)	1 (4.5)	**1 (5.0)**	**3 (15.0)**	3 (18.8)	0 (0.0)	**3 (14.3)**	**2 (20.0)**	**2 (22.2)**	0 (0.0)	**13 (9.8)**	**1 (33.3)**	**0 (0.0)**	1 (50.0)	25 (11.6)
55-64	0 (0.0)	4 (33.3)	9 (21.4)	7 (31.8)	**6 (30.0)**	**6 (30.0)**	0 (0.0)	1 (20.0)	**3 (14.3)**	**2 (20.0)**	**1 (11.1)**	1 (100)	**32 (24.2)**	**2 (66.7)**	**0 (0.0)**	1 (50.0)	52 (24.1)
65-74	0 (0.0)	4 (33.3)	17 (40.5)	12 (54.4)	**4 (20.0)**	**4 (20.0)**	6 (37.5)	2 (40.0)	**8 (38.1)**	**6 (60.0)**	**3 (33.3)**	0 (0.0)	**56 (42.4)**	**0 (0.0)**	**0 (0.0)**	0 (0.0)	81 (37.5)
75+	3 (60.0)	0 (0.0)	3 (7.1)	2 (9.1)	**7 (35.0)**	**4 (20.0)**	6 (37.5)	0 (0.0)	**5 (23.8)**	**0 (0.0)**	**3 (33.3)**	0 (0.0)	**29 (22.0)**	**0 (0.0)**	**1 (100)**	0 (0.0)	49 (22.7)
All	5 (6.2)	12 (14.8)	42 (51.9)	22 (27.2)	**20 (31.3)**	**20 (31.3)**	16 (25.0)	5 (7.8)	**21 (51.2)**	**10 (24.4)**	**9 (22.0)**	1 (2.4)	**132 (88.6)**	**3 (2.0)**	**1 (0.7)**	2 (1.3)	216 (23.2)

D; Daily, W: Weekly, M; monthly, Y: once or less than once per year. These are written in **bold**

Impact of tinnitus on daily life

Tinnitus distress scores measured with the TFI were calculated for the pathologic tinnitus participants. The median TFI score was 16.6 (IQR 21.8) (based on 212 participants, 4 missing). Participants who experienced tinnitus daily continuously had the highest median TFI score of 20.4 (IQR 29.2) (Table 3). Fifty percent (50.4%) of all pathologic tinnitus participants had a TFI score in the range 0-17 (n = 109, 4 missing). One hundred three of 216 pathologic tinnitus participants (47.7%, 4 missing) had a TFI score of 18 or higher. This is 11.1% of the complete sample (n= 932). When weighted for age and gender this changed to 83 of 932 participants (8.9%). On the different TFI subscales the highest median (43.3 (IQR 28.3)) was scored in the subscale: *sense of control* (Table 4).

On the question "How big a problem is your tinnitus at this moment?" 51 of 216 (23.6%, 1 missing) answered it is not a problem. (Table 5) One hundred five of 216 (48.6% 1 missing) judged their tinnitus to be a small problem, 43 of 216 (19.9%, 1 missing) as a reasonable problem, 12 of 216 (5.6%, 1 missing) as a large problem and 4 of 216 (1.9%, 1 missing) as a very large problem. One hundred sixty-four of 216 (75.9%, 1 missing) judged their tinnitus to be a small, reasonable, large or very large problem. This is 17.6% of the total population (164 of 932). When weighted for age and gender this changed to 147 of 932 participants (15.7%).

Table 3. Median (IQR) TFI score stratified per mid-decade age group of pathologic tinnitus participants.

Age	TFI median													
	5 to 60 minutes				Continuously				60 minutes or more				Pathologic Tinnitus	
	D	N	W	N	D	N	W	N	D	N	W	N	N	
18-24	-	0	-	0	-	0	-	0	-	0	-	0	-	0
25-34	-	0	-	0	-	0	-	0	-	0	-	0	-	0
35-44	7.4	2[b]	9.2	3[b]	25.4	2	-	0	24.4	2[b]	-	0	10.0 (17.8)	9
45-54	1.2	1[a]	8.4	3[b]	15.6 (21.8)	13	12.4	1[a]	26.6	2*[b]	19.8	2[b]	15.0 (21.4)	24
55-64	20.6 (46.6)	6	13.6 (31.4)	6	21.8 (29.3)	32	10.4	2[b]	14.0	3[b]	11.4	2[b]	19.0 (26.0)	52
65-74	12.2 (11.3)	4	24.6 (38.7)	4	21.2 (35.2)	55*	-	0	17.4 (19.2)	8	23.4 (21.6)	6	20.0 (28.4)	79
75+	11.1 (14.0)	6*	10.5 (21.5)	4	15.6 (31.2)	29	-	0	19.2 (20.2)	5	-	0	13.9 (18.8)	48
All	10.0 (12.0)	19*	9.8 (24.8)	20	20.4 (29.2)	131*	12.4	3	19.2 (18.0)	20*	19.4 (13.1)	10	16.6 (21.8)	212

* one missing. D: Daily, W: Weekly, M; monthly, Y: once or less than once per year. N = 212 (4 missing), *One missing. a The real TFI score is presented (not a median). bIQR could not be calculated

Table 4. TFI characteristics of pathologic tinnitus participants (N = 212, 4 missing).

TFI Characteristic		N (%)
TFI ranges	0-17	109 (50,4)
	18-31	52 (24,1)
	32-53	26 (12,0)
	54-72	22 (10,2)
	73-100	3 (1,4)
	Missing	4 (1.9)
TFI Subscales (median (IQR))	Intrusiveness	26.7 (32.5)
	Sense of control	43.3 (28.3)
	Cognitive	10.0 (30.0)
	Sleep	10.0 (26.7)
	Auditory	20.0 (49.2)
	Relaxation	10.0 (26.7)
	Quality of Life	2.5 (20.0)
	Emotional	6.7 (20.0)

Table 5. Answers to the question: How big a problem is your tinnitus at this moment? of pathologic tinnitus participants.

Age	No problem	Small problem	Reasonable problem	Large problem	Very large problem
18-24	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
25-34	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
35-44	2 (3.9)	5 (4.8)	2 (4.7)	0 (0.0)	0 (0.0)
45-54	7 (13.7)	15 (14.3)	3 (7.0)	0 (0.0)	0 (0.0)
55-64	16 (31.4)	22 (21.0)	9 (20.9)	3 (25.0)	2 (50.0)
65-74	16 (31.4)	39 (37.1)	19 (44.2)	4 (33.3)	2 (50.0)
75+	10 (19.6)	24 (22.9)	10 (23.3)	5 (41.7)	0 (0.0)
All	51 (23.6)	105 (48.6)	43 (19.9)	12 (5.6)	4 (1.9)

One missing (0.5%) Stratified per mid-decade.

Discussion

We evaluated the prevalence of tinnitus in the Dutch general population with different cut-offs for its definition. Frequency, duration, and the impact of tinnitus on daily life were individually assessed in an adult sample of inhabitants of the Netherlands.

Tinnitus presence.

In our study 36.6% of the participants experienced tinnitus within the last year. Tinnitus was described as: *the hearing of e.g. a beep, whistle, sissing, zoom or another sound without the actual presence of the sound in your surroundings. This can last for a very short amount of time or a whole day.* Only 23.2% (unweighted) (or 21.0% (weighted)) of the participants were defined as having pathologic tinnitus (5 – 60 minutes (daily or almost daily or weekly), ≥60 minutes or continuously (daily or almost daily or weekly or monthly)). The difference in these numbers underlines the importance of the exact definition in order to assess prevalence numbers in a population.

This is clearly illustrated in a systematic review by McCormack et al.(1) All included studies were population studies and reported only on adults showing prevalence numbers between 5.1 and 42.7%. Out of 39 included studies, eight different definitions for tinnitus were found. 26 studies used one of the following three definitions; "*tinnitus lasting for more than 5 minutes at a time" (12 studies, prevalence ranged between 11.9 – 30.3%), "do you have tinnitus" (5 studies, prevalence ranged between 10.1% - 22%)* or *"within the last year did you experience tinnitus" (9 studies, prevalence ranged range* 6.1% – 24.6%)". Even with the most commonly used definition, *tinnitus lasting for more than 5 minutes at a time*, the reported prevalence numbers ranged between 11.9% to 30.3% in included studies. (1) Our prevalence number of 23.3% (unweighted) or 21.0%% (weighted) of cases with pathologic tinnitus falls within that range. McCormack et al. reported that in those studies similar study groups in terms of age and a similar definition used *(>5 minutes)*, the prevalence numbers still varied largely (e.g. for people aged 60-70 between 13.3% and 35.5%).(1) This, again, stresses the importance of a uniform way to study tinnitus, with a similar question and similar response options.

The impact of tinnitus on daily life.

For the present study, we based our definition of the presence of pathologic tinnitus on the combination of duration and frequency. However the mere presence of tinnitus does not explain the impact of tinnitus on a person's daily life. In our study we used a multi-item questionnaire, the TFI, to measure the impact of tinnitus on daily life. A score between 0 and 17 can be interpreted as ''not a problem.''(14) In our study a majority of the participants (50.4%) defined with pathologic tinnitus, had a score between 0 and 17 on the TFI. With a TFI score of 18 or more, the tinnitus can

be interpreted as at least a small problem. We found that 49.7% of the 216 pathologic tinnitus participants (or 11% (unweighted) (103 out of 932) out of the total participants or 8.9% (weighted) (83 of 932)) had a TFI score of 18 or more. This is similar to the study by Oosterloo et al, they studied a Dutch population sample of older adults (≥ 50 years) out of 2020. They found that for 12.3% of the people with tinnitus, a positive score was noted on the single question *does the tinnitus interfere with daily life?*.(4) This underlines once again that even our definition of pathologic tinnitus entailing duration and frequency does not seem to correlate with the impact of tinnitus on daily life (as measured by the TFI). This might suggest that in order to identify people with pathologic tinnitus, one should rely on validated tinnitus measures of impact on daily life after people are indicated as having tinnitus based on the experienced sounds.(1)

However, the use of validated measures in population studies is difficult because of logistical issues due to the lengthiness of the questionnaires. Contrary Biswas et al. propose to use a single-item question to assess tinnitus severity: ''over the past year, how much do these noises in your head or ears worry, annoy or upset you when they are at their worst?"(16) Interestingly we also asked the participants a single-item question to assess severity: "how big a problem is your tinnitus at this moment?" If combined, we found that 164 of 216 (75.9%) judged tinnitus to be at least a small problem. This was 17.6% (unweighted) or 15.7% (weighted) of all 932 participants. The difference in prevalence numbers between measuring the impact of tinnitus with a multi-item questionnaire or a single-item question, again shows the importance of reaching consensus how to handle this issue. Perhaps we have still yet to find the optimal tool to measure the impact of tinnitus on daily life for similar study settings. Still, we only asked participants to fill out both the TFI and the question ''how big a problem is your tinnitus?'' if they met our definition of having pathologic tinnitus. It would also be interesting to see if those who did not meet our definition of pathologic tinnitus, but did experience tinnitus, considered their tinnitus to be a problem.

Strengths and limitations

Several strengths and limitations are applicable to this study. The first strength is that the study was performed in a sample of the Dutch population, rather than a selected cohort. The second includes the extensiveness and specificity of questioning regarding the tinnitus prevalence. Multiple factors were included in the definition and related to prevalence. The gender distribution of the participants to the questionnaire was similar to that of the Dutch population in 2018(15). However, a limitation of our study is that the age distribution of the respondents was not representative of the Dutch population.(15) The higher age in our sample and the knowledge that tinnitus prevalence increases with age could mean that our numbers overestimated

the prevalence numbers in the real population. This is also illustrated by the lower prevalence numbers when weighted for age and gender, which probably better reflect the prevalence in the population. Although, we had 932 participants, a response rate of 41.4% was reached, which could result in selection bias. Nivel consumer panel members sign up to receive questionnaires on all sorts of healthcare topics, which resulted in response rates of 50-60% historically. The low response rate to the current questionnaire could be related to the lengthiness of the complete questionnaire (eight pages), or the topic of the questionnaire.

Recommendations

The lack of a clear definition, and subsequently the lack of prevalence numbers in general populations around the world, are two important obstacles that hinder the search for a curative treatment.(6,16) The difficulties of defining tinnitus with and without suffering, have recently been addressed by the Tinnitus Research Initiative (TRI) in a conceptual book chapter.(17,18) The authors propose a different definition for tinnitus and tinnitus disorder. They argue that tinnitus becomes a tinnitus disorder ''when associated with emotional distress, cognitive dysfunction, and/or automatic arousal, leading to behavioral changes and functional disability. (14)"[p8.] Next they also advise frequency and duration to be used in the definition of tinnitus; they advise that tinnitus should occur for a minimum of five minutes a day on the majority of days. In order to find a treatment for tinnitus we believe that tinnitus research needs to go back to its basics. A clear standardized definition of pathologic tinnitus is the obvious starting point. Only then can true comparisons between different study populations be made(1). We therefore encourage all researchers to adapt the definitions as recently proposed by the TRI. (17)

Conclusion

In this study we found that 36.6% of all participants experienced tinnitus for whatever amount of time over the last year. Of those 23.2% met our definition of pathologic tinnitus, which was based on a combination of duration and frequency over the last year. When weighted for age and gender this decreased to 21.0%.. 48.6% of the pathologic tinnitus participants had a TFI score that indicates that they consider their tinnitus to be at least a small problem (11% of the total sample (unweighted) or 8.9% (weighted)). This study demonstrates that tinnitus prevalence numbers vary with different definitions. It therefore highlights the need to use a uniform definition of tinnitus to compare outcomes.

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CHAPTER 4

Differences in Characteristics between people with Tinnitus that Seek Help and that Do Not.

Scientific Reports. 2021 November 25;11(1):22949

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Abstract

Knowledge on characteristics of people that seek help for tinnitus is scarce. The primary objective of this study was to describe differences in characteristics between people with tinnitus that seek help compared to those who do not seek help. Next, we described differences in characteristics between those with and without tinnitus. In this cross-sectional study, we sent a questionnaire on characteristics in different domains; demographic, tinnitus-specific, general- and psychological health, auditory and noise- and substance behaviour. We assessed if participants had sought help or planned to seek help for tinnitus. Tinnitus distress was defined with the Tinnitus Functional Index. Differences between groups (help seeking: yes / no, tinnitus: yes / no) were described. 932 people took part in our survey. Two hundred and sixteen participants were defined as having tinnitus (23.2%). Seventy-three of those sought or planned to seek help. A constant tinnitus pattern, a varying tinnitus loudness, and hearing loss, were described more frequently in help seekers. Help seekers reported higher TFI scores. Differences between help seekers and people not seeking help were mainly identified in tinnitus- and audiological characteristics. These outcomes might function as a foundation to explore the heterogeneity in tinnitus patients.

Introduction

Although the word tinnitus originates from the Latin word 'tinnire', which translates into ''to ring'', people with tinnitus can experience many different sounds such as buzzing or humming (1). Some people even describe to hear the sound of a complete orchestra playing in their ear (2). Not only is there variance in the nature of the sound, also the location, pitch and loudness differ between patients. Besides, the consequences of tinnitus on daily life vary widely among individuals due to its associated co-morbidities such as concentration-, sleep- or mental health problems. (3) In a recent paper the authors therefore advocate to differentiate between the experience of tinnitus, and the associated suffering due to the tinnitus, which they refer to as tinnitus disorder.(4) All these factors contribute to the complexity and heterogeneity of tinnitus.(3) Tinnitus prevalence numbers range between 5.1 and 42.7% due to differences in definitions and the studied populations.(5)

It is commonly believed that one of the explanations of the heterogeneity might be the existence of subtypes of tinnitus patients. Several attempts have been made to define these subtypes, but clinically usable types remain to be found.(6) In a recent review on tinnitus subtyping, the authors identified 64 articles that had reported on tinnitus subtyping.(6) They extracted 94 different variables which were processed in a framework of the most commonly used variables in subtyping. Tinnitus severity, hearing ability, age, and depressive symptoms were found to be the top four variables that were significant or important for classification.(6) However such characteristics can cover many domains such as demographic, audiological or psychological measures. In order to understand the role of these characteristics in tinnitus patients, we first need to know the differences between people with and without tinnitus. The development of the ESIT-SQ emphasizes this. One of their objectives was to: "create a questionnaire that would allow standardized data collection from the entire adult population, tinnitus and non-tinnitus, which are essential for investigating mechanisms associated with tinnitus"(7)[p3]

Another challenge of the heterogeneous aspect of tinnitus is that there is a great variation in the help seeking behavior of those affected. Understanding the differences between those that seek help versus those that do not seek help for their tinnitus might help to illuminate the heterogeneity issue. What are the reasons from a transition from experiencing tinnitus into having tinnitus disorder? (4) A Swedish survey study, performed in 2000 in a randomly selected population sample, analyzed characteristics related to seeking help. They showed that help seeking tinnitus participants had higher scores in questionnaires assessing psychological problems such as anxiety and negative mood compared to non-help seeking tinnitus patients

(8). An Israeli study from 1993, in young male active army personnel (n = 100), with both patients with and without tinnitus, identified differences between those that sought help and those that did not. Help seekers had poorer coping techniques, and their psychiatric symptomatology was more severe than the people that did not seek help (9). A third study in tinnitus patients from a hospital setting in Sweden performed in 1993 identified differences between so-called "complainers" and ''non-complainers". ''Complainers'' more often reported a combination of tinnitus sounds and had more problems with concentration than ''non-complainers'' (10).

Combining the knowledge about the differences in characteristics between those with and without tinnitus, and those seeking help versus those not seeking help for their tinnitus is of importance. We believe descriptive studies of differences in both study groups will help the international tinnitus community in their search for tinnitus subtypes and in the ultimate goal to create effective treatments for specific subgroups affected. Besides this, this knowledge is of importance to optimize health care in terms of counselling and diagnostics of those affected.

Therefore, in this study our main objective was to describe the differences in characteristics between people with tinnitus that seek help versus those who do not seek help in a random sample of the Dutch general population. Next, to be able to interpret outcomes as a secondary aim we compared characteristics of people with and without tinnitus. Differences in demographic-, tinnitus-specific-, general health-, psychological health-, audiological characteristics, and characteristics about noise- and substance behaviour were assessed.

Methods

This paper was written according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement (11). (Supplementary Methods S1)

Study design and population

For this observational study we prospectively gathered data by means of a questionnaire send to Dutch adults. They were members of the Dutch Health Care Consumer panel.(12)

"The aim of the Nivel Dutch Health Care Consumer Panel (DHCCP) is to measure, at national level, opinions on and knowledge about health care and the expectations and experiences with health care. The Consumer Panel is a so-called 'access panel'. An access panel consists of a large number of persons who have agreed to answer questions on a regular basis. In addition, many background characteristics of these persons (for example age, level of education, income, self-reported general health) are known.(12)" At the time of this study (January 2020), the panel consisted of approximately 12,000 people aged 18 years and older. "From the access panel samples can be drawn for every separate survey. It is not possible for people to sign up on their own initiative. The panel is renewed on regular basis. Renewal is necessary to make sure that members do not develop specific knowledge of, and attention for, healthcare issues, and that no 'questionnaire fatigue' occurs. Moreover, renewal compensates for panel members who, for example, have died or moved without informing the panel about the new address."(12)

This study is part of a larger study on tinnitus prevalence, characteristics and health care usage. The study sample therefore entails those DHCCP panel members (N=2251), who agreed to combine their survey answers with health care consumption data as registered by their general practitioner.(13)A previously published study on tinnitus prevalence was based on the same data.(14)

Outcome assessment

Logistics

A questionnaire was sent to panel members of the Dutch Health Care Consumer Panel. The questionnaire was sent via postal services or online. This depended on the preference of the panel member. The postal survey was sent on 14-01-2020. One postal reminder was sent on 30-01-2020. The online survey was sent on the 16-01-2020. Two online reminders were sent on 23-01-2020 and 30-01-2020. The survey was closed on 14-02-2020. Please find the questionnaire in Supplementary Methods S2.

Questionnaire outline

The survey was created by MR (medical doctor), AS (ENT surgeon), IS (epidemiologist) and AB (senior researcher Nivel). Characteristics among different domains were collected: demographic, tinnitus-specific, general health, psychological health, audiological, and noise- and substance behaviour. The full questionnaire can be found in Supplementary Methods S2. The overall survey structure was based on the European School for Interdisciplinary Tinnitus Research Screening Questionnaire (ESIT-SQ), which consists of two parts(7). Part one consist of 17 questions regarding individual characteristics in people with or without tinnitus. The second part is only meant for people with tinnitus. It consists of 22 questions regarding tinnitus characteristics. The set-up of our survey was similar: a part to be answered by all participants, and a part that was specifically for those that had tinnitus. For the part to be answered by all participants, we directly used or used a variation on 13 of 17 questions of the ESIT-SQ part A. Survey items about the characteristics of tinnitus were based on the Tinnitus Sample Case History Questionnaire (TSCHQ) and the ESIT-SQ part B.(7,15,16) The TSCHQ consists of 35 questions concerning tinnitus history and tinnitus characteristics. We did not use the full versions of one of both questionnaires due to space limitations. Questions were either an exact copy of one of two questionnaires or questions/answer options were combined. Twelve questions were based or an exact copy of the 22 questions of ESIT-SQ part B. Twenty-three questions were based on or an exact copy of the 35 questions of the TSCHQ.

Demographics

Demographic data were gathered when people became a member of the panel and were provided by Nivel for this study. These include data about educational level, marital status, social position (e.g. employed / unemployed / student), ethnicity, age (calculated at date of sending of the questionnaire), gender, and net income of the households of the participating panel members, self-reported general health and self-reported mental health.

Tinnitus classification and definitions

We assessed the presence of tinnitus with three questions. We described tinnitus as *Tinnitus is the hearing of e.g. a beep, whistle, hissing, zoom or another sound without the actual presence of the sound in your surroundings. This can last for a very short amount of time or a whole day.* First, the participants were asked whether they experienced tinnitus over the last year. Next, a question about duration was asked (tinnitus lasting < 5 minutes, 5-60 minutes, ≥60 minutes or continuously). The third question was about the frequency of the experienced sound (daily or almost daily, weekly, monthly, less than once a year). We subsequently defined people as having tinnitus when they experienced the sound for 5 – 60 minutes (daily or almost daily or weekly), or tinnitus

for ≥60 minutes or continuously (daily or almost daily or weekly or monthly). This was based on literature and expert opinion.(5)

Tinnitus characteristics

The following items were assessed: whether the participant had sought help for tinnitus or planned to seek help and the source of the help, tinnitus pattern, subjective problem of tinnitus, acute or chronic tinnitus (<3 months, 3-6 months, ≥6 months), manner of the tinnitus start, number of different sounds, pulsatile nature, whether the tinnitus varied in loudness, the pitch and location of the tinnitus, the intrusiveness of the tinnitus, influencing factors, potential causes.

Definition of help seeking tinnitus participants

We defined participants as help seeking tinnitus participants, if they had sought help in the past or planned to seek help for their tinnitus.

Tinnitus distress

The impact of tinnitus on daily life was assessed with the multi-item Dutch translation of the Tinnitus Functional Index (TFI) questionnaire. (17,18) This questionnaire consists of 25 questions, with answers on an 11-point Likert scale. The final score ranges between 0-100; a score between 0-17 can be interpreted as not a problem, 18-31 as a small problem, 32-53 as a moderate problem, 54-72 as a big problem and 73-100 as a very big problem. The 25 questions of the TFI are a combination of scores of impact on daily life out of eight subcategories, intrusiveness, sense of control, cognition, sleep, hearing, relaxation, quality of life and emotions, each covered by 3 to 4 questions. The TFI was developed and validated in the United States of America and translated and validated from English to Dutch in 2014. The Dutch translation by Tromp et al. holds a high internal consistency (Cronbach's alpha of 0.91) (18).

General health characteristics

The following items were asked in the questionnaire to assess general health: the presence of chronic pain, family history of certain diseases, and presence of certain diseases as diagnosed by a doctor.

Psychological health characteristics

Symptoms of anxiety and depression were measured with the Hospital Anxiety and Depression Scale (HADS), The HADS is a 14-item questionnaire that measures symptoms of anxiety (HADS-A; seven items) and depression (HADS-D; seven items) on a four point scale.(19) The HADS was translated and validated to Dutch by Spinhoven et al (Cronbach's alpha ranges between 0.71 and 0.90 for both subscales and the total scale)(20). The total scores range from 0 to 21. A score of 8 or higher

indicates a potential anxiety or depression.(19,20)

Audiological characteristics
The following items were assessed in the questionnaire to assess audiological characteristics: hyperacusis, presence of hearing problems, use of hearing aids/cochlear implants/sound generator or tinnitus maskers, and auditory hallucinations.

Characteristics on noise- and substance behaviour
The following items were assessed in the questionnaire to assess noise and substance behaviour: the use of head- or earphones, exposure to potential damaging sound levels (subjectively judged), the use of hearing protection, smoking habits, drug use and alcohol consumption.

Data handling & Ethics
Data are analyzed anonymously and the privacy of the panel members is guaranteed, as is described in the privacy policy of the Dutch Health Care Consumer Panel. This complies with the General Data Protection Regulation (GDPR). According to Dutch legislation, neither obtaining informed consent nor approval by a medical ethics committee is obligatory for conducting research through the panel (CCMO, 2020). (12) The Medical Research Ethics Committee (MREC) of the University Medical Center Utrecht (UMC Utrecht) confirmed on November 20th 2019, that the Medical Research Involving Human Subjects Act (WMO) does not apply to this study and that therefore official approval by the MREC is not required under the Human Subjects Act (MREC local protocol number 19-745). This study was performed according to the declaration of Helsinki.

Statistical analysis
Statistical analyses were performed with SPSS version 26.0.0.1.(21)Normality of variables was visually assessed. Frequencies, means, standard deviation (SD), medians and interquartile ranges (IQR) were calculated for the total study group, participants with or without tinnitus and help seeking versus non-help seeking participants. A p value of 0.05 or lower was considered statistically significant. Logistic regression was only performed for a subset of the characteristics. These were based on known risk factors from the literature for tinnitus and expert opinion. The following characteristics were assessed, these were based on the answers to the different questions in the survey: tinnitus pattern, subjective problem of tinnitus, duration of tinnitus, varying loudness, tinnitus intrusiveness, TFI score and TFI grades, chronic pain, HADS-A, HADS-D, hyperacusis, hearing problems, the use of different hearing aids, auditory hallucinations, use of head/ear phones, potential damaging sound levels, use of hearing protection, gender, age and educational level.

Results

Study sample
Of the 2251 panel members who were invited to participate in the survey 932 (41.4%) filled out the questionnaire. The median age of the participants was 67.0 (IQR 17) years and 52.4% was female. (Table 1).

Tinnitus and its characteristics
Out of the 932 participants, 216 (23.2%, 26 missing) were classified as having tinnitus based on the set criteria of duration and frequency of the experienced sound. (Table 2) Out of these 216 tinnitus participants (91.7%, 1 missing,) 198 experienced their tinnitus for 6 months or more. The total TFI-score could be calculated for 212 tinnitus participants (4 missing) and the median total score was 16.6 (IQR 21.8). (Table 3)

Comparison of participants with and without tinnitus
Demographic characteristics
Female participants were less likely to have tinnitus compared to male participants (OR 0.60 (95% CI 0.44-0.82) p = 0.001). (Table 1) Compared to participants with a low level of education, participants with a higher educational level had higher odds to have tinnitus (OR 1.72 (1.07 -2.77)p = 0.025). (Table 1)

Characteristics on general- and psychological health
Compared to participants without chronic pain, participants with chronic pain were not more likely to have tinnitus (OR 0.87 (95% CI 0.57-1.32), p=0.511). Compared to not having tinnitus, Individuals with a higher score on the HADS-A or the HADS-D did not have higher odds to have tinnitus ((OR HADS-A: 0.99 (95% CI 0.94 – 1.03) p = 0.533, HADS-D (OR 0.99 (95% CI 0.94-1.04) p = 0.697).

Audiological characteristics and characteristics on noise exposure
The presence of any hearing problem was more frequent in tinnitus participants (135 of 216 (62.5%, 2 missing)) compared to non-tinnitus participants (248 of 690 (36%, 7 missing) (combination of answer options: small-, mediocre-, severe problems and I hear nothing). Compared to participants that did not report any exposure to potentially damaging sound levels, participants with more exposure to potential damaging sound levels had higher odds to have tinnitus multiple times a week but not daily (OR 2.97 (95% CI 1.27-6.92) p = 0.012), once a week (OR 2.23 (95% CI 1.04-4.81) p = 0.041), less than once a week (OR 1.49 (95% CI 1.05-2.12) p = 0.026)). (Table 4)

Table 1. Demographic characteristics.

Demographic		Total %	Tinnitus %			Help %		
			No	Yes	OR (95% CI)	No	Yes	OR (95% CI)
Gender	Male	444 (47.6)	309 (44.8)	124 (57.4)	Ref	76 (53.5)	47 (64.4)	Ref
	Female	488 (52.4)	381 (55.2)	92 (42.6)	0.60 (0.44 - 0.82)*	66 (46.5)	26 (35.6)	0.64 (0.36 - 1.14)
	Missing	0 (0.0)	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Age[1]		67.0 (17)	67 (19)	66.5 (15)	1.01 (0.996 - 1.021)	66 (16)	69 (13)	1.02 (0.997 - 1.052)
	N =	932	690	216		142	73	
Age categorized	18-39	29 (3.1)	28 (4.1)	1 (0.5)		1 (0.7)	0 (0.0)	
	40-64	349 (37.4)	261 (37.8)	85 (39.4)		60 (42.3)	25 (34.2)	
	65+	554 (59.4)	401 (58.1)	130 (60.2)		81 (57.0)	48 (65.8)	
	Missing	0 (0.0)	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Highest completed educational level	Low	157 (16.8)	118 (17.1)	27 (12.5)	Ref	16 (11.3)	11 (15.1)_	Ref
	Middle	337 (40.5)	290 (42.0)	78 (36.1)	1.18 (0.72 - 1.91)	56 (39.4)	21 (28.8)	0.55 (0.22 - 1.37)
	High	372 (39.9)	264 (38.3)	104 (48.1)	1.72 (1.07 - 2.77)*	66 (46.5)	38 (52.1)	0.84 (0.25 - 1.99)
	Missing	26 (2.8)	18 (2.6)	7 (3.2)		4 (2.8)	3 (4.1)	
Marital status	Married	617 (66.2)	449 (65.1)	152 (70.4)		103 (72.5)	49 (67.1)	
	Divorced	73 (7.8)	48 (7.0)	23 (10.6)		11 (7.7)	12 (16.4)	
	Widowed	90 (9.7)	70 (10.1)	14 (6.5)		11 (7.7)	3 (4.1)	
	Never been married	146 (15.7)	120 (17.4)	24 (11.1)		15 (10.6)	9 (12.3)	
	Missing	6 (0.6)	3 (0.4)	3 (1.4)		2 (1.4)	0 (0.0)	
Social position	School / studying	17 (1.8)	13 (1.9)	4 (1.9)		4 (2.8)	0 (0.0)	
	Employed	410 (44.0)	305 (44.2)	98 (45.4)		70 (49.3)	28 (38.4)	
	Unemployed (work seeking)	31 (3.3)	22 (3.2)	9 (4.2)		5 (3.5)	4 (5.5)	
	Incapacitated	36 (3.9)	26 (3.8)	9 (4.2)		7 (4.9)	2 (2.7)	
	Housewife/husband	118 (12.7)	90 (13.0)	20 (9.3)		16 (11.3)	4 (5.5)	
	Retired	393 (42.2)	292 (42.3)	86 (39.8)		50 (35.2)	35 (47.9)	
	Other	39 (4.2)	30 (4.3)	9 (4.2)		6 (4.2)	3 (4.1)	
	Missing	0 (0.0)		0 (0.0)				
Ethnicity[2]	Native Dutch	873 (93.7)	653 (94.6)	197 (91.2)		129 (90.8)	67 (91.8)	
	Western non-native Dutch	52 (5.6)	31 (4.5)	18 (8.3)		13 (9.2)	5 (6.8)	

Table 1, CONTINUED.

Demographic		Total %	Tinnitus %			Help %		
			No	Yes	OR (95% CI)	No	Yes	OR (95% CI)
	Non-western non-native Dutch	6 (0.6)	5 (0.7)	1 (0.5)		0 (0.0)	1 (1.4)	
	Missing	1 (0.1)	1 (0.1)	0 (0.0)		0 (0.0)	0 (0.0)	
Net income	€ 0- 2100	320 (34.3)	233 (33.8)	67 (31.0)		41 (28.9)	25 (34.2)	
	€ 2100 - 2300	70 (7.5)	56 (8.1)	13 (6.0)		10 (7.0)	3 (4.1)	
	€ 2300 - 3300	263 (28.2)	191 (27.7)	69 (31.9)		39 (27.5)	30 (41.1)	
	€>3300	241 (25.9)	176 (25.5)	64 (29.6)		52 (36.6)	12 (16.4)	
	Don't want to say	0 (0.0)	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
	Missing	38 (4.1)	34 (4.9)	3 (1.4)		0 (0.0)	3 (4.1)	

Please see Supplementary Table S2 for answer to social position, other.
[a] Median (IQR) *p<0.05. bBased on country of birth of the parent

Help seeking participants

Of the 216 tinnitus participants, 72 (1 missing, 33.3%) had sought help for their tinnitus. Of the remaining 143 of 216 (66.2%, 1 missing), one (0.7%, 2 missing) planned to seek help. We defined 73 of 216 tinnitus participants (33.8%, 1 missing), as a help seeking tinnitus participant, and 142 of 216 (65.7% 1 missing) as non-help seeking tinnitus participants. Most help seekers were treated or planned treatment at a doctor (39 of 73, (53.4% 9 missing)), followed by audiological care (21 of 73, (28.8% 9 missing)). (Table 2)

Table 2. Tinnitus participants and help seeking participants with tinnitus.

		N	%
Tinnitus for 5 – 60 minutes	*Daily or almost daily*	*20*	*31.3*
	Weekly	*20*	*31.3*
	Monthly	16	25.0
	≤ 1 time per year	5	7.8
	Missing	3	4.7
Tinnitus for ≥ 60 or continuously	*Daily or almost daily*	*153*	*80.5*
	Weekly	*13*	*6.8*
	Monthly	*10*	*5.3*
	≤ 1 time per year	3	1.6
	Missing	11	5.8
Tinnitus participant	Yes	216	23.2
	No	690	74.0
	Missing	26	2.8
Sought help	Yes	72	33.3
	No	143	66.2
	Missing	1	0.5
If no. plans to seek help	Yes	1	0.7
	No	140	97.9
	Missing	2	1.4
Source of treatment	Psychiatric	0	0.0
	Psychologic	6	8.2
	Audiological	21	28.8
	Physiotherapy	2	2.7
	Self-management	2	2.7
	Alternative medicine	8	11.0
	Doctor	39	53.4
	Other	7	9.6
	Missing	9	12.3
Help seeking tinnitus participant	Yes	73	33.8
	No	142	65.7
	Missing	1	0.5

Tinnitus participant were defined as experiencing tinnitus for 5-60 minutes daily or almost daily, or weekly or 60 minutes or more or continuously daily or almost daily, weekly or monthly. These are written cursive. Please see Supplementary Table S2 for answer to type of tinnitus help, other.

Table 3. Tinnitus characteristics.

Tinnitus Characteristics		Experiencing Tinnitus n (%)	Tinnitus help seeking n (%)		OR (95% CI)
			No	Yes	
Pattern	Constant	135 (62.5)	77 (54.2)	58 (79.5)	3.26 (1.69 – 6.30)*
	Intermittent	80 (37.0)	65 (45.8)	15 (20.5)	Ref
	Missing	1 (0.5)	0 (0.0)	0 (0.0)	
Subjective problem of tinnitus	No	51 (23.6)	48 (33.8)	3 (4.1)	Ref
	Small	105 (48.6)	70 (49.3)	35 (47.9)	8.0 (2.33 – 27.51)*
	Reasonable	43 (19.9)	20 (14.1)	23 (31.5)	18.4 (4.96 – 68.29)
	Large	12 (5.6)	4 (2.8)	8 (11.0)	32.0 (6.00 – 170.61)*
	Very large	4 (1.9)	0 (0.0)	4 (5.5)	Error
	Missing	1 (0.5)	0 (0.0)	0 (0.0)	
Tinnitus begin	< 3 months	8 (3.7)	7 (4.9)	1 (1.4)	Ref
	3 till 6 months	9 (4.2)	8 (5.6)	1 (1.4)	0.88 (0.05 – 16.74)
	≥ 6 months	198 (91.7)	127 (89.4)	71 (97.3)	3.91 (0.47 – 32.45)
	Missing	1 (0.5)	0 (0.0)	0 (0.0)	
# of different sounds	1	167 (77.3)	117 (82.4)	50 (68.5)	
	More than 1	48 (22.2)	25 (17.6)	23 (31.5)	
	Missing	1 (0.5)	0 (0.0)	0 (0.0)	
Pulsatile	Yes	23 (10.6)	15 (10.6)	8 (11.0)	
	No	170 (78.7)	114 (80.3)	56 (76.7)	
	Missing	23 (10.6)	13 (9.2)	9 (12.3)	
Manner of tinnitus' start	Gradually	147 (68.1)	103 (72.5)	44 (60.3)	
	Suddenly	61 (28.2)	34 (23.9)	27 (37.0)	
	Missing	8 (3.7)	5 (3.5)	2 (2.7)	
Varying loudness	Yes	106 (49.1)	58 (40.8)	48 (65.8)	2.97 (1.62 – 5.46)*
	No	101 (46.8)	79 (55.6)	22 (30.1)	Ref
	Missing	9 (4.2)	5 (3.5)	3 (4.1)	
Pitch	High	76 (35.2)	55 (38.7)	21 (28.8)	
	Average	75 (34.7)	48 (33.8)	27 (37.0)	
	Low	42 (19.4)	26 (18.3)	16 (21.9)	
	I don't know	16 (7.4)	9 (6.3)	7 (9.6)	
	Missing	7 (3.2)	4 (2.8)	2 (2.7)	
Intrusiveness[1]		4 (5)	3 (4)	5 (4)	1.298 (1.15 – 1.47)*
	N =	215	142	73	
Location	Right ear	17 (7.9)	9 (6.3)	8 (11.0)	
	Left ear	30 (13.9)	16 (11.3)	14 (19.2)	
	Both > right ear[2]	28 (13.0)	18 (12.7)	10 (13.7)	
	Both > left ear[3]	37 (17.1)	25 (17.6)	12 (16.4)	
	Both equal	79 (36.6)	58 (40.8)	21 (28.8)	
	Inside head	39 (18.1)	23 (16.2)	16 (21.9)	
	Other	2 (0.9)	1 (0.7)	1 (1.4)	
	Missing	9 (4.2)	5 (3.5)	3 (4.1)	

Table 3. CONTINUED.

Tinnitus Characteristics		Experiencing Tinnitus n (%)	Tinnitus help seeking n (%)		OR (95% CI)
			No	Yes	
Influence	Presence of loud sounds	57 (26.4)	36 (25.4)	21 (28.8)	
	Music or surrounding sounds	69 (31.9)	44 (31.0)	25 (34.2)	
	Head or neck movements	15 (6.9)	10 (7.0)	5 (6.8)	
	Touching the head with arms/hands	5 (2.3)	2 (1.4)	3 (4.1)	
	Sleep during the day	13 (6.0)	7 (4.9)	6 (8.2)	
	Good sleep quality	34 (15.7)	20 (14.1)	14 (19.2)	
	Stress	47 (21.8)	28 (19.7)	19 (26.0)	
	Medicine	5 (2.3)	4 (2.8)	1 (1.4)	
	Hearing aids	24 (11.1)	10 (7.0)	14 (19.2)	
	Nothing	68 (31.5)	48 (33.8)	20 (27.4)	
	Other	22 (10.2)	9 (6.3)	13 (17.8)	
	Missing	2 (0.9)	1 (0.7)	0 (0.0)	
Potential cause	Flu, cold or other infection	22 (10.2)	10 (7.0)	12 (16.4)	
	Medicinal (side) effects	9 (4.2)	5 (3.5)	4 (5.5)	
	Exposure to loud sounds	46 (21.3)	27 (19.0)	19 (26.0)	
	Change in hearing	18 (8.3)	9 (6.3)	9 (12.3)	
	Sudden deafness	6 (2.8)	3 (2.1)	3 (4.1)	
	Changes in air pressure	14 (6.5)	10 (7.0)	4 (5.5)	
	Stress/anxiety/ depression	14 (6.5)	9 (6.3)	5 (6.8)	
	Head/neck trauma	5 (2.3)	2 (1.4)	5 (6.8)	
	Jaw problems (TMD)	2 (0.9)	0 (0.0)	2 (2.7)	
	Earwax plug	9 (4.2)	4 (2.8)	5 (6.8)	
	Fullness / pressure in ears	23 (10.6)	13 (9.2)	10 (13.7)	
	Other	16 (7.4)	8 (5.6)	8 (11.0)	
	Don't know	99 (45.8)	74 (52.1)	25 (34.2)	
	Missing	2 (0.9)	1 (0.7)	0 (0.0)	
TFI[1]		16.6 (21.8)	14.7 (19.1)	22.8 (43.1)	1.04 (1.02 – 1.06)*
	N =	212	140	72	
TFI ranges	0-17	109 (50.4)	83 (58.5)	26 (35.6)	Ref
	18-31	52 (24.1)	35 (24.6)	17 (23.3)	1.55 (0.75 – 3.21)
	32-53	26 (12.0)	17 (12.0)	9 (12.3)	1.69 (0.67 – 4.24)
	54-72	22 (10.2)	4 (2.8)	18 (24.7)	14.37 (4.46 – 46.26)*
	73-100	3 (1.4)	1 (0.7)	2 (2.7)	6.39 (0.56 – 73.29)
	Missing	4 (1.9)	2 (1.4)	1 (1.4)	
TFI Subscales[1]	Intrusiveness	26.7 (32.5)	23.3 (30.0)	40.0 (38.3)	
	N =	212	139	73	
	Sense of control	43.3 (28.3)	40.0 (22.5)	50.0 (35.0)	

Table 3. CONTINUED.

Tinnitus Characteristics		Experiencing Tinnitus n (%)	Tinnitus help seeking n (%)		OR (95% CI)
			No	Yes	
	N =	213	140	73	
	Cognitive	10.0 (30.0)	6.7 (21.7)	15.0 (47.5)	
	N =	211	141	70	
	Sleep	10.0 (26.7)	3.3 (20.0)	16.7 (48.3)	
	N =	213	140	73	
	Auditory	20.0 (49.2)	13.3 (35.0)	30 (56.7)	
	N =	212	141	71	
	Relaxation	10.0 (26.7)	10.0 (20.0)	18.3 (46.7)	
	N =	212	140	72	
	Quality of Life	2.5 (20.0)	0.0 (15.0)	12.5 (47.5)	
	N =	212	140	72	
	Emotional	6.7 (20.0)	3.3 (13.3)	20 (41.7)	
	N =	213	140	73	

[1]Median (IQR) *p <0.05. [2]Both ears, more in the right ear [3]Both ears, more in the left ear. Please see Supplementary Table S2 for answer to location of tinnitus, other; influence of tinnitus, other; potential cause of tinnitus, other.

Comparison of help seekers versus non-help seekers

Demographics

Twenty-six of 73 help seekers (HS) were female (35.6%, 0 missing), compared to 66 of 142 (46.5%, 0 missing) of non-help seekers (NHS). Compared to males, females were not more likely to seek help for tinnitus (OR 0.64 (95% CI 0.36 – 1.14) p = 0.129). The help-seekers had a median age of 69 (IQR 13) years, compared to 66.0 (IQR 16) years of age in the in the non-help seekers. (Table 1)

Tinnitus characteristics

Help seeking tinnitus participants more often considered their tinnitus to be a reasonable (23 out of 73 (31.5%)) or a large problem (8 of 73 (11.0%)), compared to the non-help seekers ((respectively 20 of 142 (14.1%, 0 missing) (OR 18.4 (95% CI 4.96-68.29), p =0.000) and (4 of 142 (2.8%, 0 missing) (OR 32.0 (6.0-170.6), p = 0.000))). Individuals with a higher TFI score were more prone to seek help, compared to not seek help (OR 1.04 (95% CI 1.02-1.06), p=0.000). (Table 3) Twenty-three of 73 (31.5%, 0 missing) of the help seekers experienced more than one sound, compared to 25 of 142 (17.6, 0 missing) of the non-help seekers. The experience of a constant tinnitus pattern compared to an intermittent pattern increased the odds of seeking help (OR 3.26 (95% CI 1.69 – 6.30) p = 0.000). A varying tinnitus loudness compared to a non-varying loudness increased the odds of seeking help (OR 2.97 (95% CI 1.62 – 5.46) p=0.000).

Characteristics on general- and psychological health

In participants with or without chronic pain the odds for seeking help were equal (OR 0.86 (95% CI 0.39-1.87), p = 0.698). Participants with higher HADS-A scores or HADS-D scores were more likely to seek help ((HADS-A OR 1.11 (1.03-1.20), p =0.011), (HADS-D OR 1.10 (95% CI 1.02-1.18), p=0.012)). (Table 4) Compared to non-help seekers, help seekers had higher percentages of the following diseases diagnosed by a physician: dental problems (HS: 13 of 73, (17.8%, 0 missing), NHS: 11 of 142, (7.7%, 6 missing), depression (HS: 10 of 73, (13.7%, 0 missing), NHS: 5 of 142, (3.5%, 6 missing)), balance problems/ vertigo (HS: 13 of 73 ,(17.8%, 0 missing), NHS: 9 of 142, (6.3%, 6 missing)) and hearing loss (HS: 26 of 73, (35.6%, 0 missing), NHS: 25 of 142 (17.6%, 6 missing)). (Supplementary Table S1)

Audiological characteristics and characteristics on noise exposure

Participants who judged sounds as a mediocre problem (hyperacusis) were more likely to seek help for tinnitus than not to seek help for their tinnitus (HS: 18 of 73 (24.7%, 1 missing), NHS: 19 of 142 (13.4%, 2 missing)) compared to 'no problem' (OR 2.21 (95% CI 1.04-4.70), p = 0.039)). The subjective presence of any hearing problem was more frequent in help seeking tinnitus participants (HS: 56 of 73 (76.7%, 0 missing) versus non-help seeking participants (79 of 142 (55.6%, 2 missing) (combination of answer options: small-, mediocre-, severe problems and I hear nothing). (Table 4) Participants that had exposed themselves to potential damaging sound levels were not more likely to seek help compared to not seek help (reference: no exposure to damaging sound levels, daily: (OR 1.16 (95% CI 0.19-7.18) p = 0.88), multiple times a week: (OR 0.43 (95% CI 0.09-2.13) p = 0.43), once a week: (OR 1.44 (95% CI 0.42-5.00) p =0.56), less than once a week: (OR 0.75 (95% CI 0.39-1.44) p= 0.38)

Table 4. Characteristics on general health, psychological health, audiological characteristics and noise and substance behaviour.

Characteristic		Total %	Tinnitus %		OR (95% CI)	Help %		OR (95% CI)
			No	Yes		No	Yes	
General Health								
Chronic pain	Yes	164 (17.6)	123 (17.8)	35 (16.2)	0.87 (0.57 – 1.32)	24 (16.9)	11 (15.1)	0.86 (0.39 – 1.87)
	No	745 (79.9)	548 (79.4)	179 (82.9)	Ref	116 (81.7)	62 (84.9)	Ref
	Missing	23 (2.5)	19 (2.8)	2 (0.9)		2 (1.4)	0 (0.0)	
Family History	Tinnitus	101 (10.8)	52 (7.5)	43 (19.9)		29 (20.4)	14 (19.2)	
	Epilepsy	47 (5.0)	37 (5.4)	10 (4.6)		7 (4.9)	3 (4.1)	
	Hearing problem[3]	121 (13.0)	78 (11.3)	37 (17.1)		26 (18.3)	11 (15.1)	
	Nerve and/or muscle disease	56 (6.0)	41 (5.9)	13 (6.0)		8 (5.6)	5 (6.8)	
	Syndromes	18 (1.9)	15 (2.2)	3 (1.4)		1 (0.7)	2 (2.7)	
	Migraines	163 (17.5)	120 (17.4)	40 (18.5)		25 (17.6)	14 (19.2)	
	None of the above	538 (57.7)	421 (61.0)	106 (49.1)		68 (47.9)	38 (52.1)	
	Missing	23 (2.5)	18 (2.6)	2 (0.9)		2 (1.4)	0 (0.0)	
General Health	Excellent	73 (7.8)	57 (8.3)	14 (6.5)		9 (6.3)	5 (6.8)	
	Very good	209 (22.4)	170 (24.6)	37 (17.1)		27 (19.0)	9 (12.3)	
	Good	492 (52.8)	354 (51.3)	126 (58.3)		82 (57.7)	44 (60.3)	
	Fair	133 (14.3)	89 (12.9)	35 (16.2)		22 (15.5)	13 (17.8)	
	Bad	6 (0.6)	5 (0.7)	1 (0.5)		0 (0.0)	1 (1.4)	
	Missing	19 (2.0)	15 (2.2)	3 (1.4)		2 (1.4)	1 (1.4)	
Psychological Health								
HADS-A[2]		3.0 (5.0)	3.0 (4.0)	3.0 (5.0)	0.99 (0.94 – 1.03)	3.0 (4.0)	4.0 (6.3)	1.11 (1.03 – 1.20)*
	N =	899	667	208		138	70	
HADS-D[2]		2.0 (4.0)	2 0 (4.0)	1.0 (5.0)	0.99 (0.94 – 1.04)	1.0 (4.0)	3.0 (5.0)	1.10 (1.02 – 1.18)*
	N =	895	660	211		139	71	
Psychological health	Excellent	183 (19.6)	147 (21.3)	34 (15.7)		23 (16.2)	10 (13.7)	
	Very good	289 (31.0)	220 (31.9)	64 (29.6)		48 (33.8)	16 (21.9)	
	Good	408 (43.8)	287 (41.6)	103 (47.7)		63 (44.4)	40 (54.8)	
	Fair	43 (4.6)	31 (4.5)	12 (5.6)		6 (4.2)	6 (8.2)	
	Bad	4 (0.4)	3 (0.4)	1 (0.5)		1 (0.7)	0 (0.0)	

Table 4. CONTINUED.

Characteristic		Total %	Tinnitus %		OR (95% CI)	Help %		OR (95% CI)
			No	Yes		No	Yes	
	Missing	5 (0.5)	2 (0.3)	2 (0.9)		1 (0.7)	1 (1.4)	
Audiological								
Hyperacusis	No. no problem	624 (67.0)	484 (70.1)_	121 (56.0)	Ref	84 (59.2)	36 (49.3)	Ref
	Yes. small problem	164 (17.6)	115 (16.7)	46 (21.3)	1.60 (1.08 – 2.38)*	33 (23.2)	13 (17.8)	0.92 (0.43 – 1.95)
	Yes. mediocre problem	99 (10.6)	60 (8.7)	37 (17.1)	2.47 (1.56 – 3.89)*	19 (13.4)	18 (24.7)	2.21 (1.04 – 4.70)*
	Yes. large problem	30 (3.2)	22 (3.2)	8 (3.7)	1.46 (0.63 – 3.35)	4 (2.8)	4 (5.5)	2.33 (0.55 – 9.85)
	Yes very large problem	3 (0.3)	1 (0.1)	1 (0.5)	4.0 (0.25 – 64.41)	0 (0.0)	1 (1.4)	Error
	Missing	12 (1.3)	8 (1,2)	3 (1.4)		2 (1.4)	1 (1.4)	
Hearing problems	Yes. I hear nothing	11 (1.2)	4 (0.6)	4 (1.9)	5.51 (1.35 – 22.47)*	1 (0.7)	3 (4.1)	10.77 (1.05 – 110.21)*
	Yes. severe problems	42 (4.5)	29 (4.2)	13 (6.0)	2.47 (1.23 – 4.95)*	6 (4.2)	7 (9.6)	4.19 (1.24 – 14.12)*
	Yes. mediocre problems	110 (11.8)	56 (8.1)	47 (21.8)	4.62 (2.93 – 7.29)*	23 (16.2)	24 (32.9)	3.74 (1.71 – 8.21)*
	Yes. small problems	235 (25.2)	159 (23.0)	71 (32.9)	2.46 (1.70 – 3.55)*	49 (34.5)	22 (30.1)	1.61 (0.77 – 3.36)
	No. no problems	524 (56.2)	435 (63.0)	79 (36.6)	Ref	61 (43.0)	17 (23.3)	Ref
	Missing	10 (1.1)	7 (1.0)	2 (0.9)		2 (1.4)	0 (0.0)	
Use of	Hearing aid	120 (12.9)	74 (10.7)	40 (18.5)	1.93 (1.27 – 2.94)*	18 (12.7)	22 (30.1)	3.15 (1.55 – 6.39)*
	Cochlear Implant	4 (0.4)	2 (0.3)	1 (0.5)	1.78 (016 – 19.79)	0 (0.0)	1 (1.4)	Error
	Sound generator / Tinnitus Masker	3 (0.3)	1 (0.1)	2 (0.9)	7.14 (0.64 – 79.18)	0 (0.0)	2 (2.7)	Error
	Combination (hearing aid+masker)	2 (0.2)	1 (0.1)	1 (0.5)	3.57 (0.22 – 57.34)	0 (0.0)	1 (1.4)	Error
	None	790 (84.8)	603 (87.4)	169 (78.2)	Ref	121 (85.2)	47 (64.4)	Ref
	Missing	13 (1.4)	9 (1.3)	3 (1.4)		3 (2.1)	0 (0.0)	
Auditory hallucinations	No	842 (90.3)	637 (92.3)	183 (84.7)	0.46 (0.28 – 0.76)*[1]	123 (86.6)	59 (80.8)	0.60 (0.26 – 1.36)[1]
	Yes. understandable voices	9 (1.0)	4 (0.6)	5 (2.3)		2 (1.4)	3 (4.1)	
	Yes not understandable voices	19 (2.0)	11 (1.6)	7 (3.2)		4 (2.8)	3 (4.1)	
	Yes. music	24 (2.6)	14 (2.0)	10 (4.6)		5 (3.5)	5 (6.8)	
	Yes. telephone. doorbell. alarm. sirens	33 (3.5)	19 (2.8)	12 (5.6)		8 (5.6)	4 (5.5)	
	Yes. footsteps	4 (0.4)	3 (0.4)	1 (0.5)		1 (0.7)	0 (0.0)	
	Yes. machines or vehicles	6 (0.6)	2 (0.3)	4 (1.9)		2 (1,4)	2 (2.7)	

Table 4. CONTINUED.

Characteristic		Total %	Tinnitus %		OR (95% CI)	Help %		OR (95% CI)
			No	Yes		No	Yes	
	Yes. animals	8 (0.9)	4 (0.6)	3 (1.4)		2 (1.4)	1 (1.4)	
	Yes. other	6 (0.6)	4 (0.6)	2 (0.9)		1 (0.7)	1 (1.4)	
	Missing	18 (1.9)	10 (1.4)	6 (2.8)		4 (2.8)	2 (2.7)	
Noise and Substance Behaviour								
Use of head/ ear phones	No	550 (59.0)	416 (60.3)	115 (53.2)	Ref	80 (56.3)	34 (46.6)	Ref
	Less than once a week	162 (17.4)	123 (17.8)	37 (17.1)	1.09 (0.71 – 1.66)	22 (15.5)	15 (20.5)	1.60 (0.74 – 3.46)
	Once a week	52 (5.6)	34 (4.9)	17 (7.9)	1.81 (0.98 – 3.36)	12 (8.5)	5 (6.8)	0.98 (0.32 – 2.998)
	Multiple times a week	106 (11.4)	74 (10.7)	31 (14.4)	1.52 (0.95 – 2.42)	18 (12.7)	13 (17.8)	1.70 (0.75 – 3.85)
	Daily	50 (5.4)	35 (5.1)	14 (6.5)	1.45 (0.75 – 2.78)	8 (5.6)	6 (8.2)	1.77 (0.57 – 5.47)
	Missing	12 (1.3)	8 (1.2)	2 (0.9)		2 (1.4)	0 (0.0)	
Potential damaging sound levels	No	620 (66.5)	478 (69.3)	124 (57.4)	Ref	78 (54.9)	45 (61.6)	Ref
	Daily	14 (1.5)	8 (1.2)	5 (2.3)	2.41 (0.78 – 7.49)_	3 (2.1)	2 (2.7)	1.16 (0.19 – 7.18)
	Multiple times a week	24 (2.6)	13 (1.9)	10 (4.6)	2.97 (1.27 – 6.92)*	8 (5.6)	2 (2.7)	0.43 (0.09 – 2.13)
	Once a week	30 (3.2)	19 (2.8)	11 (5.1)	2.23 (1.04 – 4.81)*	6 (4.2)	5 (6.8)	1.44 (0.42 – 5.00)
	Less than once a week	230 (24.7)	163 (23.6)	63 (29.2)	1.49 (1.05 – 2.12)*	44 (31.0)	19 (26.0)	0.75 (0.39 – 1.44)
	Missing	14 (1.5)	9 (1.3)	3 (1.4)		3 (2.1)	0 (0.0)	
If yes. use of hearing protection (n = 298)	Never	157 (52.7)	118 (58.1)	35 (39.3)	Ref	23 (37.7)	12 (42.9)	Ref
	Sometimes	87 (29.2)	48 (23.6)	38 (42.7)	2.67 (1.51 – 4.71)*	25 (41.0)	13 (46.4)	0.997 (0.38 – 2.62)
	Often	32 (10.7)	20 (9.9)	12 (13.5)	2.02 (0.90 – 4.54)	9 (14.8)	3 (10.7)	0.64 (0.15 – 2.81)
	Always	22 (7.4)	17 (8.4)	4 (4.5)	0.79 (0.25 – 2.51)	4 (6.6)	0 (0.0)	Error
	Missing	0 (0.0)	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Smoker	Never	346 (37.1)	266 (38.6)	74 (34.3)		45 (31.7)	29 (39.7)	
	At this moment	68 (7.3)	54 (7.8)	14 (6.5)		8 (5.6)	5 (6.8)	
	Used to smoke	505 (54.2)	362 (52.5)	125 (57.9)		87 (61.3)	38 (52.1)	
	Missing	13 (1.4)	8 (1.2)	3 (1.4)		2 (1.4)	1 (1.4)	
Drug use	Never	881 (94.5)	658 (95.4)	199 (92.1)		130 (91.5)	68 (93.2)	
	Used to	22 (2.4)	15 (2.2)	7 (3.2)		4 (2.8)	3 (4.1)	
	Sometimes	9 (1.0)	5 (0.7)	4 (1.9)		4 (2.8)	0 (0.0)	

Table 4. CONTINUED.

Characteristic		Total %	Tinnitus %		OR (95% CI)	Help %		OR (95% CI)
			No	Yes		No	Yes	
	Regularly	4 (0.4)	2 (0.3)	2 (0.9)		1 (0.7)	1 (1.4)	
	Missing	16 (1.7)	10 (1.4)	4 (1.9)		3 (2.1)	1 (1.4)	
Average # of glasses alcohol a week[2]		2 (7)	2 (7)	2 (7)		3 (7)	2 (7)	
N =		888	660	205		134	70	

[1]Reference is yes [2]Median (IQR) *p <0.05 [3]hearing problem for which hearing aids were used before 60th year of age
Please see Supplementary Table S2 for answer to auditory hallucinations, other.

Discussion

In this study our primary objective was to describe differences in characteristics of help seeking versus non-help seeking tinnitus participants by means of a questionnaire. It was sent to an adult sample of inhabitants of the Netherlands.

Help seeking tinnitus participants had a higher median score on the TFI compared to non-help seeking tinnitus participants. These numbers illustrate that a higher distress score is more frequent in individuals who seek help. We defined participants as a help seeking participant when they planned to seek help for their tinnitus within the next month or had already sought help. We added no time limitations on how long ago in the past they sought help to this definition. Consequently, people could had already sought help years ago, and did not have an active wish for help at the moment of the questionnaire. Interestingly, the help seeking group consisted for 99% (72 of 73) out of participants that had already sought help for their tinnitus. Even though their initial tinnitus distress levels might have been higher, people were still experiencing a median score of 22.8 on the TFI, which indicates they consider their tinnitus to be a "small problem" even after seeking help in the past. (22) Besides this, several questions regarding tinnitus remain; what makes people transit from 'having' tinnitus towards becoming a tinnitus patient or having tinnitus disorder?(4) 35.6% of the help seekers, as identified in our study, had a TFI score ranging between 0-17, which can be interpreted as "not a problem".(17) This might illustrate the controversies between experienced distress scores by these validated instruments and the willingness/need of people to seek help.

We found an overlap in known risk factors for tinnitus in literature, with higher frequencies in help seekers.(23) This is to be expected since many studies that assessed tinnitus risk factors were performed in a hospital population of people with tinnitus. These samples include help seekers by definition. For example, hyperacusis and hearing loss were more common in those with tinnitus that sought help compared to those with tinnitus that did not sought help. These two are also two known risk factors for tinnitus and tinnitus distress in literature. (7,23,24).

Surprisingly, we did not find a statistically significant difference for age in help seekers and non-help seekers. Especially since advanced age is a risk factors of tinnitus.(23) We believe this might be caused by the advanced, and reasonably low variance in age of the complete sample.

In our study, we found no clinically relevant differences in anxiety or depression scores measured by the HADS between help seekers and non-help seekers. Even

though the odds of having a higher score on both the anxiety and depression scale were significantly higher in the help seeking tinnitus group in our study, the median scores on both scales were all below eight. A score below eight score does not indicate a possible depression or anxiety.(19) We therefore believe that these statistically significant results are not clinically relevant. However, we did find higher frequencies of a self-reported clinical diagnosis of depression in those that had sought help. This discrepancy might be caused by the difference in timing of both questions. The HADS assesses depression or anxiety at the moment of filling out the survey. A clinical diagnosis of depression might have been made years ago. We know from literature that depression is a common risk factor for tinnitus, and was also one of the four most important variables for tinnitus subtyping.(6) The low scores on the HADS might be caused by the fact that our survey was distributed among a general population sample, rather than a hospital sample. The low scores are comparable to a population study from Norway describing similar outcomes in people with and without tinnitus.(25)

With respect to tinnitus specific characteristics, we found that 31.5% of the help seekers experience more than one sound, compared to 17.6% in the non-help seeking group. We also found help seekers to experience a varying loudness more often (65.8%) compared to those that do not seek help (40.8%). This is comparable to a study by Lilllemor et al. from 1993 in a hospital setting. They reported ''complainers'' to hear more than one sound. However, contrasting to our study they report a non-fluctuating sound to be heard by complainers more often than ''non-complainers''. (10) These differences in characteristics could point out the way people cope with their tinnitus. One could hypothesize that varying loudness or several sounds make tinnitus more difficult to cope with.

Strengths and weaknesses

A strength of the presented study is the large quantity of data regarding tinnitus and individual characteristics, collected from a sample from the general Dutch population. We created unique data about people with tinnitus that seek help versus those that do not. There are several limitations applicable to this study. The first is that, while the study was set out in a sample of the Dutch population, in terms of age the individuals that responded were not representative of the Dutch population.(26) This might be due to the fact only panel members who gave permission to combine their answers of the survey with health care consumption data as registered by their general practitioner were invited for the survey. (13)The lack of representability may also partly due to the response rate of 41.4%. The response rate might have been influenced by the lengthiness of the questionnaire (with a maximum of 8 pages) or the topic of the questionnaire. This could have made people with tinnitus more inclined to fill out the questionnaire. Due to space limitations we had to take decisions on which questions

to include. Still, we did include a validated tinnitus distress measures (the TFI) and a validated anxiety and depression measure to assess these variables of importance for subtyping.(6,18,20,22) Another limitation is our definition of tinnitus. We based it on frequency and duration, but tinnitus distress was not included in our definition.

Future perspectives

Tinnitus heterogeneity is one of the main impediments that hinder the search for a curative tinnitus treatment. (27). The presented outcomes might help to gain insight in the issue of heterogeneity. However, we believe that the only way to succeed in disentangling this heterogeneity, possibly with subtypes or prediction models, is with interdisciplinary and collaborative research with sound methodology and large datasets.(3) The first steps in multidisciplinary cooperation in research as well as training have been taken, such as programs like ESIT, Tinnitus Assessment Causes Treatment (TINACT) and Unification of Treatments and Interventions for Tinnitus Patients (UNITI).(28–30)

Conclusions

This study pioneered in describing individual characteristics in the general population between people with tinnitus that sought help versus those who did not. Differences between groups were mainly identified in tinnitus characteristics and audiological characteristics. The outcomes of this study could serve as an initial step to detangle the heterogeneity in tinnitus patients.

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Supplementary Methods S1

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Check
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	X
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	X
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	X
Objectives	3	State specific objectives, including any prespecified hypotheses	X
Methods			
Study design	4	Present key elements of study design early in the paper	X
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	X
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	X
		Case-control study—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	
		Cross-sectional study—Give the eligibility criteria, and the sources and methods of selection of participants	
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed	NA
		*Case-control stu*dy—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	X
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	X
Bias	9	Describe any efforts to address potential sources of bias	X
Study size	10	Explain how the study size was arrived at	X
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	X

CONTINUED.

	Item No	Recommendation	Check
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	X
		(b) Describe any methods used to examine subgroups and interactions	X
		(c) Explain how missing data were addressed	X
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed	NA
		Case-control study—If applicable, explain how matching of cases and controls was addressed	
		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(e) Describe any sensitivity analyses	X
Results			**Check**
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	X
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	X
		(b) Indicate number of participants with missing data for each variable of interest	X
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	-
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	-
		Cross-sectional study—Report numbers of outcome events or summary measures	X
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	X
		(b) Report category boundaries when continuous variables were categorized	NA
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	X
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	X
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	X

CONTINUED.

	Item No	Recommendation	Check
Generalisability	21	Discuss the generalisability (external validity) of the study results	X
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	X

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Supplementary Methods S2

Please note, this questionnaire was freely translated from Dutch to English for the purpose of providing the reader with more information on the questions. The translations were not validated.

A. Background

1. What is your date of birth? (day-month-year)
   -

2. What is your gender?
   ☐ Male
   ☐ Female

B. Tinnitus

We would like to know how many people in the Netherlands suffer from tinnitus. Tinnitus is the hearing of e.g. a beep, whistle, sis, zoom or another sound without the actual presence of the sound in your surroundings.

3. Did you experience tinnitus in the last year? Tinnitus is the hearing of e.g. a beep, whistle, sissing, zoom or another sound without the actual presence of the sound in your surroundings This can last a very short amount of time or a whole day.
   ☐ No → ***go to question 38 (part D)***
   ☐ Yes

4. If you experience tinnitus, how long does the tinnitus last?
   ☐ Less than 5 minutes → ***go to question 5***
   ☐ Between 5-60 minutes → ***go to question 6***
   ☐ 60 minutes or more → ***go to question 7***
   ☐ Continuous (the entire day) → ***go to question 7***

5. How often do you experience tinnitus?
   ☐ Daily or almost daily
   ☐ Weekly
   ☐ Monthly
   ☐ Once or less than once a year
   → ***go to question 38***

6. How often do you experience tinnitus?
   ☐ Daily or almost daily → ***go to question 8***
   ☐ Weekly → ***go to question 8***
   ☐ Monthly → ***go to question 38***
   ☐ Once or less than once a year → ***go to question 38***

7. How often do you experience tinnitus?
   ☐ Daily or almost daily
   ☐ Weekly
   ☐ Monthly
   ☐ Once or less than once a year → ***go to question 38***

8. Which pattern best describes your tinnitus during the day?
   ☐ Continuously: you can hear it all the time or most of the time
   ☐ Intermittently: it comes and goes

9. When did your tinnitus start?
   ☐ Less than 3 months ago
   ☐ 3 to 6 months ago
   ☐ 6 months ago ore more

10. How big a problem is your tinnitus at this moment?
    ☐ No problem
    ☐ Small problem
    ☐ Reasonable problem
    ☐ Large problem
    ☐ Very large problem

11. Have you every sought help for you tinnitus? (E.g. through the internet, caregiver or physician)
    ☐ No
    ☐ Yes → ***go to question 13***

12. Are you planning to seek help for your tinnitus within now and a month?
    ☐ No → ***go to question 14***
    ☐ Yes

13. Have you ever been treated, are you currently being treated, or are you planning on getting treated with one of the next treatment for your tinnitus? You can choose multiple options.
    ☐ Psychiatric treatment
    ☐ Psychological treatment (for example Cognitive Behavioral Therapy (CBT),

Tinnitus Retraining Therapy (TRT), Mindfulness)
- ☐ Audiological treatment (for example hearing aids, tinnitus maskers)
- ☐ Physiotherapy (for example manual therapist)
- ☐ Self-management (for example nutritional supplement / medicinal herbs, self-help books)
- ☐ Alternative therapy (for example acupuncture, chiropractor, homeopathic supplies, yoga, haptotherapist)
- ☐ Visit to a physician
- ☐ Other, namely:

.....

14. How intrusive is your tinnitus at this moment?

Totally not intrusive *Extremely intrusive*

0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐

15. Do you hear one type or more sounds?
- ☐ One type of sound
- ☐ Different types of sounds

In the case you hear more than one type of sound, please choose the answer in the next questions that best describes the most bothering sound.

16. Is your tinnitus pulsatile (for example with the heartbeat)?
- ☐ No
- ☐ Yes

17. Where do you experience your tinnitus? (You can choose multiple options)
- ☐ Right ear
- ☐ Left ear
- ☐ Both ears, mostly right
- ☐ Other, namely:

.....

- ☐ Both ears, mostly left
- ☐ Both ears equally
- ☐ Inside my head

18. How was the start of your tinnitus?
- ☐ Gradually
- ☐ Suddenly

19. Does the loudness of your tinnitus vary over time?
- ☐ No
- ☐ Yes

20. What is the pitch of your tinnitus like?
- ☐ High
- ☐ Average
- ☐ Low
- ☐ I don't know

21. Is your tinnitus positively and/or negatively influenced by any of the options below? *(*You can choose multiple options*)*
- ☐ Presence of a loud sound
- ☐ Music or particular ambient noise? (like the sound of a waterfall)
- ☐ Head or neck movements (for example moving the jaw forwards, or clamping the teeth)
- ☐ If your arms/neck touch your head.
- ☐ Sleeping during the day
- ☐ Good quality of sleep
- ☐ Stress
- ☐ Medicines
- ☐ The use of hearing aids

☐ Other, namely:

.....

☐ My tinnitus is not influenced by anything

22. Was the start of your tinnitus related to? (You can choose multiple options)
- ☐ Flu, cold or another infection
- ☐ (side)effect of medicine
- ☐ Exposure to loud sounds
- ☐ Change in hearing (not sudden deafness)
- ☐ Sudden deafness
- ☐ Exposure to changes in air pressure (for example in an airplane or during scuba diving)
- ☐ Stress, anxiety or depression
- ☐ Head trauma / neck trauma (for example whiplash)
- ☐ Jaw problem (TMD)
- ☐ Earwax plug
- ☐ The feeling of fullness of the ears or pressure in the ears.
- ☐ Other, namely:

  .....
- ☐ I don't know

C. Tinnitus distress

Meikle, M. B. et al. The tinnitus functional index: development of a new clinical measure for chronic, intrusive tinnitus.[Erratum appears in Ear Hear. 2012 May;33(3):443]. Ear Hear. 33, 153–176 (2012).

Tromp R. De betrouwbaarheid en validiteit van de Nederlandstalige versie van de Tinnitus Functional Index (TFI). Univ Med Cent Groningen. (2014). Masters.

D. Mood (start question 38)

Spinhoven, P. et al. A validation study of the Hospital Anxiety and Depression Scale (HADS) in different groups of Dutch subjects. Psychol. Med. 27, 363–370 (1997).

Zigmond AS, S. R. The hospital anxiety and depression scale. Acta Psychiatr Scand 67, 361–370 (1983).

E. Questions regarding sounds, hearing and general health.

52. Have sounds been a problem for you in the last week? Sounds that were too loud or uncomfortable to you, whilst these seemed normal to others around you? *Please note, we mean all sounds other than tinnitus.*
- ☐ No, no problem
- ☐ Yes, a small problem
- ☐ Yes, a mediocre problem
- ☐ Yes, a large problem
- ☐ Yes, a very large problem

53. Do you experience problems with hearing, without using a hearing aid or another hearing tool?
- ☐ Yes, i hear nothing
- ☐ Yes, severe problems
- ☐ Yes, mediocre problems
- ☐ Yes, small problems
- ☐ No, no problem

54. Do you use one or more of the next machines? *(You can choose multiple options)*
- ☐ Hearing aids
- ☐ Cochlear implant
- ☐ Sound generator / Tinnitus masker
- ☐ A combination (hearing aid and sound generator within one machine)
- ☐ No

55. Do you experience chronic pain? (more than 6 months)
- ☐ No
- ☐ Yes

56. Tick the boxes if the next diseases / conditions occur in your family. With family we mean biological brothers/sisters, (grand)parents, uncles/aunts, (grand) children. *(You can choose multiple options)*
- ☐ Tinnitus (tinnitus)
- ☐ Epilepsy
- ☐ Hearing problem, with use of hearing aids before the 60th year of age.
- ☐ Nerve and/or muscle disease
- ☐ Syndromes
- ☐ Migraines
- ☐ None of these diseases / conditions.

57. Do you ever listen to sounds (for example music) through headphones or earphones?
- ☐ No
- ☐ Yes, less than once a week
- ☐ Yes, once a week
- ☐ Yes, multiple times a week but not daily
- ☐ Yes, daily

58. Do you ever expose yourself to potential harmful sound levels? (for example loud music in a pub, during your work (construction), shooting)
- ☐ No ➔ ***go to question 60***
- ☐ Yes, daily
- ☐ Yes, multiple times a week but not daily
- ☐ Yes, once a week
- ☐ Yes, less than once a week

59. How often do you wear hearing protection?
- ☐ Never
- ☐ Sometimes
- ☐ Often
- ☐ Always

60. Which of the following descriptions best suits your smoking behavior?
- ☐ I have never smoked
- ☐ I smoke at the moment
- ☐ I used to smoke

61. What is the average amount of glasses of alcohol you drink weekly?

62. Which of the following descriptions best suits your drug use?
- ☐ I have never used drugs
- ☐ I used to use drugs
- ☐ I sometimes use drugs
- ☐ I use drugs on a regular basis

63. Which of the conditions/disease below has a physician diagnosed you with? *You can choose multiple options.*
- ☐ Temporomandibular (jaw (joint)) pain (TMD)
- ☐ Dental problems
- ☐ Sleeping disorder
- ☐ Meningitis
- ☐ Multiple sclerosis (MS)
- ☐ Epilepsy
- ☐ Stroke
- ☐ Anxiety
- ☐ Depression
- ☐ Emotional trauma
- ☐ Excessive stress
- ☐ High blood pressure
- ☐ Heart attack
- ☐ Chronic fatigue syndrome
- ☐ Thyroid conditions
- ☐ Diabetes
- ☐ Hyperinsulinemia
- ☐ High cholesterol
- ☐ Rheumatoid arthritis
- ☐ Systemic lupus erythematosus (SLE)
- ☐ Chronic sinusitis
- ☐ Balance or vertigo problems
- ☐ Recurring ear infections
- ☐ Hearing loss
- ☐ Anemia
- ☐ Heartburn / gastroesophageal reflux
- ☐ Globus (lump in the throat)
- ☐ Other, namely:

  .....
- ☐ None of these conditions/diseases

64. Does it ever happen that you hear someone speaking, whilst nobody is there? Sounds or music can also be heard, while it is unclear where it comes from. (You can choose multiple options)
- ☐ No
- ☐ Yes, understandable voices
- ☐ Yes, not understandable voices
- ☐ Yes, music
- ☐ Yes, telephone/doorbell/alarm/sirens
- ☐ Yes, footsteps
- ☐ Yes, vehicles or machines
- ☐ Yes, other
- ☐ Yes, other, namely:

  .....

Supplementary Table S1. Diseases diagnosed by a physician.

Disease	Total n (%)	Tinnitusn (%)		Help-seekern (%)	
		No	Yes	No	Yes
TMD[1]	9 (1)	6 (0.9)	3 (1.4)	0 (0.0)	3 (4.1)
Dental problems	70 (7.5)	46 (6.7)	24 (11.1)	11 (7.7)	13 (17.8)
Sleeping disorder	52 (5.6)	33 (4.8)	15 (6.9)	9 (6.3)	6 (8.2)
Meningitis	10 (1.1)	7 (1.0)	3 (1.4)	0 (0.0)	3(4.1)
Multiple sclerosis	2 (0.2)	2 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Epilepsy	7 (0.8)	6 (0.9)	1 (0.5)	1 (0.7)	0 (0.0)
Stroke	27 (2.9)	23 (3.3)	4 (1.9)	3 (2.1)	1 (1.4)
Anxiety	21 (2.3)	16 (2.3)	5 (2.3)	3 (2.1)	2 (2.7)
Depression	50 (5.4)	33 (4.8)	15 (6.9)	5 (3.5)	10 (13.7)
Emotional Trauma	25 (2.7)	18 (2.6)	7 (3.2)	4 (2.8)	3 (4.1)
Excessive stress	7 (0.8)	5 (0.7)	2 (0.9)	2 (1.4)	0 (0.0)
High blood pressure	260 (27.9)	181(26.2)	66 (30.6)	44 (31.0)	22 (30.1)
Myocardial infarct	45 (4.8)	30 (4.3)	14 (6.7)	5 (3.5)	9 (12.3)
Chronic fatigue	7 (0.8)	2 (0.3)	4 (1.9)	2 (1.4)	2 (2.7)
Thyroid problems	50 (5.4)	41 (5.9)	9 (4.2)	7 (4.9)	2 (2.7)
Diabetes	77 (8.3)	55 (8.0)	16 (7.4)	9 (6.3)	7 (9.6)
Hyperinsulinemia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
High cholesterol	199 (21.4)	151 (21.9)	41 (19.0)	26 (18.3)	15 (20.5)
Rheumatoid arthritis	47 (5.0)	34 (4.9)	12 (5.6)	7 (4.9)	5 (6.8)
SLE	2 (0.2)	2 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Chronic sinusitis	14 (1.5)	12 (1.7)	2 (0.9)	2 (1.4)	0 (0.0)
Balance problems / vertigo	67 (7.2)	42 (6.1)	22 (10.2)	9 (6.3)	13 (17.8)
Recurrent ear infections	18 (1.9)	13 (1.9)	5 (2.3)	3 (2.1)	2 (2.7)
Hearing loss	140 (15.0)	81 (11.7)	51 (23.6)	25 (17.6)	26 (35.6)
Anemia	30 (3.2)	21 (3.0)	8 (3.7)	5 (3.5)	3 (4.1)
G.E.R.D.*	24 (2.6)	18 (2.6)	6 (2.8)	6 (4.2)	0 (0.0)
Globus	7 (0.8)	3 (0.4)	3 (1.4)	2 (1.4)	1 (1.4)
None	245 (26.3)	191 (27.7)	51 (23.6)	36 (25.4)	14 (19.2)
Missing	23 (2.5)	15 (2.2)	6 (2.8)	6 (4.2)	0 (0.0)
Other	218 (30.9)				
Tractus Digestivus	19		*Malignancies*	19	
Morbus Bechterew	4		*Pulmonary diseases*	25	
Cardiac disease	22		*Fibromyalgia*	8	
Diseases of the musculoskeletal system	54		*Gallbladder problems*	4	
Benign prostate diseases	5		*Neurological diseases*	20	
Psychiatric diseases	6		*Morbus Meniere*	2	
Vascular diseases	10		*Gynecological diseases*	3	
Skin diseases	6		*Eye diseases*	8	
Osteoporosis/penia	4		*Kidney / urological diseases*	4	
Headache / migraine	11		*Other*	47	

[1]TMD = Temporomandibular dysfunction *G.E.R.D = gastroesophageal reflux disease

Supplementary Table S2. Answers to other, namely.

Characteristic	Answer to other, namely
Type of tinnitus help (n = 7)	*No, no treatment*
	Cannot be treated
	I learned to live with it. I have tinnitus in both ears. Also, I constantly have a different melody in one or both ears. So sometimes four sounds mixed together. Luckily I am quite deaf so that little noise comes from outside.
	No
	No
	Cochlear implant
	Accept that you have it and learn to live with it yourself. If you focus your attention to something else you hear it less
Location of tinnitus(n = 2)	*A whiz in both ears and outside my head (mostly to the right of my head I hear different melodies blabla)*
	I can only hear it during the night when everything is silent, I hear a disturbing sound from way way. It seems like a stationary running car.
Influence of tinnitus (n = 22)	*Use of salt, a loud whiz with a lot of salt*
	Lying down
	Lyme
	When there is a lot of noise, I do not hear the beep any more
	Mostly when getting up
	Changes in air pressure, when I put my head on the pillow and lie on an ear, bending down. In combination with migraines, balance disorder
	Whiz is always presence, but I am only aware of it when I notice it (like now). It sometimes gets worse with a cold / the flu.
	Silence around me
	In the evening
	I try not to notice it
	Comes and goes, it gets stronger when I think about it
	In rest before I go to sleep I put a finger to / inside my ear. Very stupid.
	Yawning
	Extra distress when there is a monotonous sound or whiz or hum
	It gets worse with fatigue
	I hear it the most in silence (in bed, before falling asleep)
	With a rhinitis
	With exercise, e.g. taking the stairs
	When I shift focus (work/book) I hear them less loudly. Especially difficult when I wake up at night and I hear one of the most irritating melodies. I cannot always ignore them and
	When I give it attention, I hear it constantly. Distraction helps.
	Absence of sound
	Distraction
Potential cause of tinnitus (n = 16)	*Probably high blood pressure*
	Silence
	After a cerebral hemorrhage
	After the 4th operation above my right eye (resection meningioma right frontotemporal)
	Migraine / tension headache. Dizziness.
	Left also a perforated eardrum, influence unknown

Supplementary Table S2. CONTINUED.

Characteristic	Answer to other, namely
Potential cause of tinnitus (n = 16)	*A sudden bang in my ear*
	I know exactly what it caused and when it started
	I had a hearing limitation on one side. My sense of direction had disappeared. The family doctor gave me nasal drips and the problem was solved.
	I have hearing aids in both ears since 2010. My hearing was worse than my age (then 46). In 2013 the musical sounds (as I call them) started form one day. These musical sounds have expanded over the years.
	I experience mostly at tranquil moment. after rush.
	I think my Meniere's disease also has an influence to this. I have not been bothered by it the last 8 to 9 months, but I think the tinnitus was caused by it.
	The use of a hearing aid
	Heart attack
	I was very sick and dizzy for a whole day. The complaints increased afterwards.
	Allergies / hay fever/ itching in the ears
Auditory hallucinations (n = 6)	*Sudden bangs or other short hard sounds*
	I have also heard other sounds, like hearing one or more voices. I do not hear voices now. I learned how to cope with it.
	Because I have single sided dearness; it is hard for me to hear where (direction) a sound is coming from
	Hum, whiz, beep
	Rarely, I suddenly hear a loud sirens or blaring trumpets or loud church bells. These sound have (luckily) appeared to be temporary.
	With ambulances/flashing lights in traffic it is sometimes difficult to determine where it comes from. But I don't think I am unique in that.
Social position (n = 39)	*Freelancers (n = 21)*
	Volunteers (n = 7)
	Without income
	Sickness law UWV
	WWB
	WSW through (name of company)
	Stopped working early
	Pre retirement
	Part-time retired
	Supernumerary / flexible working
	Almost without a job (starting 22-05-2013)
	Artist

Please note, the answers are direct translations from Dutch.

CHAPTER 5

Patients with tinnitus use more primary healthcare compared to people without tinnitus.

Scientific Reports. 2021; 11:17299

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Abstract

Tinnitus is a heterogeneous condition not only in terms of nature of the sound, but also in co-morbidities such as mental health issues. Prevalence number range widely between 5% and 43%. Even though the etiologic pathway between tinnitus and its comorbidities remains unclear, in this study we aim to assess whether people with tinnitus use more primary health care than people without tinnitus.

To compare primary healthcare consumption between patients with tinnitus and people without tinnitus.

In this cross-sectional study, data on number of consultations with the general practitioner or nurse practitioner mental health services were obtained from Nivel (Netherlands Institute for Health Service Research) Primary Care Database in 2018 (n = 963 880 people). People with an open tinnitus episode (n = 8050) were defined as a patient with tinnitus and compared to all other people. Percentages, means, ranges and mean differences were calculated for the total number of consultations and for organ specific diagnoses registered as ICPC-1 code on the day of consultation. Secondary, the total number of referrals to medical specialists and number of drug prescriptions was collected. Logistic regressions were performed to predict having one or more contacts, referrals, and prescriptions,with having tinnitus, this was corrected for age and gender.

Patients with tinnitus had a mean of 9.8 (SD 10.9) primary care consultations in 2018, compared to 5.7 (SD 7.9) for people without tinnitus. More patients with tinnitus had more than one referral to medical specialists (47%) compared to people without tinnitus (25%). Patients with tinnitus have 1.2 (mean difference) more drug prescriptions than people without tinnitus. Compared to people without tinnitus, patients with tinnitus were more likely to have one or more of primary healthcare contact, independent of age group and gender.

Patients with tinnitus had more consultations in primary health care than people without tinnitus. They are more often referred to medical specialists and receive more drug prescriptions. The causal relationship between tinnitus and the higher healthcare consumption remains to be researched.

Introduction

People with tinnitus perceive a phantom sound, in absence of an external stimulus.(1) It is a complex condition that affects around 5 to 43% of the population. (1–3) Tinnitus does not only vary in terms of nature of the sound, location and pitch, but also in hindrance in a person's life.(3) Whilst some are not bothered by the tinnitus, for others it can severely impair daily life. Reported numbers indicate that up to 5% of the population are mildly to moderately disturbed by their tinnitus.(4–6) Quality of life is described to be severely reduced in 1-2% of tinnitus patients. (7)

Currently, a cure for tinnitus remains to be found. Treatment is focused on symptom reduction. Many treatments are available, however at this moment only Cognitive Behavioral Therapy (CBT) has been proven to diminish tinnitus distress. (8) Other possible treatment options for tinnitus patients with hearing loss includes hearing aids or sound therapy. (9)

In the European guideline for tinnitus health care a stepwise approach for tinnitus care is proposed. (10) In this approach, the general practitioner (GP) is advised to screen for hearing loss and bothersome tinnitus. In case of bothersome tinnitus a referral to an ENT surgeon and/or audiologist is indicated for diagnosis, assessment of the tinnitus severity and to facilitate counselling, education and hearing rehabilitation when necessary. If these steps are not sufficient, specialist tinnitus healthcare is recommended. This includes psycho-education and/or CBT. (10)

The socio-economic costs of tinnitus are considerable, due to the high prevalence, and the chronic nature of the condition.(11) Also, patients often undergo multiple different treatments.(12) In the Netherlands, the mean societal cost (healthcare costs, patient and family costs & indirect costs) of tinnitus are estimated at €6.8 billion per year, with a mean of €1.9 billion for health care costsalone.(13) In the United States annual healthcare costs for tinnitus are estimated at $660 per patient per year. (14) A recent analysis of the treatment costs for tinnitus in Great Britain resulted in an estimation of £750 million per year.(11) So far, it remains unknown if patient or tinnitus related characteristics or comorbidities influence the health consumption of people with tinnitus. This can be of importance since health care costs are incremental and the ongoing debates about the cost-effectiveness of offered experimental and non-experimental therapies.(11)

So far, different comorbidities have been reported to be associated with tinnitus. For example, in a US cohort of the general population, 26% of the tinnitus patients reported anxiety problems, 26% reported depression and people with tinnitus reported

significantly fewer hours of sleep per night compared to people without tinnitus. (15) Other studies showed that individuals with tinnitus more often encounter physical problems compared to individuals without tinnitus.(16) In a recent systematic review including 55 studies, multiple significant associations between non-otological risk factors and tinnitus presence were described. These included psychological factors, demographics, musculoskeletal and cardiovascular factors. (17)

Not all people that are aware of tinnitus sounds experience ''emotional distress, cognitive dysfunction, or autonomic arousal, leading to behavioural changes and functional disability".(18)[p8] So far, it remains unknown when a person with tinnitus becomes a person with tinnitus disorder.(18) It would be interesting to look at the role that co-morbidities play in this. We wonder whether tinnitus patients do not only seek help for tinnitus, but are in need of more health care in general. This is of interest since the relation between tinnitus and its co-morbidities remains a story of "the chicken and the egg?" Does tinnitus make people prone for other diseases? Or is it vice-versa and do other diseases make people prone for tinnitus? Even though this question will not be answered in this study, we will take a first step in assessing the differences.

In this paper, we study the differences in health care consumption between patients with tinnitus and patients without tinnitus in primary care in a cross-sectional study.

Methods

This paper was written according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.(19)

Study aim and design
In this cross-sectional study our primary objective is to asses differences in primary health care consumption of people with and without tinnitus.

Study population
The sample for this study was taken from the participants to the Nivel primary care database.(20) This is national representative longitudinal cohort of which systematical health care consumption data is registered out of the electronic health care records of Dutch primary care health care professionals.

For this study we used data derived out of electronic health records of 295 general practices contributing to the Nivel primary care database from 2018. Data was collected on the total number of consultations to the GP or mental service nurse practitioner (''Praktijkondersteuner Huisarts – Geestelijke Gezondheidzorg" (''POH-GGZ"). This was based on claims to health care insurances. In the Netherlands, all non-institutionalized inhabitants are compulsorily enlisted with a general practice, including patients who do not visit their GP on a regular basis. The GP is the first professional to consult for health problems and has a gatekeeper role for specialized care. Therefore, our data included all enlisted persons, including those that did not contact the GP or mental service nurse practitioner in 2018.

Outcomes
The data included details about total number of consultations (consultation at the practice, at home, by phone or email). Demographic data were collected including age group of the participants (18-39, 40-64, 65+ (determined at 31st of December 2018) and gender.

Diagnoses in primary health care are registered according to the International Classification of Primary Care (ICPC version 1).(21) For each consultation, a maximum of three different diagnosis codes registered on the same day were linked. ICPC codes are organized in 17 individual chapters based on body systems representing the localization of the health problem. Of these 17 chapters, we combined the chapters with psychological and social problems into psychosocial problems. All other individual chapters of the 17, except for the psychological and social problems were combined into 'other'. If no diagnosis code was registered on the day of consultation,

the consult was categorized as diagnosis unknown. Theoretically, one would expect 0 contacts for males in the ICPC code reproductive organs for females and vice-versa. However, this is not the case. For example, it could be that a contact was registered because a male had a question on female reproductive organ. For this reason the mean for gender specific ICPC codes (reproductive organs male/female and pregnancy) were only reported for males or females respectively.

Next, the number of different drug prescriptions (anatomical therapeutic chemical (ATC) classification level 3) were collected(22). For a subset of 113 general practices, data on referrals to medical specialists were available. We obtained the number of referrals to different medical specialists. Multiple referrals to the same medical specialty were counted as one.

To obtain data about the number of patients with tinnitus, we looked at prevalent cases of tinnitus in 2018 with an open diseases episode of tinnitus.(23) The open tinnitus episode was defined as a registration of tinnitus diagnosis in the patient's electronic health record within the period mid-2017 to the end of 2018.(23)

Ethical considerations

We obtained permission from the Nivel steering committee (with representatives from national associations of general practitioners) to use the data (as presented in this study), from the Nivel Primary Care Database. This study has been approved according to the governance code of Nivel Primary Care Database, under number NZR-00318.048. The use of the electronic health records for research purposes is allowed under certain conditions. When these conditions are fulfilled, neither obtaining informed consent from patients nor approval by a medical ethics committee is obligatory for this type of observational studies containing no directly identifiable data (art. 24 GDPR Implementation act Jo art.9.2. sub)

Statistical analysis

Statistical analyses were performed with SPSS version 25.0.0.2. Count data was reported with means, standard deviations and ranges. Frequencies and percentages were presented for 0 counts and >1 counts. Due to the nature of the data (count-data) and the largeness of the dataset we did not check for normality.. .(24,25) Subgroup analyses between people with and without tinnitus were performed. Statistical significance is easily reached in large datasets.(26) We therefore did not assess statistical significance between both groups. We calculated mean differences and 95% confidence intervals (CI) between subgroups. Based on expert opinion we considered a mean difference of 1 visit to be clinically relevant for the number of drug prescriptions between groups. A mean difference of 2 was considered clinically relevant for differences in the total

number of consultations between groups because patients with tinnitus are expected to have at least 1 extra consultation for their tinnitus diagnosis. We considered a mean difference of 1 between groups to be clinically relevant for the different ICPC codes. The data has a hierarchical nature, based on general practices. Since we used all 295 general practices in the analyses and because of the largeness and representability of the sample we did not use multilevel regressions. We categorized the variables: total amount of visits, referrals and prescpritions into two categories (having either 0 or ≥ 1 visits, referrals or prescriptions). We performed complete-case binary logistic regressions to assess the influence of having tinnitus on having ≥ 1 visit, referral or prescriptions. These binary logistic regressions were corrected for gender and age, since older people are more likely to use more care. We checked for multicollineairty.

Results

Data about health care consumption of 963,880 individual people were collected. 488,629 were female (51.1%). 314,421 people were 18-39 years old (32.6%), 412,842 were 40-64 years old (42.8%) and 136,617 were 65 years or older (24.5%). 8050 people (0.8%) were defined as patients having tinnitus. More males (n = 4189, 52%) than females (n = 3861, 48%) were defined as a patient with tinnitus. 6500 of 8050 patients with tinnitus (80.7%) were 40 years or older, while 642,959 of 955,830 (67.2%) of the people without tinnitus were 40 years or older. (Table 1).

Table 1. Gender, age and number of referrals of patients with and without tinnitus.

		Total number of patients *(N (%))*	**Tinnitus**	
			No (n = 955.830) *(N (%))*	**Yes (n= 8050)** *(N (%))*
Gender	Male	471,390 (48.9)	467,201 (48.9)	4189 (52.0)
	Female	492,490 (51.1)	488,629 (51.1)	3861 (48.0)
Age (years)	18-39	314,421 (32.6)	312,871 (32.7)	1550 (19.3)
	40-64	412,842 (42.8)	408,572 (42.7)	4270 (53.0)
	65+	236,617 (24.5)	234,387 (24.5)	2230 (27.7)

Number of primary care contacts

The total mean number of primary care contacts for the complete sample was 5.77 (SD 7.97) in the year 2018 (range 0-338). 762,504 (79.1%) of 963,880 had 1 or more primary care contacts in 2018. The total number of primary care contacts was higher in patients with tinnitus compared to people without tinnitus (mean difference 4.03 (95% CI 3.85 – 4.19). 754,815 of 955,830 (79%) had one or more primary care contact, compared to 7689 of 8050 patients with tinnitus (95.5%) Within these, patients with tinnitus had a mean of 1.13 more contacts related to the ICPC code ear (95% CI 1.10 – 1.17) compared to people without tinnitus. Patients with tinnitus had a mean of 0.48 (95% CI 0.41 – 0.55) more contacts related to psychological symptoms or diagnoses, and a mean of 0.44 (95% CI 0.39 – 0.49) more contacts for musculoskeletal contacts compared to people without tinnitus. Consultations for all organ system but pregnancy, were more frequent in patients with tinnitus. (Table 2) Compared to those without tinnitus, patients with tinnitus were more likely to have one or moreprimary healthcare contacts, independent of age group and gender. (OR 5.71 (95% CI 5.14 – 6.35)) (Table 3)

Table 2. Number of different diagnoses per ICPC code.

ICPC codes		**Total (n = 963,880)**	**Tinnitus**		**Mean difference (95% Confidence Interval)**
			No (n = 955,830)	**Yes(n = 8050)**	
Total Consultations	(mean (SD) (range)	5.77 (7.97) (0 – 338)	5.74 (7.93) (0 – 229)	9.76 (10.88) (0-338)	4.03 (3.79 – 4.26)
	≥1	762,504 (79.1)	754,815 (79.0)	7689 (95.5)	
General	(mean (SD) (range)	0.49 (1.46) (0 – 102)	0.49 (1.46) (0 – 102)	0.69 (1.82) (0 – 61)	0.20 (0.16 – 0.24)
	≥1	216,010 (22.4)	213,591 (22.3)	2419 (30.0)	
Musculoskeletal system	(mean (SD) (range)	0.79 (1.79) (0 – 73)	0.79 (1.79) (0 – 73)	1.23 (2.29) (0 – 29)	0.44 (0.39 – 0.49)
	≥1	312,132 (32.4)	308,526 (32.3)	3606 (44.8)	
Blood	(mean (SD) (range)	0.12 (0.97) (0 – 124)	0.12 (0.97) (0 – 124)	0.18 (1.24) (0 – 40)	0.07 (0.04 – 0.09)
	≥1	35,878 (3.7)	35.449 (3.7)	429 (53)	
Endocrine glands	(mean (SD) (range)	0.35 (1.34) (0 – 101)	0.35 (1.34) (0 – 101)	0.52 (1.75) (0 – 54)	0.17 (0.14 – 0.21)
	≥1	129,141 (13.4)	127,611 (13.4)	1530 (19.0)	
Reproductive organs (male)[1]	(mean (SD) (range)	0.16 (0.82) (0 – 81)	0.16 (0.82) (0 – 81)	0.25 (0.89) (0 – 15)	0.09 (0.06 – 0.11)
	≥1	37,485 (8.0)	36,960 (7.9)	525 (12.5)	
Reproductive organs (female)[2]	(mean (SD) (range)	0.39 (1.20) (0 – 61)	0.39 (1.20) (0 – 61)	0.57 (1.44) (0 – 26)	0.18 (0.13 – 0.22)
	≥1	90,552 (18.4)	89,598 (18.3)	954 (24.7)	
Skin / sub cutis	(mean (SD) (range)	0.64 (1.48) (0 – 104)	0.64 (1.48) (0 – 104)	0.89 (1.66) (0 – 24)	0.25 (0.21 – 0.29)
	≥1	291,162 (30.2)	287,909 (30.1)	3253 (40.4)	
Eye	(mean (SD) (range)	0.13 (0.52) (0 – 49)	0.13 (0.52) (0 – 49)	0.22 (0.68) (0 – 13)	0.09 (0.07 – 0.10)
	≥1	87,959 (9.1)	86,799 (9.1)	1160 (14.4)	
Ear	(mean (SD) (range)	0.20 (0.67) (0 – 36)	0.19 (0.65) (0 – 36)	1.32 (1.62) (0 – 25)	1.13 (1.10 – 1.17)
	≥1	116,480 (12.1)	111,064 (11.6)	5416 (67.3)	
Psychological problems	(mean (SD) (range)	0.51 (1.96) (0 – 175)	0.50 (1.94) (0 – 175)	0.98 (3.23) (0 – 137)	0.48 (0.41 – 0.55)
	≥1	145,485 (15.1)	143,470 (15.0)	2015 (25.0)	
Social problems	(mean (SD) (range)	0.11 (0.77) (0 – 48)	0.11 (0.77) (0 – 48)	0.18 (1.05) (0 – 30)	0.07 (0.04 – 0.09)
	≥1	44,995 (4.7)	44.447 (4.7)	548 (6.8)	
Circulatory tract	(mean (SD) (range)	0.56 (1.66) (0 – 54)	0.56 (1.66) (0- 54)	0.88 (2.07) (0 – 40)	0.32 (0.28 – 0.37)
	≥1	194,847 (20.2)	192.453 (20.1)	2394 (29.7)	
Digestive tract	(mean (SD) (range)	0.39 (1.41) (0 – 85)	0.39 (1.40)(0 – 85)	0.64 (1.70) (0 – 35)	0.24 (0.21 – 0.28)
	≥1	159,997 (16.6)	157,965 (16.5)	2032 (25.2)	

Table 2. CONTINUED.

ICPC codes		Total (n = 963.880)	Tinnitus		Mean difference (95% Confidence Interval)
			No (n = 955,830)	Yes(n = 8050)	
Respiratory tract	(mean (SD) (range)	0.53 (1.52) (0 – 96)	0.53 (1.52) (0 – 96)	0.76 (1.77) (0 – 31)	0.23 (0.19 – 0.27)
	≥ 1	227,813 (23.6)	225,262 (23.6)	2551 (31.7)	
Urinary tract	(mean (SD) (range	0.29 (1.24) (0 – 68)	0.29 (1.24) (0 – 68)	0.36 (1.30) (0 – 23)	0.08 (0.05 – 0.11)
	≥ 1	102,590 (10.6)	101,508 (10.6)	1082 (13.4)	
Nervous system	(mean (SD) (range)	0.16 (0.81) (0 – 75)	0.16 (0.81) (0 – 75)	0.30 (1.13) (0 – 35)	0.14 (0.11 – 0.16)
	≥ 1	77,912 (8.1)	76,792 (8.0)	1120 (13.9)	
Pregnancy[2]	(mean (SD) (range)	0.24 (0.87) (0 – 24)	0.24 (0.87) (0 – 24)	0.19 (0.79) (0 – 11)	- 0.05 (-0.03 – -0.08)
	≥ 1	56,501 (11.5)	56,168 (11.5)	333 (8.6)	
Unknown	(mean (SD) (range)	0.09 (0.45) (0 – 32)	0.09 (0.45) (0 – 32)	0.12 (0.49) (0 – 10)	0.03 (0.02 – 0.04)
	≥ 1	60,423 (6.3)	59,712 (6.2)	711 (8.8)	
Combined ICPC codes	(mean (SD) (range)				
Psychosocial		0.62 (2.17) (0 – 175)	0.61 (2.15) (0 – 175)	1.16 (3.47) (0 – 141)	0.55 (0.47 – 0.62)
	≥ 1	175,177 (18.2)	172,846 (18.1)	2331 (29.0)	
Other	(mean (SD) (range)	5.15 (7.14) (0 – 229)	5.12 (7.12) (0 – 229)	8.60 (9.18) (0 – 197)	3.48 (3.28 – 3.68)
	≥ 1	749,180 (77.7)	741,528 (77.6)	7652 (95.1)	

Psychosocial is a combination of ICPC codes: psychological problems and social problems. Other is the combination of all other ICPC codes (exception psychological problems and social problems). [1] Only calculated for males. [2]Only calculated for females.

Number of referrals to medical specialists

For 401.572 of 955.830 people without tinnitus (42.0%), referral data was available. 98,326 of 401,572 (24.5%) people without tinnitus had one or more referrals to medical specialist. Referral data was available for 3403 of 8050 (42.3%) patients with tinnitus. 1597 of 3403 patients with tinnitus (46.9%) had one or more referrals to a medical specialist. (Table 4.) Compared to those without tinnitus, patients with tinnitus were more likely to have one or more referrals, independent of age group and gender (OR 2.67 (2.49 – 2.86). (Table 3)

Numbers of prescriptions

For the complete sample a mean of 3.4 (SD 3.9) drug prescriptions were registered in 2018 (range 0-42). 715,457 (74.2% of 963,880) had one or more prescriptions in 2018. Patients with tinnitus had 1.2 (mean difference, 95% CI) 1.13 – 1.31) more drug prescriptions than people without tinnitus. (Table 4) Compared to those without tinnitus, patients with tinnitus were more likely to have one or more precreptions,independent of age group and gender (OR 2.29 (2.15 – 2.45)). (Table 3)

Table 3.Results of the logitisic regressions corrected for age and gender .

Outcome	N	Predictors		Odds Ratio 95% CI
≥ 1 contact	963,880	Tinnitus	Yes	5.71 (5.14 – 6.35)
			No	Ref
≥ 1 referral	404,975*	Tinnitus	Yes	2.67 (2.49 – 2.86)
			No	Ref
≥ 1 prescription	963,880	Tinnitus	Yes	2.29 (2.15 – 2.45)
			No	Ref

*perfomed in patients for whom referral data was available (404975)

Table 4. Number of referrals and total number of drug prescriptions of patients with and without tinnitus drug.

		Total	Tinnitus		Mean difference
			No	Yes	(95% Confidence interval)
Referrals* *(mean (SD) range)*		0.32 (0.63) (0-8)	0.31 (0.63) (0 – 8)	0.68 (0.90) (0-8)	0.37 (0.34 – 0.40)
N (%)	0	305,052 (75.3)	303,246 (75.5)	1806 (53.1)	
	≥ 1	99,923 (24.7)	98,326 (24.5)	1597 (46.9)	
*Elaboration of ≥ 1 referral (n (%))**					
	1	77,276 (19.1)	76,203 (19.0)	1073 (31.5)	
	2	17,875 (4.4)	17,503 (4.4)	372 (10.9)	
	3	3374 (0.9)	3665 (0.9)	109 (3.2)	
	4	792 (0.2)	759 (0.2)	33 (1.0)	
	5	157 (0.0)	149 (0.0)	8 (0.2)	
	6	39 (0.0)	38 (0.0)	1 (0.0)	
	7	7 (0.0)	7 (0.0)	0 (0.0)	
	8	3 (0.0)	2 (0.0)	1 (0.0)	
Drug prescriptions *(mean (SD))*		3.41 (3.95) (0 – 42)	3.4 (3.94) (0 – 42)	4.62 (4.31) (0 – 40)	1.2 (1.13 – 1.31)
	≥ 1	715,457 (74.2)	708,453 (74.1)	7004 (87.0)	

* assessed in those for whom referral data was available (n = 404975), available for 401.572 people without tinnitus and 3403 people with tinnitus.

Discussion

In this study we assessed the differences in primary health care consumption between patients with tinnitus and people without tinnitus in a Dutch cohort. 0.8% of the patients (8050 out of 963 880) had an open tinnitus episode and were therefore defined as a patient with tinnitus. Patients with tinnitus used more primary care consultations compared to people without tinnitus. Patients with tinnitus were more often referred to medical specialists compared to people without tinnitus, and patients with tinnitus were more often prescribed drugs.

We observed four more (mean difference) primary care consultations in patients with tinnitus compared to people without tinnitus. This is a larger difference than the results of a study on health care utilization in United States veterans.(27) Even though they identified a higher total healthcare usage (including medical specialist care), they only found a mean of 2.9 visits to primary health care for those with tinnitus, compared to a mean of 2.2 visits for veterans without tinnitus over a five year period. (27) This difference might be explained by the differences in health care systems or studied populations. Next, we find more annual GP visits for patients with tinnitus compared to a Dutch study by Maes et al. out of 2013.(13) They describe a mean of 7.78 contacts annually to the GP for tinnitus-related health care in people with tinnitus. This could be explained by the fact that their study was based on a sample that was referred to (and in need of) specialist tinnitus care. Moreover, we found that 0.8% of all patients that visited the GP in 2018 had an open tinnitus episode. This is different to the prevalence numbers described in the study be Maes et al.. They based their results on the assumption that 30% of individuals would experience tinnitus at some point in their life, and 10% would require medical help.(13,28,29) Apart from the differences in population, another explanation of the large variance could be the use of different definitions to determine tinnitus prevalence numbers. (2)

In our study consultations for all organ systems (except pregnancy) were more frequent in patients with tinnitus. Only consultations in the ICPC chapter ''Ears'' showed a clinically relevant difference. This could be related to the tinnitus consultation itself which is coded under this ICPC chapter or to hearing problems, which is one of the most important risk factors for tinnitus. Moreover, in our study we found a difference between those with and without tinnitus in number of consultations for psychological problems (mean difference in visits between groups 0.48) and musculoskeletal problems (mean difference in visits between groups 0.44). This is not surprising considering the fact that psychological problems such as anxiety, depression or sleep- and concentration difficulties are common comorbidities of tinnitus.(7) An increase in musculoskeletal problems in tinnitus patients might

be explained by commonly described comorbidities such as temporomandibular dysfunction (TMD) (17,30). In a systematic review from 2019 the prevalence of tinnitus in patients with temporomandibular dysfunction ranged between 3.7-70%. (31) Also a relatively large component of the difference in number of consultations between both groups was found in the circulatory tract ICPC chapter (mean difference 0.32). Cardiovascular diseases, such as high blood pressure have been described to be associated with tinnitus. Cardiovascular diseases are believed to damage inner ear circulation, and consequently cause tinnitus. (17,32)

Next, we noticed a higher number of referrals to medical specialists. 46.9% of patients with tinnitus were referred to a medical specialist at least once in 2018, compared to 24.5% of the people without tinnitus. Our data did not include information about which medical specialists were consulted. Whether the higher number of referrals can be explained by the bothersome nature of the experienced tinnitus cannot be concluded by the presented data. As a first step in tinnitus health care the severity of the tinnitus should be assessed by the primary health care provider. Only, when the tinnitus is bothersome a referral to an otorhinolaryngologists or an audiologist is indicated as described in the European guideline.(10)

Patients with tinnitus received a mean of 1.2 more drug prescriptions in 2018, compared to people without tinnitus. We did not have data about which drugs were prescribed. This is of interest since pharmaceutical treatment for tinnitus is not recommended, because of the lack of effectiveness in reducing tinnitus symptoms. However, medication is still prescribed in clinical practice.(33) In a previous study it was estimated that doctors write over 4 million off-label prescriptions annually in Europe and the United States for the relief of tinnitus.(34) These include anti-depressives, prednisolone, betahistine and anti-epileptic drugs.(35) The higher number of drug prescriptions in our data could suggest that these prescriptions are not only because of the tinnitus, but are more likely related to other morbidities of patients with tinnitus.

Strengths and limitations

The large cohort of participants to the primary care database is a representative sample of the Dutch population.(20,36) This provides unique insight in primary health care usage of those with tinnitus compared to those without. One of the limitations is our definition of a tinnitus patient. A person was defined as a tinnitus patient when they had an open episode of tinnitus in 2018. This was defined as any registration of tinnitus in the patient's electronic health record within the period mid-2017 to the end of 2018.(23) Next, there might be those that experience or suffer from tinnitus in the group "people without tinnitus". They could have visited the GP

for tinnitus in previous years or not at all. Also, we are not certain that the patients with tinnitus actually consulted the GP for the tinnitus. Next, there might be variability in the registered tinnitus diagnoses. It might differ per practice whether tinnitus was registered, some GPs might not register the tinnitus if a person contacts the GP for other reasons. Also, our study is limited to information about the number of contacts, referrals and prescriptions.) Since this study had an explorative nature, it does not entail information on the reason for referrals, to which medical specialists patients were referred or which drugs were prescribed.

In our study we demonstrated a higher number of consultations in primary care in patients with tinnitus compared to people without tinnitus. This might be the result of the fact that patients with tinnitus are less healthy or have more mental or physical complaints compared to people without tinnitus. A combination of both might also be possible, or it could be neither. This cross-sectional study does not inform us about the etiological relationship between tinnitus and co-morbidities. Large observational studies could help explore this causal relationship, which could contribute in the search for interventions. Also, a more specified analysis on the amount of visits for different comorbidities (tinnitus related or unrelated), rather than an umbrella term used in this study, for more in-depth knowledge. This would be similar to a Nivel primary care database study that looked at specific diagnoses codes in relation to inflammatory arthritis.(37)

Conclusion

We conclude that patients with tinnitus had more primary health care contacts compared to people without tinnitus, with an average of four more primary care consultations in one year. Patients with tinnitus received more drug prescriptions and were more frequently referred to the medical specialists.

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CHAPTER 6

Associations between Demographics, Tinnitus Specific-, Audiological-, General- and Mental Health Factors, and the Impact of Tinnitus on Daily Life

Journal of Clinical Medicine 2022, 11(15), 4590

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Abstract

Our objective was to study associations between demographics, tinnitus specific-, audiological-, general- and mental health characteristics, and impact of tinnitus in the general population. In this cross-sectional survey study in the Dutch population, data were prospectively gathered. Tinnitus impact was assessed with the Tinnitus Functional Index (TFI). We included participants who experienced tinnitus and for whom a total TFI score could be calculated (n = 212). We performed univariable and multivariable regression analyses. Due to logarithmical transformation, the B-scores were back-transformed to show the actual difference in points on the TFI. People who considered hyperacusis a small problem had a 12.5-point higher TFI score, those who considered it a mediocre problem had a 17.6-point higher TFI score and those who considered it a large problem had a 24.1-point higher TFI score compared to people who did not consider hyperacusis a problem. People who indicated having minor hearing problems had a 10.5-point higher TFI score, those with mediocre hearing problems had a 20.4-point higher TFI score and those with severe hearing problems had a 41.6-point higher TFI score compared to people who did not have subjective hearing problems. In conclusion, audiological risk factors, such as hearing problems and hyperacusis, have the largest association with the impact of tinnitus on daily life, compared to other assessed variables. The results of this study can be used in future research to find targeted interventions to diminish the impact of tinnitus.

Introduction

Tinnitus is a heterogeneous condition with considerable variations in onset, associated comorbidities and experienced impact on daily life. (1) Previously, McCormack et al. described a prevalence of tinnitus ranging between 5.1% and 42.7% in a systematic review. (2) However, not all individuals with tinnitus experience a negative effect on their daily life because of their tinnitus. Recently, those who suffer from its impact were defined as having a tinnitus disorder. (3)

In their systematic review, Deklerk et al. described studies that assessed risk factors for tinnitus presence. They described numerous risk factors in different domains, including cardiovascular, psychological and neurological risk factors. (4)

Factors associated with a larger experienced impact of tinnitus have also been described in various domains. Stress and mental diseases, such as anxiety or depression, have been described as psychological risk factors. (5–7) Moreover, somatic factors, such as hearing loss, or tinnitus specific risk factors, such as tinnitus loudness, have also been associated with tinnitus impact.(6–8) Nonetheless, the various studies on associations or risk factors and tinnitus impact have been performed in selected samples of patients, particularly studies focusing on patients seeking help for tinnitus. However, not all individuals who experience tinnitus seek help. (5–7,9,10)

Detailed information about the associations between patient- and tinnitus-related characteristics and the impact of tinnitus on daily life could be of interest. Because not all people with tinnitus attend a healthcare provider, information about individuals with tinnitus among the general population is needed. This information can be used as a basis to design preventive strategies. Secondly, this could facilitate the identification of tinnitus subtypes in order to stratify individual treatment pathways. Therefore, in this study, we aim to provide insight into the associations between demographics, tinnitus characteristics, audiological-, mental- and general health factors, and tinnitus impact in a random sample of the general population.

Materials and Methods

This paper was written according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement. (11)

Study Aim and Design

In this cross-sectional study, we aimed to assess risk factors with respect to the impact of tinnitus on daily life in a sample of the general population. Data were prospectively gathered with a postal or online survey (depending on the preference of the panel member) in January–February 2020. We sent the postal survey on 14 January 2020, and one postal reminder was sent on 30 January 2020. The online survey was sent on 16 January 2020, with two online reminders on the 23 January 2020 and 30 January 2020. The final date to fill out the survey was 14 February 2020. The survey was sent to members of the Nivel Dutch Health Care Consumer panel. (12) This panel was founded to measure, at a national level, opinions on and knowledge about health care, as well as expectations of and experiences with health care. (13)

The Consumer Panel is a so-called 'access panel'. An access panel consists of a large number of persons who have agreed to answer questions on a regular basis. In addition, many background characteristics of these persons (for example age, level of education, income and self-reported general health) are known. From the access panel, samples can be drawn for separate surveys. It is not possible for people to sign up on their own initiative. The panel is renewed on regular base. Renewal is necessary to make sure that members do not develop specific knowledge of and attention to healthcare issues and that no 'questionnaire fatigue' occurs. Moreover, renewal compensates for panel members who, for example, have died or moved without informing the panel of their new address. (13)

This study is part of a larger study designed to describe tinnitus prevalence, tinnitus characteristics and healthcare usage. The sample for this larger study included panel members (n = 2251) who allowed for linkage of their survey answers with healthcare consumption data as registered by their general practitioner. (14) We recently published two studies on the same database. (10,15) The complete survey can be found in the appendix of Rademaker et al. (10) For the current study, we included only data of participants with tinnitus for whom a total score of the impact of tinnitus on daily life measured by the Tinnitus Functional Index (TFI) could be calculated. (16)

Outcome

The Impact of Tinnitus on Daily Life

As part of the survey, the impact of tinnitus on daily life was assessed with the multi-item TFI questionnaire. (16)Participants were asked to answer the TFI questions if they were defined as having tinnitus based on the frequency and duration of the experienced tinnitus, as previously described by Rademaker et al. (10) To this end, people were classified as having tinnitus when they experienced tinnitus for 5–60 min (daily or almost daily or weekly) or >60 min or continuously (daily or almost daily or weekly or monthly).

25 questions on a 11-point Likert scale, make up the TFI. The final score alters between 0 and 100. (16) A score between 0 and 17 can be interpreted as not a problem, 18–31 as a small problem, 32–53 as a moderate problem, 54–72 as a big problem and 73–100 as a very big problem. (16,17)The 25 questions of the TFI are a combination of scores of impact on daily life out of eight subcategories (each subcategory is measured with 3 to 4 questions): intrusiveness, sense of control, cognition, sleep, hearing, relaxation, quality of life and emotions. The TFI was developed and validated in the USA, Tromp et al. translated it from English to Dutch and validated the translation in 2014. The Dutch translation exhibits high internal consistency (Cronbach's alpha of 0.91). (16–18)

Variables

The choice of variables to be addressed was based on known risk factors for tinnitus impact reported in the literature and based on expert opinion. Please see Supplementary Method S2 of Rademaker et al. for the exact wording of the questions and answer options with respect to the categorical variables.(10)

Tinnitus Specific Variables

The following items were assessed as tinnitus specific variables: being a help seeker (defined as when participant had either sought help for tinnitus or planned to seek help (yes/no)), tinnitus pattern (continuous/intermittent), subjective problem of tinnitus (no problem/small problem/moderate problem/large problem/very large problem), when did the tinnitus start (<3 months ago, 3–6 months ago, ≥6 months ago), whether the tinnitus varied in loudness (yes/no) and the tinnitus pitch (high/average/low/I don't know).

General Health Variables

The following general health item was assessed: subjective presence of chronic pain (yes/no).

Mental Health Variables

Symptoms of anxiety and depression were measured with the Hospital Anxiety and Depression Scale (HADS). (19,20) This is a 14-item questionnaire that uses a four-point scale to measure symptoms of anxiety (HADS-A; seven items) and depression

(HADS-D; seven items). The HADS was translated to Dutch and validated (Cronbach's alpha 0.71 and 0.90 for HADS-A, HADS-D and total scale). The total scores for the anxiety and depression scales range from 0 to 21. A score of ≥ eight indicates a possible depression or anxiety.(20)

Audiological Variables

We used the questions about whether sounds were a problem (no problem/small problem/mediocre problem/large problem/very large problem), hereafter referred to as hyperacusis, and the presence of hearing problems (no problems/small problems/mediocre problems/severe problems/I hear nothing) as audiological variables.

Demographic Variables

The following items were assessed as demographic variables: age (at date of questionnaire submission), gender and level of education (low/middle/high). These were gathered when participants joined the panel and were provided by Nivel for this study.

Data Handling and Ethics

Data were analyzed anonymously, and the privacy of the panel members is guaranteed, as is described in the privacy policy of the Dutch Health Care Consumer Panel. (13) This complies with the General Data Protection Regulation (GDPR). According to Dutch legislation, it is not obligatory to obtain informed consent or approval from a medical ethics committee for research conducted through the panel (CCMO, 2020). The Medical Research Ethics Committee (MREC) of the University Medical Center Utrecht (UMC Utrecht) confirmed on 20 November 2019, that the Medical Research Involving Human Subjects Act (WMO) does not apply to this study and that therefore, official approval of the MREC is not required under the Human Subjects Act (MREC local protocol number 19–745). This study was performed according to the Declaration of Helsinki.

Statistical Analysis

Statistical analyses were performed with SPSS version 25.0.0.2. (21). Normality of variables was visually assessed. Frequencies, means, standard deviation (SD), medians and interquartile ranges (IQR) were calculated for the variables of the total study group. To assess the relative importance of the characteristics to the TFI score, both univariable linear regression analyses and multivariable linear regression analyses were performed (complete case). The following patient characteristics were assessed: gender, age, level of education, tinnitus pattern, subjective problem of tinnitus, start of tinnitus, varying loudness, tinnitus pitch, being tinnitus help seeker, having chronic pain, HADS-A and HADS-D score, presence of hyperacusis and hearing problems.

Based on expert opinion and literature reports, in a second analysis, we adjusted for the following potential confounders: gender, age and presence of hearing loss. Multivariable analyses were performed for all above-mentioned variables to assess their effect on TFI score (except for the single-item score of the subjective problem of tinnitus, as this outcome resembles the multi-item TFI score). The risk factors of gender, age and presence of hearing loss were each corrected for the other two potential confounders. To satisfy the assumption of normal distribution of residuals, the TFI was logarithmically transformed. Afterwards, residuals were approximately normally distributed. All other assumptions were satisfied. The outcomes were presented as B (95% CI) of this logarithmic scale and back-transformed to show the actual difference in points on the TFI scale according to each variable. Categorical variables were dummy-coded. A p value of 0.05 or lower was considered statistically significant.

Results

The survey was sent to 2251 panel members. Nine hundred and thirty-two (41.4%) panel members filled out the questionnaire. Out of these 932 respondents, 216 (23.2%) participants were classified as a tinnitus participant based on the stated definition. We were able to calculate the total TFI for 212 of 216 participants (98.1%, 4 missing); therefore, 212 participants were included in this study.

The mean age of the 212 participants was 66.2 (SD 10.8) years. A total of 122 of 212 (57.5%) were male. Among the participants, 135 (63.7%) had a continuous pattern of tinnitus, compared to 77 (36.3%) who had an intermittent pattern. The loudness of the tinnitus varied for 105 (49.5%) of the participants. A total of 72 of 212 (34.0%) participants were defined as help seekers. A total of 35 of 212 (16.5%) of the participants experienced chronic pain. Furthermore, 78 (36.8%) of 212 did not experience any hearing problems, whereas 70 (33.0%) experienced small hearing problems, 47 (22.2%) experienced mediocre problems, 13 (6.1%) experienced severe problems and 4 (1.9%) experienced complete hearing loss (Answer option: "yes, I hear nothing") (Table 1).

Demographic Variables

Age or gender were not statistically significantly associated with TFI score in the univariable and adjusted analyses (age: univariable: B = −0.003 (95% CI −0.014–0.009), p = 0.664, adjusted: −0.01 (−0.02–0.00), p = 0.49/gender: univariable (male = reference) female B = 0.19 (95% CI −0.7–0.44), p = 0.15, adjusted B = 0.18 (95% CI −0.07–0.43), p = 0.16) (Table 1).

Tinnitus Specific Variables

Participants with a continuous tinnitus pattern had a significantly higher TFI score in the univariable and adjusted regression analyses than those with an intermittent tinnitus pattern (univariable, B = −0.52 (95% CI −0.77–0.27), p = 0.000, adjusted: B = −0.45 (95% CI −0.70—0.20), p = 0.000). When back-transformed, this resulted in an 8.1-point higher score on the TFI for a continuous pattern compared to an intermittent pattern in the univariable analysis and a 11.1-point higher score in the adjusted analysis (Table 1).

In the univariable analysis, the score for the question about experiencing problems with having tinnitus (scale 1 to 5; no problem to very large problem) was associated with a higher TFI. When back-transformed, we found that the answer option "no problem" corresponded to a TFI score of 6.5, "small problem" to a score of 16.2, "moderate problem" to a score of 31.3, "large problem" to a score of 55.9 and "very large problem" to a score of 73.9.

Table 1. Baseline characteristics, Univariable and Multivariable B-scores and back transformed TFI scores.

		N (%)	Median TFI Score	Univariable (B (95% CI))	Univariable Back-Transformed	Multivariable [1] (B (95% CI))	Multivariable Back-Transformed
Demographic							
Gender	Male	122 (57.5)	14.2 (22.8)	Ref		Ref	
	Female	90 (42.5)	20.2 (20.2)	0.19 (−0.07–0.44)		0.18 (−0.07–0.43)	
	Missing/constant	0 (0)		2.72)		3.19	
Age [1] (n = 212)	Median (IQR)	66 (15)		−0.003 (−0.01–0.01)		−0.01 (−0.02–0.00)	
	Constant			2.97		3.19	
Education	Low	27 (12.7)	30.4 (46.1)	0.47 (0.08–0.86) *	23.8	0.45 (0.06–0.84) *	38.5
	Middle	74 (34.9)	15.0 (20.0)	0.06 (−0.21–0.34)		0.07 (−0.20–0.34)	
	High	104 (49.1)	14.8 (21.7)	Ref	14.9	Ref	24.5
	Missing/constant	7 (3.3)		2.70		3.20	
Tinnitus specific							
Pattern	Continuous	135 (63.7)	20.0 (25.2)	Ref	19.9	Ref	30.6
	Intermittent	77 (36.3)	11.6 (16.2)	−0.52 (−0.77—0.27) *	11.8	−0.45 (−0.70—0.20) *	19.5
	Missing/constant	0 (0.0)		2.99		3.42	
Subjective problem	No problem	50 (23.6)	7.4 (6.1)	Ref	6.5		
	Small problem	103 (48.6)	16.4 (15.6)	0.91 (0.68–1.14) *	16.2		
	Moderate problem	43 (20.3)	40.4 (33.6)	1.57 (1.29–1.84) *	31.3		
	Large problem	12 (5.7)	60.2 (11.1)	2.15 (1.72–2.57) *	55.9		
	Very large problem	4 (1.9)	73.6 (11.3)	2.43 (1.74–3.12) *	73.9		
	Missing/constant	0 (0.0)		1.87			
When did it start?	<3 months ago	7 (3.3)	8.8 (23.6)	−0.44 (−1.14–0.26)		−0.62 (−1.31–0.06)	
	3–6 months ago	9 (4.2)	16.4 (25.7)	0.15 (−0.47–0.77)		0.22 (−0.38–0.81)	
	≥6 months	196 (92.5)	17.7 (21.5)	Ref		Ref	
	Missing/constant	0 (0.0)		2.81		3.29	
Varying loudness	No	99 (46.7)	14.0 (20.4)	Ref	13.1	Ref	17.3
	Yes	105 (49.5)	21.6 (27.4)	0.45 (0.20–0.70) *	20.6	0.36 (0.10–0.61) *	24.7
	Missing/constant	8 (3.8)		2.57		2.85	
Tinnitus pitch	High	75 (35.4)	14.8 (22.0)	Ref		Ref	

Table 1. CONTINUED.

		N (%)	Median TFI Score	Univariable (B (95% CI))	Univariable Back-Transformed	Multivariable [1] (B (95% CI))	Multivariable Back-Transformed
	Average	73 (34.4)	15.6 (22.8)	0.04 (−0.26–0.34)		0.02 (−0.28–0.32)	
	Low	42 (19.8)	20.6 (28.3)	0.22 (−0.13–0.58)		0.21 (−0.14–0.56)	
	I don't know	16 (7.5)	21.6 (18.6)	0.08 (−0.43–0.58)		0.01 (−0.49–0.51)	
	Missing/constant	6 (2.8)		2.74		3.27	
Tinnitus help seeker	No	140 (66.0)	14.7 (19.1)	Ref	13.7	Ref	21.5
	Yes	72 (34.0)	22.8 (43.1)	0.55 (0.94–0.81) *	23.8	0.47 (0.21–0.73) *	34.3
	Missing/constant			2.62		3.07	
General health							
Chronic pain	No	177 (83.5)	14.8 (19.0)	Ref	15.3	Ref	23.5
	Yes	35 (16.5)	31.6 (36.0)	0.46 (0.13–0.79) *	24.2	0.44 (0.12–0.76) *	36.4
	Missing/constant	0 (0.0)		2.73		3.16	
Mental health							
HADS-A [1] (n = 207)	Median (IQR)		3.0 (5.0)	0.12 (0.09–0.15) *		0.11 (0.08–0.14) *	
	Constant			2.34		2.14	
HADS-D [1] (n = 209)	Median (IQR)		1.0 (5.0)	0.10 (0.07–0.13) *		0.09 (0.06–0.12) *	
	Constant			2.47		2.48	
Audiological							
Hyperacusis	No, no problem	120 (56.6)	12.4 (15.3)	Ref	12.5	Ref	22.7
	Yes, small problem	45 (21.2)	20.4 (28.0)	0.50 (0.19–0.80) *	20.5	0.44 (0.14–0.75) *	35.2
	Yes, mediocre problem	37 (17.5)	30.0 (41.8)	0.71 (0.39–1.03) *	25.4	0.58 (0.23–0.92) *	40.3
	Yes, large problem	8 (3.8)	53.6 (56.8)	0.99 (0.36–1.62) *	33.5	0.72 (0.07–1.38) *	46.8
	Yes, very large problem	1 (0.5)	21.1 **	0.53 (−1.21–2.26)	NS	−0.18 (−2.30–1.95)	NS
	Missing/constant	1 (0.5)		2.53		3.12	
Hearing problem	No, no problems	78 (36.8)	12.4 (14.9)	Ref	12.2	Ref	24.2
	Yes, small problems	70 (33.3)	19.8 (22.1)	0.36 (0.07–0.65) *	17.5	0.36 (0.07–0.7) *	34.7
	Yes, mediocre problems	47 (22.2)	20.8 (35.2)	0.49 (0.16–0.82) *	19.99	0.61 (0.27–0.95) *	44.6
	Yes, severe problems	13 (6.1)	47.6 (51.0)	0.82 (0.29–1.35) *	27.8	1.00 (0.45–1.55) *	65.8
	Yes, I hear nothing	4 (1.9)	39.0 (47.3)	1.06 (0.16–1.97) *	35.5	1.14 (0.22–2.05) *	75.7
	Missing/constant	0 (0.0)		2.51		3.19	

* Statistically significant, p < 0.05; ** no IQR presented because n < 4. Ref = reference. The back-transformed TFI score was calculated with the reference value as zero in the case of a statistically significant association. 1 Corrected for age, gender and hearing problems. The variable age, gender and hearing problems themselves were corrected for the other two problems (e.g., age was corrected for gender and hearing problems). For continuous risk factors, the back-transformed TFI score was based on the median score of the risk factor.

Individuals with a varying loudness of tinnitus had a significantly higher TFI score than those with non-varying tinnitus loudness (univariate B = 0.45 (95% CI 0.19–0.70) p = 0.000, adjusted: 0.36 (0.10–0.61) p = 0.006). This resulted in a 7.5-point higher TFI score for a varying loudness compared to a non-varying loudness in the univariate analysis and a 7.4-point difference in the adjusted analysis.

General Health Variable

Having chronic pain was associated with a higher TFI than not experiencing chronic pain in univariable analysis (B = 0.46 (95% CI 0.13–0.79), p = 0.007), as well as in the adjusted analyses (B = 0.44 (95% CI 0.12–0.76), p = 0.008). This resulted in an 8.9-point higher score on the TFI for participants with chronic pain compared to those without chronic pain in the univariable analyses and 12.9 in the adjusted analyses.

Mental Health Variables

In the univariable and adjusted analyses, both the HADS-A and the HADS-D were associated with a higher TFI score ((HADS-A univariable B = 0.12 (95% CI 0.09–0.15), p = 0.000), HADS-D B = 0.10 (95% CI 0.07–0.13), p = 0.000/adjusted HADS-A B = 0.11 (95% CI 0.08–0.14), p = 0.000, HADS-D B = 0.09 (95% CI 0.06–0.12), p = 0.000). Based on the adjusted analyses, this resulted in a TFI score of 11.8 in those with a median HADS-A score (3.0). If an individual's HADS-A score increased by one (to 4.0), it would result in a TFI score of 13.2. For the HADS-D, the median score was one. The TFI score was 13.1 for those with a median HADS-D score (1.0) and 14.2 for those with an increase in the median HADS-D score of one (2.0).

Audiological Variables

Having hyperacusis was associated with a higher TFI score in univariable and adjusted analyses (small problem: univariable B = 0.50 (95% CI 0.19–0.80), p = 0.001 (back-transformed TFI = 20.5), adjusted B = 0.44 (95% CI 0.14–0.75), p = 0.005 (back-transformed TFI = 35.2), mediocre problem: univariable B = 0.71 (95% CI 0.39–1.03), p = 0.000 (back-transformed TFI = 25.4), adjusted B = 0.58 (95% CI 0.23–0.92), p = 0.001 (back-transformed TFI = 40.3) and large problem: univariable B = 0.99 (95% CI 0.36–1.62), p = 0.002 (back-transformed TFI = 33.5), adjusted B = 0.72 (95% CI 0.07–1.38), p = 0.031 (back-transformed TFI = 46.8).

Hearing problems were associated with significantly higher TFI scores in both the univariable and adjusted analyses (small problem: univariable B = 0.36 (95% CI 0.07–0.65), p = 0.02 (back-transformed TFI = 17.5), adjusted B = 0.36 (95% CI 0.07–0.7), p = 0.016 (back-transformed TFI = 34.7), mediocre problems: univariable B = 0.49 (95% CI 0.16–0.82), p = 0.003 (back-transformed TFI = 20.0), adjusted B = 0.61 (95% CI 0.27–0.95), p = 0.001 (back-transformed TFI = 44.6), severe problems: univariable B = 0.82 (95% CI

0.29–1.35), p = 0.003 (back-transformed TFI = 27.8), adjusted B = 1.00 (95% CI 0.45–1.55), p = 0.000 (back-transformed TFI = 65.8), I hear nothing: univariable B = 1.06 (95% CI 0.16–1.97), p = 0.02 (back-transformed TFI = 35.5), adjusted B = 1.14 (95% CI 0.22–2.05), p = 0.015 (back-transformed TFI = 75.7).

Discussion

In this cross-sectional study of a general population sample, we assessed whether several demographic-, tinnitus specific-, general- and mental health characteristics were associated with the impact of tinnitus on daily life as measured with the TFI.

We included different domains of variables in our survey. Audiological factors were most important compared to the other assessed risk factors in terms of association with tinnitus impact. Tinnitus specific characteristics seemed to be less important, which is in line with the results of a study by Beukes et al. (9) In this cross-sectional study in a hospital population, the authors concluded that tinnitus-related comorbidities were more strongly associated with tinnitus impact in comparison to demographic variables (including tinnitus specific factors). (9)

When back-transformed, the variables of hearing loss, hyperacusis and chronic pain had a difference of more than 13 points on the TFI between two answer options in the multivariable analyses. A 13-point difference in TFI score is considered to be the minimal clinically important difference to be perceived as an effect or change. (17) Therefore, these factors can potentially make a difference in terms of an individual's experienced impact of tinnitus on daily life according to on our study results. These three factors have also been identified as risk factors in other studies. (9,22–24)

Anxiety and depression are commonly described to be associated with tinnitus. (4) In our study, the association found between HADS-A and HADS-D and the TFI was relatively small. This might be explained by several reasons, such as the nature of the sample (general population) or by the fact that these measures only scored symptoms instead of having an anxiety or a depressive disorder itself. In addition, we did not correct for any potential treatment or medications for anxiety or depression that might have altered anxiety or depressive symptoms and therefore the observed association.

The outcome of the single question, "how big of a problem is your tinnitus", with a scoring in five categories, was found to be associated with the scales of impact defined for the TFI score. (16,17) Specifically, in three out of five categories, this single-item score was very close or within the cut-off values of the originally defined TFI scales. (17) For example, the answer option, 'large problem' on the single-item question predicted a TFI score of 55.9 points, which falls within the range of the defined TFI scale 'large problem' (TFI score 54–72). Currently, lengthy questionnaires are used to assess tinnitus impact. The results of our study could be of interest for population studies wherein tinnitus prevalence and impact are assessed. (2) Rather than having

to administer a lengthily questionnaire, a single-item question may suffice.

The major strength of the current study is the assessment of associations with tinnitus impact in a non-clinical sample. Nonetheless, certain limitations are applicable to our study. First, although we invited a sample of the Dutch population to participate in our survey, the response resulted in a sample of participants with a higher mean age than is representative of the overall Dutch population. (25) Secondly, in survey research, there is always a balance between the urge to ask more questions and the limitations of the length of the questionnaire in terms of burden on the participant. The already-lengthy questionnaire might have been of consequence to the limited response rate (41.4%). We only asked participants who experienced tinnitus sounds of a certain frequency and duration to fill out the TFI to measure the impact of tinnitus on daily life. (10,15) In hindsight, it would have been interesting to assess the impact of the experienced tinnitus more broadly. Consequently, we might have missed several participants who did not meet our criteria of being a tinnitus participant but in whom tinnitus might have affected their daily life.

How can the outcomes of our study be used in clinical care and future research? The associations we found highlight the effect of comorbidities on tinnitus impact, not only in those who seek help but also in those in the general population. Based on the present study, we cannot draw any conclusions about the causality or mechanisms of the found associations, nor about the appropriateness of findings fitting one of the current pathophysiological models of tinnitus. (26–28) However, in clinical care, it might be helpful to ask patients about the studied associations with tinnitus impact. Future preventive measures for tinnitus impact might be targeted at the associations found in this study and could be targeted toward these groups. However, whether therapy or preventive measures that focus on common risk factors actually diminishes the impact of tinnitus on daily life remains to be determined by further research.

Conclusions

In this study, we assessed associations between demographics, tinnitus specific-, audiological-, general- and mental health factors, and the impact of tinnitus on daily life, as measured with the TFI. Based on the ultimate effect on the TFI score of the different variables, we can conclude that audiological variables, such as hearing problems and hyperacusis, have the largest effects on the TFI compared to the other variables assessed.

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6

CHAPTER 7

Prediction Models for Tinnitus Presence and the Impact of Tinnitus on Daily Life: A Systematic Review

Journal of Clinical Medicine 2023, 12(2), 695

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Abstract

The presence of tinnitus does not necessarily imply associated suffering. Prediction models on the impact of tinnitus on daily life could aid medical professionals to direct specific medical resources to those (groups of) tinnitus patients with specific levels of impact. Models of tinnitus presence could possibly identify risk factors for tinnitus. We systematically searched the PubMed and EMBASE databases for articles published up to January 2021. We included all studies that reported on multivariable prediction models for tinnitus presence or the impact of tinnitus on daily life. Twenty-one development studies were included, with a total of 31 prediction models. Seventeen studies made a prediction model for the impact of tinnitus on daily life, three studies made a prediction model for tinnitus presence and one study made models for both. The most used predictors in the final impact on daily life models were depression- or anxiety-associated questionnaire scores. Demographic predictors were most common in final presence models. No models were internally or externally validated. All published prediction models were poorly reported and had a high risk of bias. This hinders the usability of the current prediction models. Methodological guidance is available for the development and validation of prediction models. Researchers should consider the importance and clinical relevance of the models they develop and should consider validation of existing models before developing new ones.

Introduction

Prediction models are made to inform clinical decision making. They quantify the relative importance of findings, characteristics and different types of factors when evaluating an individual patient.(1) Over the past decade, there has been a steep increase in the number of prediction models in clinical research. Before it can be decided whether models on tinnitus prediction could be applied in clinical care and research, more clarity regarding the quality, performance and outcomes of these models is necessary.

Tinnitus can be described as the hearing of a phantom sound. The sheer presence of tinnitus does not necessarily imply associated suffering. Quality of life is severely reduced in 0.5–1% of the population due to tinnitus. (2) Because of this, recently two operational definitions have been proposed to distinguish between the two: tinnitus and tinnitus disorder. (3) To measure the impact of tinnitus on daily life multi-item questionnaires are used in clinical practice such as the Tinnitus Functional Index (TFI), the Tinnitus Handicap Inventory (THI) and the Tinnitus Questionnaire (TQ) or single-item questions.(3–6)

Adequate prediction of the experience of tinnitus or the impact of tinnitus on daily life could be beneficial for preventive or therapeutic purposes. Prediction models on the impact of tinnitus on daily life could aid medical professionals to direct specific medical resources to those (groups of) tinnitus patients with specific levels of impact. Models on tinnitus presence could possibly identify risk factors for tinnitus. Through this, preventive measures could be taken to avoid the potential negative impact of tinnitus on daily life.

In prediction models, the patient specific value of each included factor is taken and combined to calculate risk estimates on the outcome for each individual. For adequate development of a clinically useful prediction model, three steps are needed. In the first step, the model is derived. This phase includes the identification of predictors, for which weights are obtained. Model validation is the second phase. During the development of a model, internal validation serves to assess and correct overfitting in the model. With external validation, the performance of the model is assessed in a different dataset. In the third and last phase, the model's clinical impact is assessed by using the prediction rule as a decision rule. (7) In prognostic model development, it is advised that one should search, review, critically appraise and externally validate already existing prediction models before one starts to develop a new prediction model. (7) We aimed to systematically review the published prediction models of tinnitus presence and impact on daily life.

Materials and Methods

In this systematic review, we followed the Cochrane guidance for critical appraisal and data extraction for systematic reviews of prediction modelling studies (the CHARMS checklist) and the preferred reporting items for systematic reviews and meta-analyses (PRISMA). (8,9)The protocol for this systematic review was registered at the international prospective register of systematic reviews (PROSPERO) with registration number CRD42021240493. (10)

Search Strategy

We searched the electronic literature databases of PubMed and EMBASE on the 21st of January 2021. The Ingui filter for finding studies on clinical prediction models was used in our search. (11) The search syntax can be found in Appendix A. In addition to the electronic database searches, reference lists were screened to identify additional studies. We searched for developmental as well as validation studies.

Study Selection/Eligibility Criteria

We included all studies that reported on multivariable prediction models. Multivariable models were defined as having two or more predictors included. Models were included when predicting the presence of tinnitus in adults or the effect of tinnitus on daily life. We included a broad range of outcomes to measure tinnitus-related effects on daily life. These included, but were not restricted to: tinnitus burden, tinnitus severity, tinnitus distress, tinnitus-associated quality of life, tinnitus-associated annoyance and tinnitus intrusiveness. These outcomes could be measured by using single-question and multiple-question questionnaires. We excluded letters to editors, reviews and animal studies. If articles reported multiple prediction models with a unique combination of predictors, we considered these as separate models.

We differentiated between articles reporting on the development and the external validation of studies. Articles were classified as developmental studies if the authors described the development of one or multiple models in their objectives or conclusions or if it was clear from other information (like information in the methods section) that a prediction model was developed in the study.

Screening Process

Two researchers (I.S., M.M.R.) independently screened the title and abstract of the articles for eligibility after removal of duplicates. Subsequently, the selected studies were reviewed for full text screening using predefined inclusion and exclusion criteria. Disagreements were resolved by discussion.

Data Extraction and Analysis

We created a data extraction form. This was based on the CHARMS checklist and previous research projects. (9,12,13) The following items were extracted from the included studies and included in the data extraction form: authors of the study, year of publication, journal of publication, the continent where the research was conducted, study design, study setting, instrument(s) used to measure the impact of tinnitus on daily life or tinnitus presence, the provided definition of tinnitus, percentage of patients with tinnitus in the study, mean impact of tinnitus on daily life measured with questionnaires or single questions, duration of tinnitus, number of research centres, number of participants, gender of the included patients, age of the included patients, horizon of prediction, number of predictor candidates, number of included predictor candidates in the final model, the number of predictor models, missing data, used statistical methods and the results of the prediction model. The data extraction form was triple checked by S.M.M.

Critical Appraisal (CAT)

The risk of bias (RoB) of the included studies was independently assessed by two researchers (M.M.R., I.S.) using the prediction model RoB assessment tool (PROBAST). (14). The PROBAST tool consists of 20 signaling questions divided over four domains: participants, predictors, outcome and analysis. These domains were scored on RoB and applicability as low, high or unclear risk, based on the criteria that were provided by PROBAST. (14) PROBAST provided specific definitions for different domains to detect RoB. For example: the reasonable number of participants with a specific outcome relative to the number of candidate predictor candidates is defined as >20 (EPV >20) in model development studies. For the specific definition per domain and more explanation see: Moons et al. 2019: PROBAST: A tool to assess Risk of Bias and applicability of prediction model studies: Explanations and Elaboration. (15) Disagreements between the two researchers were solved by discussion.

Descriptive Analyses

The results of the data-extraction were summarized with descriptive statistics. No quantitative analyses were performed as this was beyond the scope of our study

Results

Search Results

Our search yielded 3241 hits on PubMed and 5217 hits on EMBASE. After deduplication (n = 2718), we screened 5740 articles on title and abstract. Of those, we read the full text of 73 articles. One study was screened after cross referencing and was not included in the final selection. Based on the predefined inclusion and exclusion criteria, we included 21 studies in this systematic review. Of those, 21 were developmental studies and 0 involved external validation of studies. (Figure 1: flowchart)

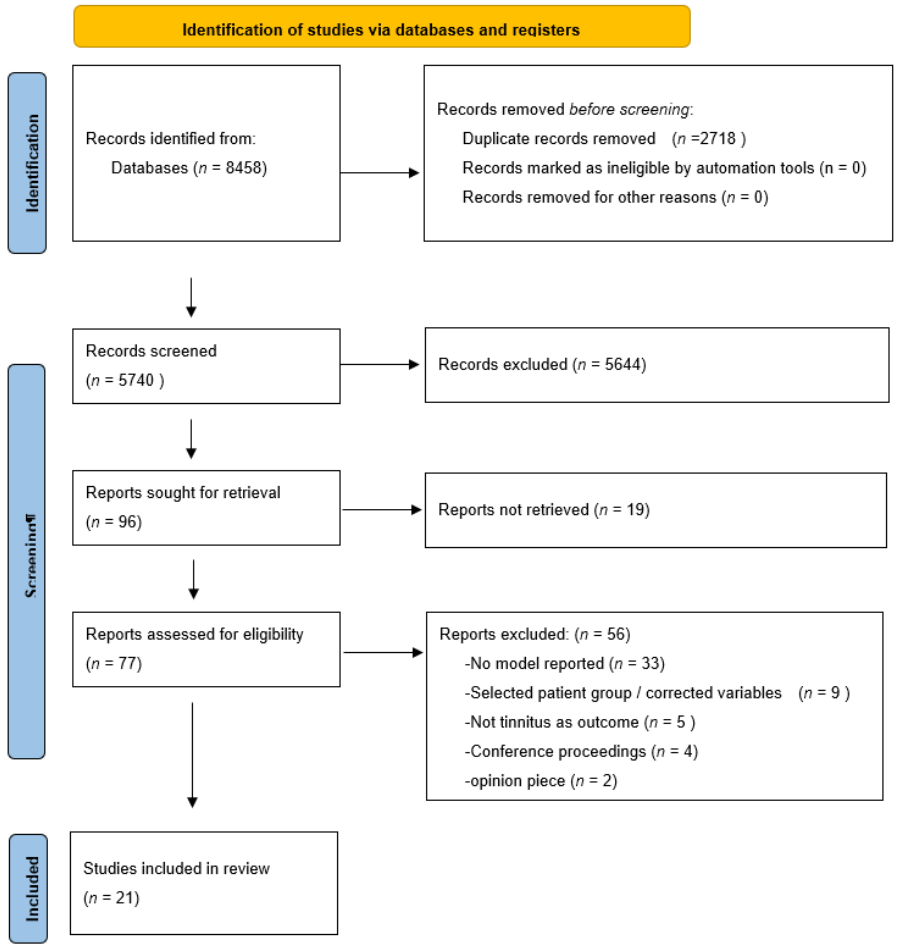

Figure 1. PRISMA flowchart.

Developmental Studies

Study Design and Study Populations

The 21 developmental studies were published between 1999 and 2021. Of these, 71% took place in Europe. Fourteen out of the 21 studies reported on one prediction model. Dawes et al., Andersson 2005 et al. and Beukes et al. reported on three models(16–18) and four studies reported on two models (19–22). Four studies were retrospective cohort studies (20,23–25), two studies were prospective cohort studies (21,26)and 13 studies had a cross sectional design (16–19,22,27–35). One had a nested case control design. (36) Twelve out of 21 studies were performed in a hospital setting at an outpatient clinic (17,18,20,22–26,29,30,32,35) seven studies were performed in the general population (16,19,21,27,28,31,34), one in a general practice setting and one in a combination of a hospital and the general population (33,36). The number of participants per study varied between 44 and 168348. The reported mean age varied between 35.8 years and 69 years. The percentage of female participants ranged between 27.7% and 66.5%. The mean duration of tinnitus was reported in nine studies and ranged between 1.6 weeks and 12.5 years. (17,18,20,22,24–26,29,32) (see Table 1).

Risk of Bias

Based on the criteria that were provided by PROBAST (14), the overall RoB was judged to be high in all studies, mainly due to a high RoB in the analysis domain. No studies accounted for overfitting, underfitting or optimism. No studies reported on relevant model performance measures. The RoB in the participants, predictor and outcome domain was low. Ten studies reported on a reasonable number of participants with the outcome (16,17,19,21,27–29,31,33,36), and for four studies no information on this account was provided (25,26,34,35). Eight studies did not handle missing data appropriately (16,18,20,23,25,27,29,31), and thirteen studies did not provide any information on missing data (17,19,21,22,24,26,28,30,32–36). The applicability of the participants, predictor and outcome domain was judged to be low (see Table 2: CAT).

Outcomes of Prediction Models

A total of 31 prediction models were described in the 21 included studies. Seventeen studies made a prediction model for the impact of tinnitus on daily life (17–20,22–27,29–35) three studies made a prediction model for tinnitus presence (21,28,36) and one study made models for both (16).

Table 1. Study characteristics

	Number of models	Aims to predict tinnitus	Setting	Location	Design	Number of centers	N = in study	N= in model	Age in years mean (SD, range)	Gender (% female)	Mean duration of tinnitus in years (SD)
Aazh 2017(23)	1	Impact	Outpatient clinic	Europe	RCS	1	184	148	69, (NR, NR)	NR	NR
Andersson 1999 (24)	1	Impact	Outpatient clinic	Europe	RCS	1	216	207	50.6 (13.8,14-77)	41%	7 (7.5)
Andersson 2005 (17)	3	Impact	Outpatient clinic	Europe	CSS	1	256	256	51 (13.6, 18-83)	43%	10.3 (13.6)
Basso 2020 (19)	2	Impact	General population	Europe	CSS	NA	7615	7615	35.8 (12.44, 11-84)	56.5%	NR
Beukes 2021 (18)	3	Impact	Outpatient clinic	Europe	CSS	3	326	326	55.5 (12.7, 22-83)	43%	10.3 (11.4)
Bhatt 2018 (27)	1	Impact	General population	North America	CSS	NA	678	289	NR (NR, 18-30)	66.5%	NR
Bruggeman 2016 (35)	1	Impact	Outpatient clinic	Europe	CSS	1	531	140	49 (13.29, 16-59)	53%	NR
Couth 2019 (28)	1	Presence	General population	Europe	CSS	NA	22936	5727	53.9 (7.87, NR)	27.7%	NR
Dawes 2020 (16)	3	Impact and Presence	General population	Europe	CSS	NA	168348	29861▲	58.7 (7.58, NR)	47.2%	NR
Degeest 2016 (32)	1	Impact	Outpatient clinic	Europe	CSS	1	81	81	47.6 (14.4, 18-73)	35%	4.1 (6.2)
Han 2019 (22)	2	Impact	Outpatient clinic	Asia	CSS	1	248	248	Female: 55.8 (14.5, 20-82)Male: 52,2 (13.4, 20-82)	54%	Female: 29.1 (64.5)*Male: 42.1 (81.2)*
Hesser 2015 (29)	1	Impact	Outpatient clinic	Europe	CSS	1	362	316	59.6 (11.6, NR)	48%	12.5 (9.4)
Hoekstra 2014 (20)	2	Impact	Outpatient clinic	Europe	RCS	1	309	309	51 (NR, 17-82)	32.7%	7 (2-48)*
Holgers 2005 (30)	1	Impact	Outpatient clinic	Europe	CSS	1	127	127	Female 57 (16, NR) Male 52 (13, NR)	42.5%	NR
Kim 2015 (34)	1	Impact	General population	Asia	CSS	NA	19290	4234	NR (NR,NR)	57%	NR

Table 1. CONTINUED.

	Number of models	Aims to predict tinnitus	Setting	Location	Design	Number of centers	N = in study	N= in model	Age in years mean (SD, range)	Gender (% female)	Mean duration of tinnitus in years (SD)
Kostev 2019 (36)	1	Presence	General practices	Europe	Nested case control	NA	37692	37692	57.5 (16.6, NR)	55.5%	NR
Langenbach 2005 (25)	1	Impact	Outpatient clinic	Europe	RCS	1	44	34	47.3 (NR, 19-78)	36.4%	1.6 (1.1)**
Moore 2017 (21)	2	Presence	General population	North America	PCS	NA	4950	4950	NR (NR, NR)	NR	NR
Strumilla 2017 (33)	1	Impact	Hospital & general population	Europe	CSS	1	212	212	48 (14.02, NR)	50.9%	NR
Unterrainer 2003 (26)	1	Impact	Outpatient clinic	Europe	PCS	2	149	149	51.6 (14.2, NR)	48.3%	711 (98.8)*
Wallhausser 2012 (31)	1	Impact	General population▾	Europe	CSS	NA	4705	4705	58.6 (11.76, 18-94)	40.9%	NR

Symbols and abbreviations of table 1:, RCS= retrospective cohort study, PCS= prospective cohort study, CSS = cross sectional study NR = not reported *= in months , **= in weeks ▲= in the methods section n= 29861 tinnitus sufferers were reported and n=9751 patients with bothersome tinnitus. In table 3 n=80380 tinnitus sufferers were mentioned. Age and gender are extracted from table 2. ▾= Survey sent to members of the German tinnitus association

Table 2. Critial Appraisal of Topic (CAT)

	Signaling questions	Aazh 2017 (23)	Andersson 1999 (24)	Andersson 2005 (17)	Basso 2020 (19)	Beukes 2021 (18)	Bhatt 2018 (27)	Bruggeman 2016 (35)	Couth 2019 (28)	Dawes 2020 (16)	Degeest 2016 (32)	Han 2019 (22)	Hesser 2015 (29)	Hoekstra 2014 (20)	Holgers 2005 (30)	Kim 2015 (34)	Kostev 2019 (36)	Langenbach 2005 (25)	Moore 2017 (21)	Strumilla 2017 (33)	Unterrainer 2003 (26)	Wallhausser 2012 (23)
1.Participant selection	1	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES
	2	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES
	Risk of bias	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW
	1	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES
	Applicability	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW
2.Predictors	1	YES	PY	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES
	2	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES
	3	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	Risk of bias	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW
	Applicability	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW
3.Outcome	1	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES
	2	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES
	3	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES
	4	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES
	5	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES
	6	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES
	Risk of bias	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW
	Applicability	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW
4.Analysis	1	NO	NO	YES	YES	NO	YES	NI	YES	YES	NO	NO	YES	NO	NO	NI	YES	NI	YES	YES	NI	YES
	2	YES	YES	YES	NO	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	NO	PY	YES	YES	YES	YES	NO
	3	NO	YES	PY	PY	YES	YES	NO	YES	YES	YES	YES	YES	YES	YES	YES	PY	YES	YES	YES	YES	YES
	4	NO	NI	NI	NI	NO	NO	NI	NI	NO	NI	NI	NO	NO	NI	NI	NI	NO	NI	NI	NI	NO
	5	YES	NO	NO	NO	NO	YES	YES	YES	YES	NO	YES	YES	NO	NO	NI	YES	NO	YES	YES	YES	YES
	6	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	YES	NI	NI	NI	NI	NI	NI

Table 2. CONTINUED.

	Signaling questions	Aazh 2017 (23)	Andersson 1999 (24)	Andersson 2005 (17)	Basso 2020 (19)	Beukes 2021 (18)	Bhatt 2018 (27)	Bruggeman 2016 (35)	Couth 2019 (28)	Dawes 2020 (16)	Degeest 2016 (32)	Han 2019 (22)	Hesser 2015 (29)	Hoekstra 2014 (20)	Holgers 2005 (30)	Kim 2015 (34)	Kostev 2019 (36)	Langenbach 2005 (25)	Moore 2017 (21)	Strumilla 2017 (33)	Unterrainer 2003 (26)	Wallhausser 2012 (23)
	7	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
	8	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
	9	NA	NA	Na	NA	NA	NA	NA	NA	NA	Na	NA	NA	NA	Na	NA	NA	NA	NA	NA	NA	NA
	Risk of Bias	High	High	High	High	High	high	High	high	High	high	High	High	High	High	High	High	High	high	High	High	High
Overall	Risk of Bias	High	High	High	High	High	High	High	High	High	High	High	High	High	High	High	High	High	High	High	High	High
	Applicabilty	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW

Abbreviations:. No information = NI, Probably YES = PY, Probably NO = PN. NA not applicable

Tinnitus Impact

The impact of tinnitus on daily life was assessed by using different multi-items in 13 studies (17,18,20,22,23,25–27,29,31–33,35). The THI was used in eight studies. (20,22,23,26,27,29,32,33). The TQ was used by two studies (20,35) and the psychological distress scale of the TQ was used by one study (25). The mini Tinnitus Questionnaire (mTQ) was used in one study. (31) One study used the Tinnitus Reaction Questionnaire (TRQ). (17) One study used the Klockhoff and Lindblom classification of tinnitus severity scale. (24) Three studies used single-item questionnaires to measure the impact of tinnitus. (16,19,30) The questions and answer possibilities used are reported in Table 3.

The reported mean THI scores varied between 38.3 and 48.3 points. Bhatt also used the THI but did not report the mean THI score. (27) Instead, they reported that 88.5% of the patients had a THI score <16, whereas 8.6% had a score >18. Beukes et al. did not report the mean TFI score, but subdivided the TFI score into three categories demonstrating that 10% had a score below 25 (mild tinnitus), 30% had a score between 25 and 50 (significant tinnitus) and 60% had a sore above 50 (severe tinnitus). (18) Wallhauser-Franke et al. categorized outcomes of scores using the mTQ: 37.6% had a total score of seven or lower, 49% had a total score between 8 and 18, and 13.4% had a total score of 19 or higher. (31) Andersson (2005) used the TRQ and reported a mean of 37.4. (17) . The studies using single-item questionnaires reported 'bothersome tinnitus' with different definitions in 9.1–30.9% of the cases. (16,19,28)

Predictors of Tinnitus Impact

The number of candidate predictors reported in the included studies varied between two and 70. (16–20,22–27,29–35) In three studies, the number and type of predictor candidates were not (clearly) reported and therefore the predictor candidates could not be extracted(25,26,34)The five most common candidate predictors for tinnitus impact were: depression-related questionnaire scores (in 15 models), anxiety-related questionnaire scores (in 15 models), age (in 14 models), gender (in 9 models) and tinnitus duration (in 10 models) (Table 4/Appendix B).

The number of final model predictors for impact models differed between two and 13. In the prediction models on the impact on daily life, scores of questionnaires in which depressive symptoms (n = 12) were assessed or symptoms of anxiety (n = 8) were most commonly used. In addition, age (n = 5), gender (n = 3), alcohol use (n = 2), smoking (n = 2), occupational noise exposure (n = 2), music noise exposure (n = 2), tinnitus duration (n = 2) and tinnitus location (n = 1) were used.

Table 3. Studies with impact of tinnitus on daily life as outcome.

	Outcome	Method Modelling	Mean Outcome of Measured Impact of Tinnitus on Daily Life	Prediction Horizon	# Predictor Candidates	# Predictors in Model
Aazh 2017 (23)	THI	Multiple linear regression	45.8 (23) [1]	CS	11	7
Andersson 1999 (24)	Klockhoff and Lindbloms classification	Discriminant function analysis	grade I 5% Grade II 57% Grade III 38%	CS	21	4
Andersson 2005 (17)	TRQ (all)	Multiple linear regression	37.4 (26.8) [2]	CS	8	8
	TRQ (Male)	Multiple linear regression	NR	CS	8	8
	TRQ (female)	Multiple linear regression	NR	CS	8	8
Basso 2020 (19)	Single question [3] (female)	Multivariable adjusted regression	9.1%	CS	37	13
	Single question [3] (male)	Multivariable adjusted regression	9.2%	CS	37	8
Beukes 2021 (18)	TFI	Hierarchical linear multiple regression	10% mild [4] 30% significant 60% severe	CS	23	3
Bhatt 2018 (27)	THI	Linear regression	88.5% THI < 16 8.7% THI > 18	CS	10	10
Bruggeman 2016 (35)	TQ	Multiple regression	34.73 (16.38) [5]	CS	13	8
Dawes 2020 (16)	Single question [6]	Multinomial logistic regression	5.8%	4.3 y (2–7)	13	13
Degeest 2016 (32)	THI	Stepwise multiple regression	44.2 (24.9)	CS	22	2
Han 2019 Female	THI (female)	Stepwise multiple linear regression	43 (25.9)	CS	9	2
(22)Male	THI (male)	Stepwise multiple linear regression	38.3 (25.9)	CS	9	3
Hesser 2015(29)	THI	Multiple ordinary least square regression analysis	39.15 (22.2)	CS	7	7
Hoekstra 2014 (20)	TQ	Stepwise multiple regression	40 (17)	CS	28	4
	THI	Stepwise multiple regression	45 (23)	CS	28	5
Holgers 2005(30)	Severe tinnitus [7]	Stepwise forward regression analysis	24%	18 months	70	3
Kim 2015 (34)	Single question [8]	Multiple logistic regression, backward elimination, complex sampling	30.9%	CS	NR	5
Langenbach 2005 (25)	Psychological distress of TQ scale	Multiple stepwise regression	NR	6 months	NR	3
Strumilla 2017 (33)	THI	Stepwise forward linear regression models	48.3 (22.54)	CS	2	2

Table 3. CONTINUED.

Outcome		Method Modelling	Mean Outcome of Measured Impact of Tinnitus on Daily Life	Prediction Horizon	# Predictor Candidates	# Predictors in Model
Unterrainer 2003 (26)	THI	Ordinal logit regression	NR	CS	NR	9
Wallhausser 2012 (31)	Mini TQ_	Binary stepwise logistic regression	≤7: 37.6% 8-18: 49% ≥ 19: 13.4%	CS	15	8

Symbols and abbreviations: # = total number CS = cross sectional. [1] = mean of n = 178, model was made in n = 148. [2] = only provided for model including females and males. [3] = Question: "Is there a constant ringing in the ears or do you have any other bothersome sound in the ears (tinnitus)? Answer: Constant and bothersome: "All the time, the sound is very bothersome" or Intermittent and non-bothersome: "Sometimes, but the sound doesn't bother me". [4] = mild = 0–25 points, significant 25–50 points, severe = 50 or more points. [5] = of all participants, model in n = 140. [6] = How much do these noises worry, annoy or upset you when they are at their worst?'; severely, moderately, slightly or not at all. In this analysis, 'bothersome' tinnitus was identified on the basis of responses of either 'moderately' or 'severely'. [7] = Severe tinnitus suffering (STS) refers to patients who fulfilled the following criteria: (1) Absence from work more than one consecutive month, (2) more than three visits to the therapist or the audiological physician. The STS and non-STS patient groups were compared. [8] = Have you heard any ringing, buzzing, roaring, or hissing sounds without an external acoustic source in the past year? If yes: do these sounds bother you? No, a little annoying, and very annoying

Table 4. Most frequently used predictor candidates and included predictors.

Predictor Category	Predictor Candidates		In Final Model	
	# Predictor Candidates in Tinnitus Presence Models	# Predictor Candidates in Model on Tinnitus Impact on Daily Life	# Used in Tinnitus Presence Models	# Used in Models on Tinnitus Impact on Daily Life
Demographic				
Age	4	15	2	5
Gender	4	9	3	3
Risk factors				
Alcohol use	1	5	1	2
Smoking	1	5	2	2
Noise exposure				
Occupational noise exposure	3	2	1	2
Music noise exposure	2	2	1	2
Tinnitus specific				
Duration	0	10	0	2
Location	0	9	0	1
Depression				
Depression questionnaires combined	0	15	0	12
Anxiety				
Anxiety questionnaires combined	0	12	0	8

= total number

Modelling Method and Prediction Horizon in Tinnitus Impact Models

Multiple different modelling methods were used: Multiple linear regression (17,23), Stepwise multiple regression (20,25,32), multivariable adjusted regression (19), hierarchical linear multiple regression (18), ordinal logit regression(26) , discriminant function analysis (24), linear regression (27), multiple regression (35), stepwise multiple linear regression (22), multiple ordinary least square regression analysis (29), stepwise forward regression analysis (30,33), multiple logistic regression, backward elimination with complex sampling (34), binary stepwise logistic regression (31), and multinomial logistic regression (16). Only the studies by Dawes et al., Holgers et al. and Langebach et al. had a reporting horizon of, respectively, 4.2 years, 18 and 6 months (16,25,30). All other studies were cross-sectional designs.

Model Presentation and Predictive Performance in Tinnitus Impact Models

All except Andersson 1999 et al. (24) and Andersson 2005 et al. (17) presented a regression slope, and two studies also presented a intercept (18,30). Overall model performance was reported by the proportion of variance (R2) in eleven studies. (17–20,23–25,27,31,33). Holgers et al. used a probability regression plot. (30) The other studies did not report about predictive performance. (22,26,28,29,35,36). (Table 5)

Table 5. Overall reported performance measures.

		Prediction Models on Tinnitus Impact on Daily Life	Prediction Models on Tinnitus Presence
Overall performance measures	R^2	11 (16–20,23–25,27,29,32)	(16,32)
	Other	1 (30)	1 (21)
	Any	-	
Discrimination and calibration measures	C statistic/AUC	-	
	Other	-	
	Hosmer Lemeshow	-	
	Other	-	
Internal validation		-	

Abbreviations: R2 = R-squared; AUC = Area under the receiver operating characteristic curve.

Tinnitus Presence

Tinnitus presence was assessed with different questions. The questions and answer possibilities used are reported in Table 4. In Kostev et al., tinnitus presence was defined using the first International Classification of Diseases (ICP) diagnosis of tinnitus. (36) Patients with ICP diagnosed tinnitus were matched 1:1 with persons without tinnitus. (Table 6). The presence of tinnitus reported in the four studies varied between 17.3% and 59%. (16,21,28,36)

Predictors of Tinnitus Presence

The number of candidate predictors reported in the included studies varied between 16 and 125. (16,21,28,36) The most common candidate predictors for tinnitus presence were: Gender (in 5 models), age (in 3 models) and occupational or music noise exposure (both in 3 models). In the final models the most commonly used predictors were gender (n = 3) followed by age (n = 2). (Table 4/Appendix B).

Modelling Method and Prediction Horizon in Tinnitus Presence Models

Multiple different modelling methods were used: logistic hierarchical regression (28) , multinomial logistic regression (16), Stepwise multivariate logistic regression (36), multinomial logit regression model (21). Only the study of Dawes et al. had a prediction horizon of respectively 4.3 years. (16)The other studies had a cross-sectional design.

Model Presentation and Predictive Performance in Tinnitus Presence Models

All studies presented a regression slope. Couth et al. reported an intercept. (28) . Overall model performance was reported by proportion of variance (R2) by two studies. (16,28) Moore et al. (21) used the Akaike Information Criterion. (37) Kostev et al. did not report their predictive performance. (36) (Table 6)

Validation Studies

Zero studies were internally validated.

Table 6. Studies with tinnitus presence as an outcome.

	Outcome	Method Modelling	Presence	Prediction Horizon	# Predictor Candidates	# Predictors in Model
Couth 2019 (28)	Single question [1]	Logistic hierarchical regression	17.29%	CS	16	16
Dawes 2020 (16)	Single question [2]	Multinomial logistic regression	17.7%	4.3 y (2–7)	13	13
Kostev 2019 (36)	ICP diagnosis of tinnitus [3]	Stepwise multivariate logistic regression	1:1 matched cohort with 18,846 tinnitus patients	CS	125	20
Moore 2017 (21)	Tinnitus frequency (rate of occurrence) [4]	Multinomial logit regression models (se regression)	59%	CS	12	6

Abbreviations and symbols: CS = cross sectional. [1] 'Do you get or have you had noises (such as ringing or buzzing) in your head or in one or both ears that last more than 5 min at a time?" (a) Yes, now, most or all of the time; (b) Yes, now, a lot of the time; (c) Yes, now, some of the time; (d) Yes, but not now, but have in the past; (e) No, never; (f) Do not know; or (g) Prefer not to answer. The presence of tinnitus was characterized by participants currently having symptoms at least "now some of the time. [2] 'Do you get or have you had noises (such as ringing or buzzing) in your head, or in one or both ears, that last for more than five min at a time?' yes most of the time', 'yes a lot of the time' or 'yes some of the time. [3] Patients who had received a first tinnitus diagnosis (International Classification of Diseases, 10th revision [ICD-10]: H93.1). [4] How often nowadays do you get tinnitus (noises such as ringing or buzzing in your heard or ears) that lasts for more than.

Discussion

In this systematic review, we presented the published prediction models on tinnitus presence, and the impact of tinnitus on daily life. We identified 21 different studies with a total of 31 models. Of these 31 models, five reported on tinnitus presence and 26 on the impact of tinnitus on daily life. For models of tinnitus presence, the most common predictors were age, gender and smoking. For models in which the impact of tinnitus of daily life was predicted, scores of depression-associated questionnaires and anxiety-associated questionnaires were the most common. Model performance was mostly reported by using the proportion of variance (R2).

Despite the high number of developed models, the quality of prognostic modelling in tinnitus research is low. To date, regrettably, no models have been validated. Due to the lack of validation and impact analyses, the models cannot be used in clinical care. None of the included models were tested for calibration and discriminative performance. (38) Earlier studies showed that the discriminative and calibration abilities of models which are based on small datasets with simple statistical methods are generally poor. The use of categorized instead of continuous data further lowers that performance. (39) Therefore, it is necessary that sufficient statistical methods are used in the context of prediction modelling. (38)

Van Royen et al. recently described the difficulties of model adaptation to clinical care. The authors described four reasons why the adaptation of prediction models can fail. (7) The first reason is that models do not fit a clinical purpose, for example when a model includes a patient population that does not correspondent with the patient population in the clinic. A second reason is that the model is not validated, or reporting is incomplete. As demonstrated in this manuscript, this is applicable for the present tinnitus models. This makes it difficult for clinicians and researchers to further develop and use the models. The third reason is that there are difficulties with the implementation—for example, when the model has no impact on decision making, or when local or national regulations are a hindrance to the implementation. The last reason is failed model adaption. Examples include non-useful or non-trusted predictions, or outdated models. Most of these reasons seem to fit the tinnitus literature, whereby the lack of validation, lack of fitness for purpose due to different opinions about outcome measures, included populations and poorly reported models seem to be most prominent.

Collaboration between different research groups can lead to less accumulation or repeating of studies. (40) An improvement in tinnitus prediction research might be to improve and intensify these collaborations. Currently, there is still room for improvement. For example, many similar predictor candidates were used by the different models, of which only a minority are used in the final model. We noticed that tinnitus-specific variables and variables on somatic comorbidities are most frequently used as predictor candidates. However, the tinnitus specific variables were only used in about 25% of the final models. This is in contrast to demographic factors and somatic or psychological comorbidities. These groups of variables tend to end up in the final model in about 50%. This raises the question of whether or not we should continue researching the predictive value of tinnitus-specific variables or put the scope on other domains of characteristics. This review might serve as a base for future research groups to critically assess which predictor candidates or predictors they should use, to improve prediction models' performance and their application in clinical practice. The focus could then be shifted towards model validation, rather than more model development studies.

Prediction models aim to provide guidance in clinical decision making, and should therefore be handled with care by those who develop the models. In all these stages of prediction model development, clinical knowledge about the setting, patients and pathways should be combined with the statistical and methodological know-how of model development. Therefore, we advise researchers to develop prediction models in a collaborative effort involving clinicians, statisticians and epidemiologists. The use of reporting tools can also be a helpful next step in improving tinnitus prediction modelling. Guidance can further be found in the PROBAST statement, which can help with identifying the risk of bias in prognostic studies, whereas the TRIPOD statement is suitable for guidance in reporting. (14,41)As demonstrated in our study, the majority of studies based their model on statistical methods. However, it is recommended to build models based on clinical expertise and previous literature, rather than making them purely data driven. (42) Other ideas to improve the quality of future research are the use of prospective, large, population-based studies, and the consequent use of similar, validated, outcome measures such as the TFI. (3) This would help compare prediction models in meta-analyses, and would ease external validation. This might help to create clinically applicable prediction models.

Conclusions

We identified 21 different studies, which report a total of 31 models on either the presence or the impact of tinnitus on daily life. All included models were in the development stage. The reporting of the models was found to be poor and the risk of bias high. No studies regarding model validation or risk assessment were found. Knowing the impact prediction models can have on clinical decision making as well as on directing future research and policy making, we need to improve the quality of our prediction research. Better reporting of methods, collaboration between research groups and disciplines could aid future prediction model development.

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Appendix A

Table A1. Search strategy.

	PubMed	(("Tinnitus"[Mesh] OR Tinnitus [tiab])
	AND	(("Risk Factors"[Mesh] OR "Predictive Value of Tests"[Mesh] OR prediction model*[tiab] OR prediction rule*[tiab] OR decision support*[tiab] OR predictive model*[tiab] OR risk prediction*[tiab] OR risk scoring system*[tiab] OR scoring scheme*[tiab] OR risk assessment*[tiab] OR risk appraisal*[tiab] OR risk assessor*[tiab] OR risk calculation*[tiab] OR risk factor*[tiab] OR predict*[tiab] OR scoring system*[tiab]) OR ((Validat*[tiab] OR Predict*[tiab] OR Rule*[tiab]) OR (Predict*[tiab] AND (Risk*[tiab] OR Model*[tiab] OR Decision*[tiab] ((Criteria[tiab] OR Scor*[tiab]) AND (Predict*[tiab] OR Model*[tiab] OR Decision*[tiab] OR Prognos*[tiab]) OR (Decision*[tiab] AND (Model*[tiab] OR logistic models[mesh])) OR (Prognostic[tiab] AND (Criteria[tiab] OR Scor*[tiab] OR Model*[tiab])))))) OR (("Discrimination"[tiab] OR "Discriminate"[tiab] OR "c-statistic"[tiab] OR "c statistic"[tiab] OR "Area under the curve"[tiab] OR "AUC"[tiab] OR "Calibration"[tiab] OR "Algorithm"[tiab]))))) OR (((tinnitus[Title/Abstract]) OR (tinnitus[MeSH Terms])) AND ((characterist*[Title/Abstract]) OR (risk*[Title/Abstract]))))
	EMBASE	'Tinnitus'/exp OR Tinnitus :ti,ab,kw
	AND	('risk factor'/exp OR 'risk assessment'/exp OR 'predictive value'/exp OR 'prediction'/exp OR prediction model*:ti,ab,kw OR prediction rule*:ti,ab,kw OR decision support*:ti,ab,kw OR predictive model*:ti,ab,kw OR risk prediction*:ti,ab,kw OR risk scoring system*:ti,ab,kw OR scoring scheme*:ti,ab,kw OR risk assessment*:ti,ab,kw OR risk appraisal*:ti,ab,kw OR risk assessor*:ti,ab,kw OR risk calculation*:ti,ab,kw OR risk factor*:ti,ab,kw OR predict*:ti,ab,kw) OR (validat*:ti,ab,kw OR predict*:ti,ab,kw OR rule*:ti,ab,kw OR (predict*:ti,ab,kw AND (risk*:ti,ab,kw OR model*:ti,ab,kw)) OR ((criteria:ti,ab,kw OR scor*:ti,ab,kw) AND (predict*:ti,ab,kw OR model*:ti,ab,kw OR decision*:ti,ab,kw OR prognos*:ti,ab,kw)) OR (decision*:ti,ab,kw AND (model*:ti,ab,kw OR logistic) AND 'models'/exp) OR (prognostic:ti,ab,kw AND (criteria:ti,ab,kw OR scor*:ti,ab,kw OR model*:ti,ab,kw)
	OR	**((Tinnitus:ti,ab,kw OR 'tinnitus'/exp) AND (characterist*:ti,ab,kw OR risk*:ti,ab,kw))**

Table A2. Used predictor candidates per study.

Predictor Categories			Tinnitus Presence Studies		Impact on Daily Life Studies	
Demographic		# used as predictor candidate for different (final) models	candidates	In final model	candidates	In final model
	Age	6	Couth 2019, Moore (2x), Dawes (1x)	Couth 2019, Dawes (1x)	Aazh, Basso 2020 (2x), Beukes 2020 (3x), Degeest 2016, Han 2019 (2x), Hesser 2016, Hoekstra 2014 (2x), Wallhauser 2012, Dawes (1x), Holgers 2005	Basso 2020 (2x), Hesser 2016, Kim 2015, Dawes (1x)
	Gender	5	Couth 2019, Moore (2x), Dawes (1x)	Couth 2019, Dawes (1x)	Beukes 2020 (3x), Bhatt 2018 (1x), Degeest 2016, Hoekstra 2014 (2x), Wallhauser 2012, Dawes (1x)	Bhatt 2018 (1x), Kim 2015, Dawes (1x)
	Ethnicity	2	Couth 2019	Couth 2019	Bhatt 2018 (1x),	Bhatt 2018 (1x)
	SES	2	Dawes (1x)	Dawes (1x)	Dawes (1x)	Dawes (1x)
	Townsend Quartiel	1	Couth 2019	Couth 2019		
	Marital Status	1			Basso 2020 (2x)	Bruggemann 2016
	Employment	1			Basso 2020 (2x), Hoekstra 2014 (2x)	Basso
	Industry type (vs finance)					
	Agricultural	1	Couth 2019	Couth 2019		
	construction	1	Couth 2019	Couth 2019		
	Music	1	Couth 2019	Couth 2019		
	Income level				Holgers 2005	
	Educational level	2			Basso 2020 (2x), Hoekstra 2014 (2x), Holgers 2005	Basso 2020 (2x), Hoekstra 2014 (1x)
Risk Factors	Alcohol use	2	Couth 2019	Couth 2019	Basso 2020 (2x), Dawes (2x), Holgers 2005	Dawes (2x)
	Smoking	3	Couth 2019	Couth 2019	Basso 2020 (2x), Bhatt 2018 (1x), Dawes (1x), Holgers 2005	Bhatt 2018 (1x), Dawes (1x)

Table A2. CONTINUED.

Predictor Categories			Tinnitus Presence Studies		Impact on Daily Life Studies	
	Snus use	1			Basso 2020 (2x)	
	Drug use	1			Basso 2020 (2x)	
	Ototoxic medication	3	Couth 2019, Dawes (1x)	Couth 2019, Dawes (1x)	Dawes (1x)	Dawes (1x)
Noise exposure	Loud noise exposure	0			Beukes 2020 (3x)	
	Occupational noise exposure	3	Couth 2019, Moore (2x)	Couth 2019	Dawes (2x)	Dawes (2x)
	Music noise exposure	3	Couth 2019, Moore (2x)	Couth 2019	Dawes (2x)	Dawes (2x)
			Tinnitus specific			
	Pitch	1			Degeest 2016	Andersson 1999
	Pitch (VAS)	1			Hoekstra 2014 (2x)	Unterrainer 2003
	Tinnitus loudness	2			Bhatt 2018 (1x), Degeest 2016, Hesser 2016	Bhatt 2018 (1x), Hesser 2016
	Loudness VAS	4			Aazh, Han 2019 (2x), Hoekstra 2014 (2x)	Aazh (1x), Hoekstra 2014 (2x), Unterrainer 2003
	Duration	2			Beukes 2020 (3x), Bhatt 2018 (1x), Degeest 2016, Han 2019 (2x), Hoekstra 2014 (2x), Wallhauser 2012	Bhatt 2018 (1x), Bruggemann 2016
	Variability in pitch and loudness	1			Hoekstra 2014 (2x)	Hoekstra 2014 (1x)
	How often is the tinnitus heard				Beukes 2020 (3x)	
	Complex sound	1			Hesser 2016	Hesser 2016
	Family history of tinnitus	0			Degeest 2016	
	Pulsatile	0			Beukes 2020 (3x)	

Table A2. CONTINUED.

Predictor Categories			Tinnitus Presence Studies	Impact on Daily Life Studies	
	Initial onset (gradual/ abrupt)	0		Degeest 2016, Hoekstra (2x) Wallhauser 2012	
	Location	1		Beukes 2020 (3x), Degeest 2016, Han 2019, (2x) Hoekstra (2x), Walhauser 2012	Wallhauser 2012
	Age at onset	0		Hoekstra 2014 (2x)	
	Type of tinnitus	0		Beukes 2020 (3x), Hoekstra 2014 (2x)	
	Number of sounds	0		Hoekstra 2014 (2x)	
	Tinnitus awareness	2		Degeest 2016, Hoekstra 2014 (2x)	Hoekstra 2014 (2x)
	Permanent awerenss	1		Wallhauser 2012	Wallhauser 2012
	Tinitus awareness vas	0		Han 2019 (2x)	
	Tinnitus presence (vas)	0		Hoekstra 2014 (2x)	
	Tinnitus annoyance (VAS)	2		Aazh, Han 2019 (2x)	Aazh, Han 2019 (1x)
	Tinnitus effect on life (VAS)	2		Aazh, Han 2019 (2x)	Aazh, Han 2019 (1x)
	Tinnitus Acceptance questionnaire	1		Hesser 2016	Hesser 2016
	Change in perception over time	0		Hoekstra 2014 (2x)	
	Tinnitus changed significantly	0		Beukes 2020 (3x)	
	Working less because of tinnitus	0		Beukes 2020 (3x)	
	Tolerance in relation to onset	1			Andersson 1999
Influence on tinnitus	masking of tinnitus by environmental/external sounds	0		Degeest 2016, Hoekstra 2014 (2x)	
	Influence of head and neck movement	0		Degeest 2016	

Table A2. CONTINUED.

Predictor Categories			Tinnitus Presence Studies		Impact on Daily Life Studies	
	sounds distract or mask tinnitus	0			Beukes 2020 (3x)	
	Somatosensory modulation	0			Hoekstra 2014 (2x)	
Tinnitus treatment	medication to help tinnitus or comorbidities	0			Beukes 2020 (3x)	
	Previous tinnitus treatment	0			Beukes 2020 (3x)	
Hearing loss	Hearing ability	1			Basso 2020 (2x)	Basso 2020 (2x)
	Hearing related difficulties	2	Dawes (1x)	Dawes (1x)	Degeest 2016, Wallhauser 2012, Dawes (1x)	Dawes (1x)
	Hearing related difficulties in social situations	2			Basso 2020 (2x)	Basso 2020 (2x)
	Self-reported hearing loss	1			Beukes 2020 (3x), Bhatt 2018 (1x)	Bhatt 2018 (1x)
	Presence of hearing loss	0			Han 2019 (2x)	
	Hearing disability (HHIA-S)	2			Beukes 2020 (3x)	Beukes 2020 (2x)
	Hearing aids	1			Beukes 2020 (3x), Degeest 2016, Wallhauser 2012	Wallhauser 2012
Hyperacusis	Hyperacusis subjective	0			Hoekstra 2014 (2x)	
	Hyperacusis Questionnaire	2			Aazh, Beukes 2020 (3x), Degeest 2016	Aazh, DeGeest 2016
	Subjective noise tolerance	0			Degeest 2016	
	Sound sensitivity	1			Hesser 2016	Hesser 2016
	Sound level tolerance	1			Bhatt 2018 (1x)	Bhatt 2018 (1x)
	Distortion of sound	0			Hoekstra 2014 (2x)	
			Audiological measures			
	PTA	0			DeGeest 2016, Hoekstra 2014 (2x)	

Table A2. CONTINUED.

Predictor Categories			Tinnitus Presence Studies		Impact on Daily Life Studies	
	PTA worse ear	0			Aahz	
	PTA better ear	0			Aahz	
	PTA (0.5,1,2 Hz) right ear	0			Holgers 2005	
	PTA (0.5,1,2 Hz) left ear	0			Holgers 2005	
	PTA (0.5,1,2 Hz) both ears	0			Holgers 2005	
	PTA (2,4,6 Hz) right ear	0			Holgers 2005	
	PTA (2,4,6 Hz) left ear	0			Holgers 2005	
	PTA (2,4,6 Hz) both ears	0			Holgers 2005	
	Hearing loss	1				Kim 2015
Speech perception	Speech in noise right ear	0			Holgers 2005	
	Speech in noise left ear	0			Holgers 2005	
	Speech in noise both ears	0			Holgers 2005	
	SRT better ear	2	Dawes (1x)	Dawes (1x)	Dawes (1x)	Dawes (1x)
Loudness/Hyperacusis tests	average ULL in ear with lowest ULL	0			Aazh	
	Loudness discomfort Levels	0			Degeest 2016, Hoekstra 2014 (2x)	
Masking	MMI white noise	0			Degeest 2016	
	MMI narrow band noise					
	Residual inhibition	0			Degeest 2016, Hoekstra 2014 (2x)	
			Tinnitus			
	Loudness matchting	0			DeGeest 2016, Hoekstra 2014 (2x)	
	Pitch matching	0			Degeest 2016, Hoekstra 2014 (2x)	
	Audiometric maskability	0			Hoekstra 2014 (2x)	
	Minimal masking levels	1			Degeest 2016, Hoekstra 2014 (2x)	Andersson 1999

Table A2. CONTINUED.

Predictor Categories			Tinnitus Presence Studies		Impact on Daily Life Studies	
Comorbidities	**Sleep**					
	Poor sleep quality	2			Basso 2020 (2x)	Basso 2020 (2x)
	Sleep problems	1			Wallhauser 2012	Wallhauser 2012
	Insomnia (ISIS)	3			Aazh (1x), Beukes 2020 (3x)	Aazh, Beukes 2020 (2x)
	Sleep disturbances	0			Basso 2020 (2x)	
	Initial insomnia (van structrd tnitus interview)	1				Langebach 2005 (1x)
Cardiovascular	Cardiovascular disease	2	Couth 2019	Couth 2019	Basso 2020 (2x)	Basso 2020 (1x)
	Hypertension	0	Couth 2019	Couth 2019	Basso 2020 (2x)	
	Hyperlipedemia	2	Couth 2019	Couth 2019	Basso 2020 (2x)	Kim 2015
	Diabetes	0	Couth 2019	Couth 2019	Basso 2020 (2x)	
	BMI	1	Couth 2019	Couth 2019	Holgers 2005	
			Pain			
	Pain complaints	0			Hoekstra 2014 (2x)	
	Chronic pain	1			Wallhauser 2012	Wallhauser 2012
	Fibromyalgia	1			Basso 2020 (2x)	Basso 2020 (1x)
	Chronic shoulder pain	2			Basso 2020 (2x)	Basso 2020 (2x)
			Ear			
	Vertigo	0			Hoekstra 2014 (2x)	
	Otalgia	0			Hoekstra 2014 (2x)	
	Ear fullness	0			Hoekstra 2014 (2x)	
	Recurring ear infections	1			Bhatt 2018 (1x)	Bhatt 2018 (1x)
	Dizziness	0			Wallhauser 2012	
	Morbus Meniere	1			Basso 2020 (2x)	Basso 2020 (1x)
Neurological	Epilepsy	1			Basso 2020 (2x)	Basso 2020 (1x)
	Multiple sclerosis	0			Basso 2020 (2x)	
Other	Asthma	0			Basso 2020 (2x)	
	Thyroid disease	1			Basso 2020 (2x)	Basso 2020 (1x)

Table A2. CONTINUED.

Predictor Categories			Tinnitus Presence Studies		Impact on Daily Life Studies	
	Metabolic risk	2	Dawes (1x)	Dawes (1x)	Dawes (1x)	Dawes (1x)
	Rheumatoid arthritis	0			Basso 2020 (2x)	
	Systematic lupus erythematosus	0			Basso 2020 (2x)	
	Somatic complaints	1			Hoekstra 2014 (2x)	Hoekstra 2014 (1x)
	Migraine	0			Basso 2020 (2x)	
	Osteoarthritis	1			Basso 2020 (2x)	Basso 2020 (1x)
	Somatic comorbidities	0			Wallhauser 2012	
	Health history	1			Bhatt 2018 (1x)	Bhatt 2018 (1x)
	Comorbidity	1				Unterrainer 2003
			Comorbidities psychological			
	Depression	0			Basso 2020 (2x)	
	HADS-D	5			Aazh, Andersson 2005 (3x), Hesser 2016	Aazh, Andersson 2005 (3x), Hesser 2016
	BDI	2			Han 2019 (2x)	Han 2019 (2x)
	PHQ9/15	2			Beukes 2020 (3x), Wallhauser 2012	Beukes 2020 (1x), Wallhauser 2012
	Algemeines depression skala (ADS)	1				Unterrainer 2003
	Self reported depression and/or anxiety	2			Hoekstra 2014 (2x)	Hoekstra 2014 (2x),
Anxiety	Hads A	5			Aazh, Andersson 2005 (3x), Hesser 2016	Aazh, Andersson 2005 (3x), Hesser 2016
	Generalized anxiety syndrome	1			Basso 2020 (2x)	Basso 2020 (1x)
	GAD	1			Beukes 2020 (3x), Wallhauser 2012	Wallhauser 2012

Table A2. CONTINUED.

Predictor Categories			Tinnitus Presence Studies		Impact on Daily Life Studies	
	Panic disorder	0			Basso 2020 (2x)	
	Agoraphobia	0			Basso 2020 (2x)	
	Social anxiety	0			Basso 2020 (2x)	
	Anxiety (SCL-90-R)	1				Langebach 2005 (1x)
Stress	PTSS	0			Basso 2020 (2x)	
	Perceived Stress Questionnaire	1				Bruggemann 2016
	Bepsi-K	1			Han 2019 (2x)	Han 2019 (1x)
	traumatic/stressful experiences	0			Basso 2020 (2x)	
	Stress	1				Kim 2015
Other	Burnout	1			Basso 2020 (2x)	Basso 2020 (1x)
	Bipolar	0			Basso 2020 (2x)	
	Obsessive compulsive disorder	0			Basso 2020 (2x)	
	PHQ15	0			Wallhauser 2012	
	Diagnosed with a psychological condition	0			Beukes 2020 (3x)	
	'Avoidance of situations because of tinnitus'	1				Andersson 1999
QoL	Satisfaction of life (SWLQ)	0			Beukes 2020 (3x)	
Cognition	cognitive failures (CFq)	0			Beukes 2020 (3x)	
Other	Noise dose	1			Bhatt 2018 (1x)	Bhatt 2018 (1x)
	Physical activity	3	Couth 2019, Dawes (1x)	Couth 2019, Dawes (1x)	Dawes (1x)	Dawes (1x)
	Neuroticism	1			Dawes (1x)	Dawes (1x)
Personality	Life satisfaction (freiburger personalitatinvntar)	1				Langebach 2005 (1x)
	Five Big Personality dimensions scale	1			Strumila 2017	Strumila 2017

Table A2. CONTINUED.

Predictor Categories			Tinnitus Presence Studies	Impact on Daily Life Studies	
Internal Locus of control		1			Unterrainer 2003
external locus of control		1			Unterrainer 2003
Fatalistic externality		1			Unterrainer 2003
	Perception of illeness	1			Unterrainer 2003
Perfectionism	concern over mistake	3		Andersson 2005 (3x)	Andersson 2005 (3x)
	personal standards	3		Andersson 2005 (3x)	Andersson 2005 (3x)
	parental expectations	3		Andersson 2005 (3x)	Andersson 2005 (3x)
	parrental criticism	3		Andersson 2005 (3x)	Andersson 2005 (3x)
	doubts about action	3		Andersson 2005 (3x)	Andersson 2005 (3x)
	organisation	3		Andersson 2005 (3x)	Andersson 2005 (3x)
TSQ_	1 how much does tinnitus reduce the quality of life overall	0		Holgers 2005	
	2. when you are in a quiet environment, but not trying to sleep, how much discomfort does your tinnitus cause	0		Holgers 2005	
	3. how often do you notice tinnitus during your waking hours	0		Holgers 2005	

Table A2. CONTINUED.

Predictor Categories			Tinnitus Presence Studies	Impact on Daily Life Studies
	4. how often does tinnitus impair your concentratio, for example when reading	0		Holgers 2005
	5. how often is it difficult for you to go to sleep, and get back to sleep, due to tinnitus?	0		Holgers 2005
	how often can you surpress or forget your tinnitus by some acitivy, for example watching TV or talking to somebody?	0		Holgers 2005
	7. if you are exposed to every day sounds, how easily do these sound reduce or drown you rtinnitus	0		Holgers 2005
	8. how often does tinnitus make you feel anxious or worried?	0		Holgers 2005
	9. how often does tinnitus makeyou feel tense or irritable?	0		Holgers 2005
	10. how often does tinnitus make you feel depressed and miserable?	0		Holgers 2005
Nottingham health profile (NHP)	emotional distrubances	0		Holgers 2005
	sleep distrubances	0		Holgers 2005
	energy	0		Holgers 2005
	pain	0		Holgers 2005
	physical mobility	0		Holgers 2005
	social isolation	0		Holgers 2005

Table A2. CONTINUED.

Predictor Categories			Tinnitus Presence Studies	Impact on Daily Life Studies	
NHP Emotional disturbances	I feel that life is not worth living	1		Holgers 2005	Holgers 2005
	Worry is keeping me awake at night	0		Holgers 2005	
	I feel as if im losing control	0		Holgers 2005	
	Things are getting me down	0		Holgers 2005	
	I've forgotten what it's like to enjoy myself	0		Holgers 2005	
	I wake up feeling depressed	0		Holgers 2005	
	I lose my temper easily these days	0		Holgers 2005	
	The days seem to drag	0		Holgers 2005	
	I'm feeling on edge	0		Holgers 2005	
NHP sleep disturbances	I lie awake for most of the night	0		Holgers 2005	
	I take tablets to help me sleep	0		Holgers 2005	
	I sleep badly at night	1		Holgers 2005	Holgers 2005
	It takes me a long time to get to sleep	0		Holgers 2005	
	I'm waking up in the early hours of the morning	0		Holgers 2005	
NHP energy	Everything is an effort	0		Holgers 2005	
	I'm tired all the time	0		Holgers 2005	
	I soon run out of energy	0		Holgers 2005	
NHP Pain	I'm in constant pain	0		Holgers 2005	
	I have unearable pain	0		Holgers 2005	
	I have pain at night	0		Holgers 2005	

Table A2. CONTINUED.

Predictor Categories			Tinnitus Presence Studies	Impact on Daily Life Studies	
	I'm in pain when I walk	0		Holgers 2005	
	I find it painful to change position	0		Holgers 2005	
	I'm in pain when I'm sitting	0		Holgers 2005	
	I'm in pain when I'm standing	0		Holgers 2005	
	I'm in pain when going up and down stairs	0		Holgers 2005	
NHP Physical mobility	I am unable to walk at all	0		Holgers 2005	
	I find it hard to dress myself	0		Holgers 2005	
	I need help to walk about outside	0		Holgers 2005	
	I can only walk about indoors	0		Holgers 2005	
	I find it hard to bend	0		Holgers 2005	
	I have trouble getting up and down stairs	0		Holgers 2005	
	I find it hard to stand for long	0		Holgers 2005	
	I find it hard to reach for things	0		Holgers 2005	Holgers 2005
NHP social isolation	I feel I am a burden to people	0		Holgers 2005	
	I feel lonely	0		Holgers 2005	
	I feel there is nobody I am close to	0		Holgers 2005	
	I'm finding it hard to make contact with people	0		Holgers 2005	
	I'm finding it hard to get on with people	0		Holgers 2005	

Table A2. CONTINUED.

Predictor Categories			Tinnitus Presence Studies		Impact on Daily Life Studies
International classification of disease 10th revision (ICD-10)	**Diseases of the ear (diseases of middle ear and mastoid) [H65–H75]**	0	Kostev 2019		
	H65 Nonsuppurative otitis media	1	Kostev 2019	Kostev 2019	
	H66 Suppurative and unspecified otitis media	1	Kostev 2019	Kostev 2019	
	H68 Eustachian salpingitis and obstruction	1	Kostev 2019	Kostev 2019	
	Diseases of inner ear [H80–H83]	0	Kostev 2019		
	H81.0 Menieres disease	1	Kostev 2019	Kostev 2019	
	H81.1 Benign paroxysmal vertigo	1	Kostev 2019	Kostev 2019	
	H81.2 Vestibular neuronitis	1	Kostev 2019	Kostev 2019	
	H81.9 Disorder of vestibular function, unspecified	1	Kostev 2019	Kostev 2019	
	Other disorders of ear [H90–H95]	0	Kostev 2019		
	H91.9 presbycusis	1	Kostev 2019	Kostev 2019	
	H92 Otalgia and effusion of thee ar	1	Kostev 2019	Kostev 2019	
	Diseases of the upper respiratory tract (J30–J39)	0	Kostev 2019		
	J30 Allergic rhinitis	1	Kostev 2019	Kostev 2019	
	J31 Chronic rhinitis	1	Kostev 2019	Kostev 2019	
	J32 Chronic sinusitis	1	Kostev 2019	Kostev 2019	
	Mental disorders (organic, including symptomatic,mental disorders [F00–F09]	0	Kostev 2019		

Table A2. CONTINUED.

Predictor Categories		Tinnitus Presence Studies		Impact on Daily Life Studies
Mood [affective] disorders [F30–F39]	0	Kostev 2019		
F32, F33 Depression	1	Kostev 2019	Kostev 2019	
Neurotic, stress-related, and somatoform disorders [F40–F48]	0	Kostev 2019		
F41 Anxiety disorder	1	Kostev 2019	Kostev 2019	
F43 Reaction to severe stress, and adjustment disorders	1	Kostev 2019	Kostev 2019	
F45 somatoform disorders	1	Kostev 2019	Kostev 2019	
Diseases of the nervous system (extrapyramidal and movement disorders [G20–G26]	0	Kostev 2019		
Other degenerative diseases of the nervous system [G30–G32]	0	Kostev 2019		
Demyelinating diseases of the central nervous system [G35–G37]	0	Kostev 2019		
Episodic and paroxysmal disorders [G40–G47]	0	Kostev 2019		
G43 migraine	1	Kostev 2019	Kostev 2019	
Endocrine diseases (disorders of the thyroid gland [E00–E07]	0	Kostev 2019		
Diabetes mellitus [E10–E14]	0	Kostev 2019		
Diseases of the circulatory system (hypertensive diseases) [I10–I15]	0	Kostev 2019		

Table A2. CONTINUED.

Predictor Categories		Tinnitus Presence Studies		Impact on Daily Life Studies
Cerebrovascular diseases [I60–I69]	0	Kostev 2019		
Atherosclerosis [I70]	2	Kostev 2019	Kostev 2019	
I24, I25 coronary heart disease	1	Kostev 2019	Kostev 2019	
other and unspecified disorders of the circulatory system [I95–I99]	0	Kostev 2019		
I95 hypotension	1	Kostev 2019	Kostev 2019	
hemolytic anemias (nutritional anemias [D50–D53]	0	Kostev 2019		
hemolytic anemias [D55–D59]	0	Kostev 2019		
aplastic and other anemias [D60–D64]	0	Kostev 2019		

CHAPTER 8

Development and internal validation of a prediction model for the presence of tinnitus in a Dutch population-based cohort

Frontiers in Neurology; 2023 August 3;14:1213687

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Abstract

Objectives
In this study we aim to develop and internally validate a prediction model in a representative sample of the Dutch general population on tinnitus experience.

Methods
We developed a multivariable prediction modeling using elastic net logistic regression on data from the Dutch Lifelines Cohort Study. This is a multigenerational cohort study on adults out of the northern parts of the Netherlands. The model was internally validated using 10-fold cross validation. The outcome of the model was tinnitus presence, for which we used 24 candidate predictors on different domains (among others demographic-, hearing specific- and mental health- variables). We assessed the overall predictive performance of the model, discrimination and calibration.

Results
Data on 122.884 different participants were included, of which 7965 (6.5%, 0 missings) experienced tinnitus. Nine variables were included in the final model (sex, hearing aids, hearing limitations, arterial blood pressure, quality of sleep, general health, symptom checklist of somatic complaints, cardiovascular risk factors and age). In the final model the Brier score was 0.056 and 0.787 in internal validation.

Conclusion
We derived and internally validated a prediction model on tinnitus presence in a multigenerational cohort of the Dutch general population. From the 24 candidate predictors, the final model included nine predictors.

Introduction

Tinnitus is a heterogeneous condition that manifests itself differently, in terms of the etiology of the disease, different courses, and comorbidities. (1,2) The concept of tinnitus consists of two components: the sole sensory component, which can be expressed in terms of loudness, frequency, or pitch, and an affective component, which reflects the patient's emotional reaction and related suffering. The first is referred to as tinnitus and the second as tinnitus disorder. (3) Considering the prevalence of tinnitus, a recent meta-analysis showed that the pooled prevalence of any type of tinnitus in adults was 14.4% (95% CI 12.6 -16.5%), which results in approximately 740 million people globally.(4) The high prevalence and chronicity of tinnitus leads to ample socio-economic costs. For example, in the Netherlands the average societal costs are approximated at €6.8 billion per year. (5) Whilst healthcare costs alone for tinnitus are estimated at 1.9 billion euros in the Netherlands, at £750 million per year in Great Britain and at $660 per patient annually in the United States.(5–7) Identifying and predicting which people are at a higher risk of developing tinnitus could help to design preventive measures and dedicate health care programs for those at risk. These might improve quality of life and reduce costs.

The literature on associations with tinnitus experience is elaborate. Associations between experiencing tinnitus and otologic risk factors but also among others, demographic-, cardiovascular-, dietary, psychological-, and neurological risk factors have been studied.(8) However in a recent systematic review hearing loss, occupational noise exposure, otitis media, diabetes, temporomandibular disorder and ototoxic platinum exposure were identified as most reliable associations.(9) Additionally, prediction models can provide individual risk estimates, and can inform decision making in the clinical setting. (10) In a recent systematic review of our research group, we identified four prediction models for assessing tinnitus presence. While the sample sizes of these studies were sufficient (n = 4950 to 168.348 per study), the statistical analyses were often a source of bias. (11)

To produce a reliable prediction model that is useful in clinical settings the development of a prediction model should be based on three phases.(10) The first phase is the model derivation phase. This includes the identification of predictors and fitting of the model. In the second phase, the model validation phase, the performance of the model is evaluated. In this stage internal validation is used to evaluate the performance of the prediction model. Lastly, one should assess the impact of the model. (10) It is essential to adhere to this methodology and properly report these steps in order to produce high-level, clinically useful models.

Based on the high prevalence of tinnitus in the general population, its impact, related societal and health care costs, we aim to develop and internally validate a prediction model on tinnitus experience in a representative sample of the Dutch general population.

Methods

This study was reported in accordance with the TRIPOD statement. (12)

This study is performed in the Dutch Lifelines Cohort Study. (13) Lifelines is a multi-disciplinary prospective population-based cohort study examining in a unique three-generation design the health and health-related behaviours of 167,729 persons living in the North of the Netherlands. It employs a broad range of investigative procedures in assessing the biomedical, socio-demographic, behavioural, physical and psychological factors which contribute to the health and disease of the general population, with a special focus on multi-morbidity and complex genetics. The first participants were included in 2006 and will be followed for at least 30 years. The baseline assessment took place from 2007-2013 and included questionnaires (1A) as well as different measurements (1A1) as well as biological samples (1A2). (figure 1) As part of the assessment, participants are asked to fill out surveys, with follow-up surveys approximately once every 1.5 years. The first follow up questionnaire (1B) was sent from 2011-2014. For more information on the Lifelines Cohort please see the study by Scholtens et al. (13) The Lifelines initiative has been made possible by subsidy from the Dutch Ministry of Health, Welfare and Sport, the Dutch Ministry of Economic Affairs, the University Medical Center Groningen (UMCG), Groningen University and the Provinces in the North of the Netherlands (Drenthe, Friesland, Groningen).

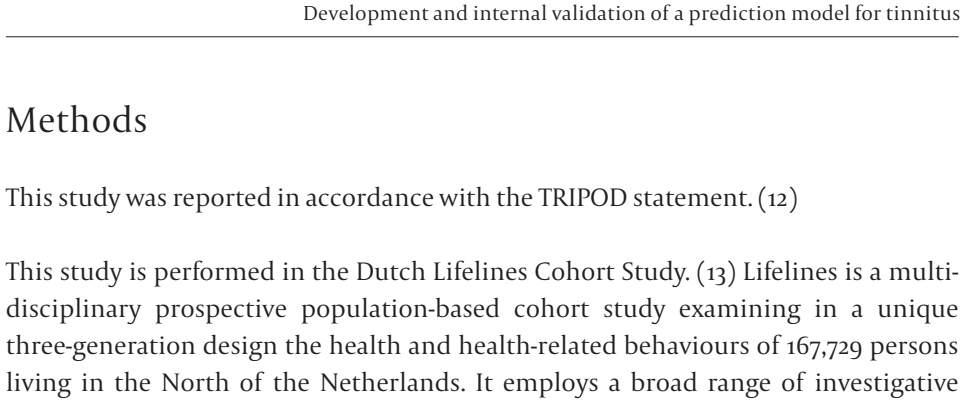

Figure 1. Data collection proces of Lifelines(39)

The Lifelines Cohort Study is performed in accordance with the principles of the Declaration of Helsinki and in accordance with the University Medical Center Groningen (UMCG) research code. All participants provided written informed consent. The Lifelines protocol was approved by the UMCG Medical ethical committee under number 2007/152

Variables
In this study, we included data from questionnaires at moment 1A and 1B, and data from measurements at visit 1A1. For several variables, items out of the questionnaire from both moments were collected. For example, the presence of cancer was asked at both moment 1A and 1B. For these variables a new variable was created that combined the information from both points in time. Please see the Lifelines website for the exact formulation of each variable, the answer options or calculation methods. (14)

Model outcome
Tinnitus presence (1B) was assessed with the following question: 'do you hear ringing or whistling in your ear/ears?', with the answer options 'No never, 'Yes, sometimes' or 'Yes, always'. In this study participants were defined as having tinnitus when they answered: ''Yes, always." If participants answered 'No, never' or 'Yes, sometimes' they were defined as not having tinnitus.

Candidate predictors
We included 24 different variables over different domains. These variables were considered as being candidate predictors of tinnitus experience based on the literature and expert opinion (discussion by MR, AL and IS). (8,9)

Demographic
The following demographic variables were assessed: educational attainment (low, middle, high) (1a), age (if available at 1B, else at 1A) and sex (male, female).

Mental health
Subjective mental health
The following subjective variables were assessed within the mental health domain: presence or history of anxiety disorders (1A & 1B), depression (1A & 1B) and burnout (1A & 1B). The variable anxiety disorder was a combination of presence or history of either/or anxiety disorder (1A), social phobia (1A), agoraphobia (1A & 1B) and panic disorder (1A & 1B).

Symptom checklist
We used the Symptom Checklist (SCL-90) to assess somatic complaints at 1B. (15,16) The list consists of 12 questions, with answer options on a 5-point Likert scale (1 not at all - 5 very much). The sum score was calculated. Total sum scores range between 12 and 60 in which higher scores indicate a higher severity of somatic symptoms

Emotional affect
The positive and negative affects schedule (PANAS) was used to assess emotional

affect (17) (1A). The PANAS consists of twenty items, 10 for a positive affect, 10 for a negative affect. All questions had to be answered with 5-point Likert scales (1 not at all – 5 extremely). Scores can range from 10 – 50, with lower scores indicating lower levels of a positive or negative affect and higher scores indicating higher levels of positive or negative affect.

Personality
Personality was assessed with the NEO personality inventory (NEO-PI-R) (1A) (18,19). This self-report tool measures the five most significant aspects of personality; neuroticism, extraversion, openness, agreeableness, and conscientiousness with 240 items on a 5-point Likert scale. At baseline, Lifelines used two shorter versions of the NEO-PI-R, which focusses on conscientiousness, extraversion and neuroticism. These domains were also assessed in this model.

Quality of sleep
The Pittsburgh sleep quality index (PSQI) was used to measure sleep quality (1B). (20) The questionnaire measures sleep quality and disturbances over a 1-month time interval. In 19 questions seven component scores are assessed. The total score is a sum score of the component scores. This was dichotomized by Lifelines into either a good (PSQI >5) or a bad quality of sleep (PSQI ≤ 5).(21)

Cognition
Cognition was measured by the Ruff Figural Fluency Test (RFFT) at 1A. (22) The RFFT measures the cognitive function domain nonverbal fluency. The test is made up of five parts. In these parts the patient is presented with different pattern of dots. A fixed time period is set, and the patient is asked to draw as many unique designs as possible. The number of unique designs is a measure of nonverbal fluency and was used as a predictor.

Hearing health
The following variables were assessed within the ear domain; disturbance of daily life because of hearing loss (1B) and the use of hearing aids (1B).

Cardiovascular disease
We combined several variables to create two predictor candidates. The first was cardiovascular disease, this included presence or a positive medical history of either/or hypertension (1A), high cholesterol (1A) and diabetes (1A & 1B). The second was major adverse cardiac events (MACE), this included presence or a positive medical history of either/or heart attack (1A & 1B), stroke 1A & 1B), carotid stenosis (1A), stenosis for which an angioplasty or bypass surgery was necessary (1A), angioplasty (1A & 1B),

atherosclerosis (1A), claudication (1b).

Cancer
The presence or history of cancer was scored as one variable based on a positive answer to this question at either baseline or follow-up. (1A and 1B)

Neurological disorders
The presence or history of neurological disorders was based on the presence or medical history of Parkinson's (1A) and/or multiple sclerosis 1A))

Physical activity
The Short QUestionnaire to Assess Health-enhancing physical activity (SQUASH) was used to assess physical activity. The sum score was used to categorize participants into meeting the recommended Dutch level of exercise as determined by the Dutch Health Board (23,24) (1A)

General Health
The question: 'How would you rate your health, generally speaking' (excellent, very good, good, fair or poor) was used to assess general health at moment 1B. This question is part of the RAND-36 Quality of Life questionnaire. (25)

Physical status
The following measurements of physical status were performed at baseline and included as candidate predictors; BMI and mean arterial pressure. (1A1)

Statistical analyses
Data cleaning was conducted in SPSS version 27. (26) Other statistical analyses were performed in R studio (version 22.02.0) using the glmnet and caret package. (27,28)A sample size calculation was performed in R with the pmsampsize package. (29)

Frequencies and percentages of categorical variables were calculated. For continuous data normality was assessed. Normally distributed data was presented as means with standard deviation (SD). Non-normally distributed data was presented as medians with interquartile range (IQR).

Missing data (Missing at random) was imputed with multiple imputation, with 30 imputation sets. All missing data was imputed, except for the missing data of the original tinnitus question, of which 22829 cases were missing. These were excluded from the data; therefore, the analyses were formed only on those data of which an answer to the original tinnitus question was known.

A multivariable elastic net logistic regression model was used to develop the prediction model. Elastic net is a combination of Lasso selection and ridge penalization. (30) A 10-fold cross validation was used to minimize cross validating deviance, by determining the optimal tuning parameters (alpha and lambda values) of the model.

An elastic net model was fitted on each of the 30 imputations set. Estimates of the optimal tuning parameters (alpha and lambda), and model performance measures were calculated for each model. The mean was calculated for each of those in the final model, which is presented in this manuscript by Rubins Rules. Estimates were included in the final model if the value was > 0.001 in positive numbers or > -0.001 in negative number in 16 or more times. The model was internally validated by 10-fold cross validation.

Model performance of the model as well as the internal validation was assessed with the RMS package. (31) Pseudo R2 and Brier score were calculated as overall performance measures. The c-statistic was calculated to assess discrimination and the calibration intercept and slope were calculated as calibration measures.

Results

Baseline characteristics

Data was collected of 151.113 participants. Of those 83.756 (55.4%, 22.829 missing) answered 'no, never' to the question 'do you hear ringing or whistling in your ear/ ears'. 31.163 (20.6%, 22829 missing) answered 'yes sometimes', and 7965 (5.3%, 228229 missing) answered 'yes always'. 112.884 participants did not answer the question about tinnitus, therefore the total number included in the analyses was therefore 122.884, of those, according to our definition, 7965 (6.5%, 0 missing) experienced tinnitus, 114.919 did not (93.5%, 0 missing). (Table 1)

Table 1. Baseline characteristics on tinnitus

Variable		N	%
Do you hear ringing or whistling in your ear / ears?			
	No never	83756	55.4
	Yes sometimes	31163	20.6
	Yes always	7965	5.3
	Missing	228229	18.7
*Tinnitus**			
	No	114919	93.5
	Yes	7965	6.5

*tinnitus as to our definition. The missing data were not included in the analyses. .

The majority of the participants were female (72.862, 59.3%, 0 missing), of those with tinnitus the majority were male 4557 (57.2%, 0 missing). The mean age was 45.0 years of age (SD 12.8), the mean age of participants without tinnitus was 44.5 years of age (SD 12.7) and of the participants with tinnitus 52.6 (SD 11.6). Most participants were not disturbed in their daily life because of hearing loss (106.285, 86.5% (384 missing). However, 663 (0.5%, 384 missing) participants were severely limited in their daily life because of hearing loss, and 15.552 (12.7%) were a bit limited. See table 2 for the baseline characteristics of the analyzed data.

Model

The mean alpha of the elastic net models was 0.197, the lambda 0.046. Nine variables with 10 categorical sub variables made up the final model, all other variables were removed from the model after shrinkage. (Table 3). The following variables were selected in the final model: male sex (ref = female, OR 1.2982), no hearing aids (ref = yes, OR = 0.6811), hearing limitations (a bit, ref = severely limited, OR = 1.4903), hearing limitations not at all (ref = severely limited, OR = 0.3879), mean arterial blood pressure (OR = 1.0013), a bad quality of sleep on the PSQI (Ref = good quality of sleep,

OR = 1.00571), fair score on the Rand general health (ref= excellent score, OR =1.07358), SCL somatic sum score (OR = 1.0736), CVD risk factors (ref = no CVD risk factors, OR =1.0027), age (OR = 1.01714)

Table 2. Baseline characteristics

		Total		Tinnitus No		Tinnitus Yes	
Variable		**N**	**%**	**N**	**%**	**N**	**%**
Sex							
	Male	50022	40.7	45465	39.6	4557	57.2
	Female	72862	59.3	69454	60.4	3408	42.8
	Missing	0	0	0	0	0	0
Educational attainment							
	Low	35682	29.04	32.584	28.4	3098	38.9
	Middle	48164	39.2	45.496	39.6	2668	33.5
	High	37675	31.1	35.599	31.0	2076	26.1
	Missing	1363	1.11	1240	1.1	123	1.5
Hearing aid (do you need a hearing aid?)							
	Yes	4052	3.3	2876	2.5	1176	14.8
	No	118518	96.5	11769	97.3	6749	84.7
	Missing	314	0.3	40	0.5	315	0.3
Disturbance of daily life because of hearing loss							
	Yes, severely limited	663	0.5	362	0.3	301	3.8
	Yes, a bit limited	15552	12.7	12037	10.5	3515	44.1
	No, not limited at all	106285	86.5	102.168	88.9	4117	51.7
	Missing	384	0.3	352	0.3	32	0.4
Squash exercised norm							
	Yes	63239	51.5	588559	51.0	4680	58.8
	No	49544	40.3	46900	40.8	2644	33.2
	Missing	10101	8.2	9460	8.2	641	8
PSQI quality score							
	Good sleep quality	87619	71.3	82.450	71.7	5169	64.9
	Poor sleep quality	31399	25.6	28.920	25.2	2479	31.1
	Missing	3866	3.2	3549	3.1	317	4.0
Rand general health score							
	Excellent	9339	7.6	8951	7.8	388	4.9
	Very good	30882	25.1	29.423	25.6	1459	18.3
	Good	70804	57.6	66.012	57.4	4792	60.2
	Fair	10756	8.8	9571	8.3	1185	14.9
	Poor	755	0.6	641	0.6	114	1.4
	Missing	348	0.3	321	0.3	27	0.3
Burnout							
	Yes	12495	10.2	11.417	9.9	1078	13.5
	No	110389	89.8	103.502	90.1	6887	86.5
	Missing	0	0	0	0	0	0
Depression							
	Yes	12845	10.5	11749	10.2	1096	13.8

Table 2. CONTINUED.

		Total		Tinnitus No		Tinnitus Yes	
Variable		**N**	**%**	**N**	**%**	**N**	**%**
	No	110039	89.6	103.170	89.8	6869	86.2
	Missing	0	0	0	0	0	0
Cancer							
	Yes	5800	4.7	5197	4.52	603	7.57
	No	116978	95.2	109623	65.39	7355	92.34
	Missing	106	0.09	99	0.09	7	0.09
Anxiety							
	No	115685	94.1	108.309	94.2	7376	92.6
	Yes	7199	5.9	6610	5.8	589	7.4
	Missing	0	0	0	0	0	0
Neurologic disease							
	No	122454	99.7	114521	99.7	7933	99.6
	Yes	430	0.4	398	0.3	32	0.4
	Missing	0	0	0	0	0	0
Risk factor Cardiovasculair disease							
	No	85849	69.86	81.238	70.7	4611	57.9
	Yes	37033	30.1	33680	29.3	3353	42.1
	Missing	2	0.002	1	0.0009	1	0.01
Major adverse cardiovascular event							
	No	118822	96.7	111.351	69.9	7471	93.8
	Yes	4062	3.3	3568	3.1	494	6.2
	Missing	0	0	0	0	0	0
BMI	Median (IQR)	25.4	5.09	25.34	5.06	26.0	4.8
	Missing	77	0.06	73	0.06	4	0.05
BP average arterial mean	Mean (SD)	93.16	10.24	92.98	10.19	95.8	10.6
	Missing	113	0.09	101	0.09	12	0.15
Age	Mean (SD)	45.01	12.82	44.5	12.74	52.6	11.58
	Missing	0	0	0	0	0	0
Panas positive	Median (IQR)	36	5	36	5	35	6
	Missing	3443	2.8	3215	2.8	228	2.9
Panas negative	Median (IQR)	20	7	20	7	20	7
	Missing	3443	2.2	2313	2.01	169	2.12
RFFT som unique design	Median (IQR)	82	33	82	32	76	33
	Missing	45254	36.8	42129	36.7	3125	39.2
SCL somatic	Median (IQR)	15	4	15	4	15	6
	Missing	7553	6.1	6805	5.9	748	9.4
Neuroticism	Median (IQR)	26	9	26	9	26	10
	Missing	10.493	8.5	9158	8.0	1335	16.8
Extraversion	Median (IQR)	36	12	37	12	36	15
	Missing	10573	8.6	9236	8.04	1337	16.8
Conscientiousness	Median (IQR)	46	7	46	7	46	9
	Missing	10.495	8.5	9160	8.0	1335	16.8

Table 3. Coefficients of the apparent performance model

Variable	Coefficient	Odds ratio
Intercept	-3.029	0.0484
Sex, female	Reference	
Sex, male	0.261	1.2982
Hearing aid, yes	Reference	
Hearing aid, no	-0.384	0.6811
Hearing limitation, severly limited	Reference	
Hearing limitation, a bit	0.399	1.4903
Hearing limitation, not at all	-0.947	0.3879
Mean arterial blood pressure	0.0013	1.0013
PSQI Good quality of sleep	Reference	
PSQI Bad quality of sleep	0.0057	1.0057
Rand general health, excellent	Reference	
Rand general health, fair	0.071	1.0736
SCL somatic sum score	0.0189	1.0191
CVD risk factors, no	Reference	
CVD risk factors, yes	0.0027	1.0027
Age	0.017	1.0017

Discrimination

Discrimination expresses how well the risk model distinguishes between cases and non-cases. The area under the curve (AUC) of the model was 0.789 in the apparent performance.

Calibration

Calibration refers to the level of agreement between calculated risks and observed outcomes. Figure 2 shows the calibration curve of the model. Calibration was expressed as an intercept of 0.75, with a slope of 1.315 (table 4). The R2 was 0.155 and the Brier score was 0.056.

Internal validation

We internally validated the model with 10-fold cross validation. Figure 2 shows the calibration curve. Of the internally validated model the R2 was 0.158 and the Brier score was 0.056.

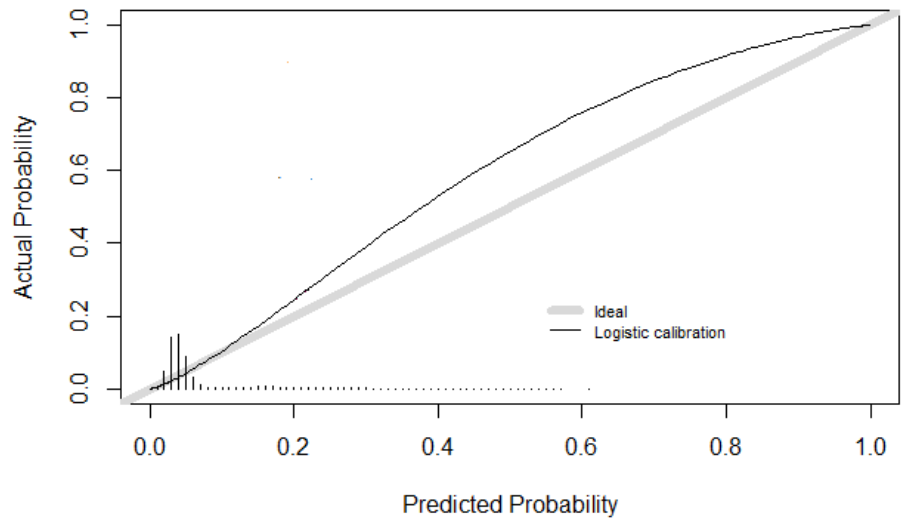

Figure 2. Calibration Curve

Table 4. Model performance measures

Model performance measure	Apparent performance model	Internally validated model
Overall performance		
Pseudo R2	0.155	0.158
Brier	0.056	0.056
Discrimination		
C-statistic	0.789	0.787
Calibration		
Intercept	0.750	0.634
Slope	1.315	1.268

Discussion

We developed and internally validated a model on the experience of tinnitus. We created this model in a large representative dataset of the adult Dutch general population (122.884 participants were included in our model).(13) We developed a prediction model and internally validated it to assess the performance. The final model included nine different predictors, out of twenty-four candidate predictors.

One of the challenges in making a tinnitus prediction model, and in tinnitus research, are the multiple different definitions of tinnitus. (3,32,33) Amongst others, one can differentiate between having tinnitus based on cut-offs for frequency and duration of the experienced sound, but also on the experienced impact. Differences in used cut-offs and definitions result in differences in outcomes of studies concerning tinnitus. This is also the most important limitation of our study. The exact wording of the question asking for the experience of tinnitus was ”do you hear ringing or whistling in your ear/ears?” The answer options were: “No, never”, “Yes, sometimes” or “Yes, always” and categorized in tinnitus experience yes or no. Besides this, tinnitus is not limited to merely a ringing or whistling sound as indicated in the question. Those examples might have confused participants or resulted in a selection of those answering positive to the question and not including people having other kinds of tinnitus sounds. (34)

Another limitation of our study is the use of variables based on multi-item questionnaires. As explained in a recent paper van Royen et al., including costly or time-intensive variables in prediction models is one of the reasons why adaption of prediction models fails in clinical practice. (35) In the current model we used different time-intensive and not readily available assessments of personality, emotional affect, verbal fluency, somatic complaints and sleep quality. However, most of these variables were shrunken out of the final model; in which only the SCL somatic sum score and the PSQI were included. We were aware of this limitation before we started the development of this model, but did decide to include these variables since we wanted to approach the concept of these predictors. Future research should consider several, more accessible derivates of these variables to maximize clinical applicability. This model is of added value for research purposes as well as (preventative) policies. Finally, model performance of the internal validation might be slightly optimistic due to using nested cross validation rather than bootstrapping.(36)

In a recent systematic review on prediction models, we noticed that demographic factors were mostly used as predictors in the final models on tinnitus experience. Whereas comorbidities were mostly used as predictors in models on tinnitus impact.

(11) In the current model on tinnitus experience we find both demographic factors and co-morbidities to be predictors. Of the nine predictors in the final model, two are hearing related co-morbidities. Although there is debate in the literature on this issue, it should be emphasized that hearing-related difficulties are widely seen as causal to experiencing tinnitus. (9,37) The outcome of the present study is in line with this statement.

Future research that focusses on creation of a prediction model on tinnitus impact would be helpful for clinical practice. Next, in this study we did not perform an external validation of our prediction model. This should be considered for future studies to assess the model's accuracy, reproducibility and generalizability in a different dataset. (10,38)

Conclusion

In this study we developed and internally validated a prediction model on tinnitus experience. The predictors included were male sex (compared to female sex), the use of hearing aids (compared to no use), the presence of hearing limitations, mean arterial blood pressure, a bad quality of sleep (compared to a good quality), a fair subjective opinion of their general health (compared to an excellent opinion), somatic complaints, the presence or history of cardiovascular risk factors (compared to no presence of history), and age. This manuscript stresses to the potential incremental value of co-morbidities, especially hearing related co-morbidities for the purpose of predicting tinnitus.

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CHAPTER 9

Summary and General Discussion

Summary

Tinnitus is a heterogeneous disease. This heterogeneity presents methodological challenges in tinnitus research into effective therapies. The aim of this thesis was to explore tinnitus heterogeneity.

In **chapter 2** we assessed which outcome measures are important for tinnitus patients. With a discrete choice experiment, we researched the preference in outcome measures with a hypothetical treatment in one hundred and twenty-seven people with tinnitus. Four attributes (tinnitus loudness, tinnitus acceptance, quality of sleep and concentration) were assessed with three different levels, an increased, decreased or similar level. The results of the mixed-logit analysis showed that the choice of a therapy was affected significantly by all levels in all outcome measures, apart from a similar level in concentration and tinnitus acceptance. Compared to the other attributes, we identified tinnitus loudness to be the most important. In the analysis we noticed a heterogeneity in preferences which could not be explained by correlating attributes. In order to further explore this heterogeneity, we conducted a latent class analysis. We identified two different classes, the first is very similar to the results of the mixed logit analysis (apart from no significance in similar quality of sleep and tinnitus acceptance). However, in the second class participants prefer an increased tinnitus acceptance and similar quality of sleep. Among others, this study showed that tinnitus heterogeneity is also found in preferences of outcome measures.

In **chapter 3** we assessed the prevalence of tinnitus in the Dutch general population with different cutoffs for the definition. In a cross-sectional study, we sent a questionnaire to 2251 people of the Dutch general population. We assessed the prevalence of tinnitus with different criteria in our sample of 932 respondents. We found that 36% of our sample experienced tinnitus for an undefined amount of time during the past year. 23% of our sample met our definition of having pathologic tinnitus, of those 48.7% had a TFI score of 18 or higher. This chapter illustrated the difficulties with defining tinnitus, and stressed the importance of a uniform definition.

In **chapter 4** we describe a study that assessed the difference in characteristics between people with tinnitus that seek help and those that do not. We assessed differences and similarities on different domains, including demographic-, general- and mental health-, tinnitus specific- and audiological characteristics. In the same dataset that was used in **chapter 3 and 6**, we found that 34% of those with tinnitus were identified as tinnitus help seekers. We described differences between help-seekers and non-help-seekers in tinnitus characteristics and audiological characteristics.

In **chapter 5** we describe the results of a study in 963,880 people, of those 8050 were defined as tinnitus patients. We used the Nivel Primary Care Database of 2018 to explore the primary health care consumption of patients with tinnitus and people without tinnitus. We concluded that, compared to people without tinnitus, patients with tinnitus had a higher average amount of consultations, were more often referred to medical specialists and received more prescriptions.

Chapters 6, 7 and **8** focus on prediction of tinnitus and tinnitus disorder. In the **chapter 6** we commence with this final part with a study on associations between different variables and the Tinnitus Functional Index (TFI), a measure of the impact of tinnitus on daily life. These were demographic-, tinnitus specific-, audiological-, general- and mental health variables. We assessed the TFI score in 212 survey participants. We performed univariable and multivariable regression analyses to assess these associations with the TFI. We concluded that audiological variables such as hearing problems and hyperacusis have the largest association with tinnitus impact.

In **chapter 7** we describe a systematic review on prediction models for tinnitus presence and the impact of tinnitus on daily life. We included 21 studies, that described 31 different predictions models. 17 studies described a prediction model for tinnitus impact, 3 for tinnitus presence and 1 study described one on each. Depression or anxiety were mostly used as predictors in models on tinnitus impact. For models on tinnitus experience demographic factors were most commonly used as predictor candidates. We noticed a high risk of bias and poor reporting in all studies.

In **chapter 8** we developed and internally validated a prediction model on tinnitus presence. The model was derived on 122.884 participants from the Lifelines database, 7965 (6.5%) of them experienced tinnitus. 24 candidate predictors on different domains were used to predict tinnitus presence with an elastic net logistic regression. The model was internally validated. From 24 candidate predictors, the final model included nine predictors; male gender (compared to female gender), the use of hearing aids (compared to no use), the presence of hearing limitations, mean arterial blood pressure, a bad quality of sleep (compared to a good quality), a fair subjective opinion of their general health (compared to an excellent opinion), somatic complaints, the presence or history of cardiovascular risk factors (compared to no presence or history), and age. This study highlighted the value of co-morbidities, especially hearing related co-morbidities in the prediction of tinnitus experience.

General Discussion

Tinnitus definition

Challenges with defining tinnitus have been thoroughly described in this thesis. Even in this thesis itself one can discover various definitions over the different chapters. For example, tinnitus was based on duration and frequency in **chapters 3**, **4** and **6**. Whilst in **chapter 5** we used a general practice registrar's code to define tinnitus, and in **chapter 8** we defined people as having tinnitus when they answered "*yes, always*" to the question: "*do you hear ringing or whistling in your ear/ears?*" These differences illustrate the variety in definitions to identify those with tinnitus.

The use of a uniform definition is important to better understand tinnitus. For example, to measure the exact prevalence of the disease. In order to approach uniformity in tinnitus definitions, a proposal for a definition has recently been made. (1) Two different and broad definitions of tinnitus and tinnitus disorder were proposed. The newly proposed definitions were "*Tinnitus is the conscious awareness of a tonal or composite noise for which there is no identifiable corresponding external acoustic source, which becomes Tinnitus Disorder "when associated with emotional distress, cognitive dysfunction, and/or autonomic arousal, leading to behavioural changes and functional disability."* (1)[p4] The authors propose a time frame of minimal 5 minutes per day, on the majority of days. One can wonder whether the proposed timeframe is adequate. For instance, should people who experience tinnitus for 4 hours during two days not also be classified as having tinnitus? In **chapter 2** we also used the 5-minute cut-off, but used a broader definition for frequency.

Even though distinguishing these two concepts will be helpful for clinicians and researchers, there are still impediments when it comes to measuring tinnitus or tinnitus disorder.

Tinnitus assessment

Currently it is not possible to objectify tinnitus, even though different research groups have tried to find one by using biomarkers, MRI scans or electroencephalographic measurements. (2–4) We are still dependent of subjective measures for tinnitus and tinnitus disorder. The difficulties with measuring tinnitus in a proper and uniform method complicates data comparison.

Issues with tinnitus assessment can be subclassified into two sub questions. First what should we assess and second, how should we assess it?

First, what should we asses? Different studies have measured different tinnitus

outcomes, with different tinnitus outcome measures. For example, one study might research the beneficial effects of treatment X on the experience of tinnitus, whilst the next study assesses this on the loudness of tinnitus. This heterogeneity makes it difficult to compare studies, but also to decide where research gaps are. If we are not able to compare studies or study outcomes, there is no way we can assess the true absences in knowledge.

Initiatives such as the COMiT'ID are therefore of tremendous importance for the future of tinnitus research. (5,6) The COMiT'ID group conducted a Delphi study to assess outcome measures for different types of tinnitus therapy. In this study all stakeholders were included: patients, industry and caregivers/medical staff. The researchers advised to use certain outcome measures for different types of therapies. For sound-based therapies they advised to assess tinnitus intrusiveness, the ability to ignore, concentration, quality of sleep and sense of control. For psychological interventions, the researchers also advise to measure tinnitus intrusiveness, but rather tinnitus acceptance, mood, negative thoughts and beliefs, and the sense of control. For drug-based therapies, tinnitus intrusiveness was advised, as well as assessing tinnitus loudness. (5,6) In **chapter 2** we concluded that loudness was the most important outcome measure for tinnitus patients, irrespective of type of intervention. In addition, in the latent class analysis we also saw a variance in preferences among participants. This indicates that tinnitus heterogeneity is also an issue in outcome measures.

Apart from to the query of what should be evaluated, we also have to address the query of how to evaluate these. In the assessment of tinnitus disorder, different single-item and multi-item questionnaires have been published. Different tinnitus multi-item questionnaires such as the Tinnitus Handicap Inventory (THI), Tinnitus Questionnaire (TQ) or Tinnitus Functional Index (TFI) measure different constructs, and some of them have been poorly developed or criticized. (7–10) For example, the Tinnitus Handicap Questionnaire (THQ) is criticized for not providing a measure of severity and almost half of all questions are related to the psychological/emotional aspects (10,11) Even though the THI has been developed to measure severity, it does not measure treatment effect and has a disproportional number of questions that relate to the emotional aspects. (10) The most recently developed multi-item survey to measure the impact of tinnitus on daily life was the TFI. Compared to the other multi-item questionnaires, the different constructs are more evenly weighed. (10) Furthermore, the TFI aims to measure tinnitus-related complains, but also to detect a potential change in the severity of tinnitus. (12) Some remarks with regards to the functioning of the TFI should be made. For example, the TFI quality of life subscale does not assess generic quality of life. (12)

In May 2012 the Tinnitus Research Initiative. advised to use the THI as a measure of tinnitus severity, due to its wide use and validation in multiple languages. (13) However, this advice was published simultaneously to the development paper on the TFI. (14) Since the need of uniform measures in tinnitus research is high and considering the previously mentioned limitations, one could recommend researchers to use the TFI rather than the THI in order to measure tinnitus disorder. Specifically, since the TFI has a separate subscale for intrusiveness, in which questions on awareness, loudness, and annoyance are asked. Remarkably, loudness is advised to be used as an outcome measure based by the COMiT'ID study, as well as by **chapter 2.** (6)

The need for uniform data collection has also been stressed by the Tinnitus Research Initiative (TRI) database project in 2007 and emphasized by the European School for Interdisciplinary Tinnitus research (ESIT) in 2019. (15,16) In 2007, the Tinnitus Sample Case History Questionnaire (TSCHQ) was proposed to standardize the collection of data on tinnitus patients. In 2019 the ESIT initiative proposed an improved data collection with the European School for Interdisciplinary Tinnitus research Screening Questionnaire (ESIT-SQ). Compared to the TSCHQ, the ESIT-SQ can also be answered by people without tinnitus, and focusses more on "tinnitus relevant" comorbidities. Part A is applicable for both those with or without tinnitus, and explores general medical history. The second part of the questionnaire, which is only applicable for those who experience tinnitus, contains 22 questions on tinnitus characteristics. The main aim of the ESIT-SQ is to provide a standardized framework in order to better understand tinnitus heterogeneity and to provide a tinnitus profiling framework. (15,16) Based on this thesis and specifically **chapter 7** and **8**, we can conclude that research aimed at predicting tinnitus should focus on exploring co-morbidities, rather than tinnitus specific characteristics. With respect to the results of this thesis, one can question the added benefit of the second part of the questionnaire with regard to prediction.

Apart from uniform data collection, large data-sets are believed to be crucial for the assessment of tinnitus subtypes. (16) Since the ESIT dataset was only recently launched, results of uniform data collection and for example subtype analysis will take some time. In mean time there is still a lack of knowledge on the causality of tinnitus. This is enforced by the recent systematic review by Biswass et al. The authors conclude that different associations between various hearing related factors and non-otological factors with tinnitus have been identified, but that data on causality for tinnitus is still very scarce. (17) Data on causality will not only provide new insights in etiology, but might help with individualizing tinnitus treatments. Longitudinal prospective population studies are of importance to assess causality.

It will be of importance to differentiate between tinnitus and tinnitus disorder. Identifying those who develop tinnitus and identifying those who are at risk for a tinnitus disorder, would help with preventative strategies.

Creating large-datasets should not only be dependent on initiative such as the TRI and ESIT, but also on international collaboration. (15,16) Data-sharing is still suboptimal, as was also experienced over the course of this PhD. Due to different (inter)national legislation, excellent and benevolent initiatives of data sharing can be obstructed. Commitments of data sharing between different stakeholders can make it difficult to decide, what rights a new research partner has to access the data. Open science, and open-data are ideas that are potentially very helpful for advancements in tinnitus research. Still, currently many legislative impediments and perceived barriers have to be overcome before this will be general practice. If data will be made public, one could wonder how research partners as used in this thesis (Nivel and Lifelines) will be able to be financially sane. (18–20) Since these companies are dependent upon payments before they can grant researchers access to their data. It would be a tremendous shame if these companies would seize to exist because of open access initiatives. This might imply that a lot of very useful knowledge would no longer be gathered.

Tinnitus care

As argued before we believe tinnitus research should go back to its basics; adherence to a sound definition, consensus on outcome measures and measurements tools, and research in causality. We could also go one step further back: to define what the exact problem of tinnitus is.

For example, we believe that tinnitus is a problem because people suffer from it. However, the societal impact is largely unknown and undefined. In addition, there is little available data on the full range of health care costs related to tinnitus complaints and care. For example, how many people spent money on over-the-counter pills? How many, and how often, are non-evidence-based therapies actually being performed? The true daily practice of tinnitus care is still a black box. We all agree that step-wise care is the way forward to help those that suffer from tinnitus. (21) But how many are actually receiving this type of health-care and is this care accessible for those in need? Studies that investigate the referral pathways of tinnitus patients could therefore be of interest. How many people with tinnitus are actually referred for otological and audiological screening? How many people with tinnitus are referred for psycho-education, or one step further for cognitive behavioral therapy?

Moreover, there is currently no literature on the knowledge of general practitioners and ENT-surgeons or other health care professionals on this topic. Survey studies with random health care professionals involved in tinnitus care (among others: general practitioners (GP), otorhinolaryngologists, audiologists, psychologists) could provide us with insight to see how they deal with tinnitus patients and to check whether they act with up-to-date knowledge to counsel and refer patients. For example, when considering the prevalence numbers referred to and found in this thesis, it is quite surprising that there is no GP guideline for tinnitus specifically.

Apart from assessing the knowledge of health care professionals, it would also be of interest to assess the patient's beliefs and knowledge on tinnitus. Moreover, it would be of interest to know if patients have found their way to evidence-based information? Easy-accessible websites of Dutch GP's, including understandable (web) articles can be of importance for this. Since psycho-education is a big part of tinnitus therapy, we could perhaps help people with tinnitus before it develops into tinnitus-disorder with the simple action of writing an informative, evidence-based article.

These simple measures like informing health care professionals of guidelines and informing patients with evidence on tinnitus, could perhaps be very beneficial for tinnitus care. Especially in the day and age we live in now; where Dutch healthcare costs are spiraling out of control and economizing on health care is every day's business. (22) Decreasing healthcare costs by delivering the right care at the right spot to the right patients.

Finally, we believe the only way to take real steps in tinnitus researchers and tinnitus care is with combined effort. Multidisciplinary research, with multi-center collaborations should be encouraged to optimize research ideas and conduct.

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APPENDICES

Nederlandse samenvatting

Tinnitus, oftewel oorsuizen, is het horen van een geluid, in afwezigheid van een externe stimulus. (1) Mensen kunnen verschillende soorten geluiden horen. Voorbeelden hiervan zijn onder andere een piep, brom of een suis. Behalve de aard, ervaren mensen ook verschil in onder andere de locatie van het geluid, de intensiteit van het geluid en de hoeveelheid verschillende geluiden. Sommigen beschrijven zelfs dat zij een heel orkest horen spelen in hun oren. Kortom, tinnitus is een aandoening met veel verschillende gezichten. Verschillende co-morbiditeiten worden vaak beschreven in relatie tot tinnitus, namelijk angst, depressie en slaap- of concentratieproblemen. (2) Naast het horen van een geluid, is het belangrijk de last van de tinnitus te bepalen. Terwijl sommigen de tinnitus slechts horen, bezoeken andere één of meerdere hulpverleners, en weer anderen overwegen zelfmoord. De kwaliteit van leven is ernstig verminderd in 1-2% van de patiënten met tinnitus. (2–4) De prevalentie van oorsuizen wisselt tussen de 5.1% en 42.7%. (5) Eén van de redenen van de grote variatie, is de afwezigheid van een duidelijke, uniforme en breed geaccepteerde definitie. (5)

Tinnitus is een heterogeen ziektebeeld, niet alleen in tinnitus-specifieke karakteristieken of de ervaren last, maar ook in de definitie en de beoordeling van het oorsuizen. Deze heterogeniteit zorgt voor problematiek in wetenschappelijk onderzoek. Op dit moment is er nog geen genezende behandeling voor tinnitus, wel is het mogelijk de last te verminderen met cognitieve gedragstherapie. (6,7) Het doel van dit proefschrift was om de heterogeniteit van tinnitus te exploreren.

In **hoofdstuk 2** hebben wij onderzocht welke uitkomstmaten na tinnitus therapie belangrijk zijn voor tinnitus patiënten met behulp van een discreet keuze experiment. 127 deelnemers kregen een vragenlijst toegestuurd. Wij hebben onderzocht welke combinatie van vier attributen (tinnitus luidheid, tinnitus acceptatie, kwaliteit van leven en concentratie) met drie niveaus (toename van, gelijk niveau of afname van) de voorkeur had bij een fictieve behandeling. De uitkomsten toonden dat de keuze voor een behandeling significant werd beïnvloed door de combinatie van alle niveaus met uitkomsten, met uitzondering van een gelijk niveau van concentratie en acceptatie. In vergelijking met alle attributen, werd tinnitus luidheid als het meest belangrijk ervaren. In de uitkomsten viel op dat er sprake was van heterogeniteit die niet verklaard kon worden door correlaties tussen de attributen. Om dit nader te onderzoeken hebben we een latente klasse analyse uitgevoerd. Uit deze analyse kwamen 2 klassen. In de eerste klasse waren de voorkeuren overeenkomend met de hoofdanalyse, behalve geen significantie in gelijke kwaliteit van slaap en acceptatie. In de tweede klasse zagen wij een significante voorkeur voor toename van acceptatie, en

een gelijke kwaliteit van slaap. Kortom luidheid werd gezien als de meest belangrijk uitkomst maat, maar we zien verschil in voorkeuren. Deze studie benadrukt het belang van onderzoek naar tinnitus heterogeniteit maar ook naar therapieën die de luidheid van tinnitus verminderen.

In **hoofdstuk 3** hebben we nader onderzoek gedaan naar de prevalentie van oorsuizen in de Nederlandse populatie met verschillende afkapwaardes voor de definitie. In deze cross-sectionele studie in samenwerking met het Nivel, hebben we een vragenlijst gestuurd naar 2251 verschillende inwoners. 932 personen hebben de vragenlijst beantwoord. We vonden dat 36% van de deelnemers het afgelopen jaar tinnitus heeft ervaren voor een ongedefinieerde tijdsduur. 23% voldeed aan onze definitie van het ervaren van pathologische tinnitus. Van deze deelnemers hebben we de tinnitus last gemeten met de Tinnitus Functional Index (TFI). 48.7% van de deelnemers met pathologische tinnitus, had een TFI-score van 18 of hoger. Dit geeft aan dat zij dit minstens als een klein probleem beschouwen. In deze studie wordt het belang van een uniform en wijd geaccepteerde definitie van tinnitus benadrukt.

Hoofdstuk 4 beschrijft een studie naar de verschillen in karakteristieken tussen mensen met oorsuizen die hulp zoeken, en zij die dat niet doen. In **hoofdstuk 4** wordt gebruik gemaakt van dezelfde dataset als beschreven in **hoofdstuk 3**, deze werd ook in **hoofdstuk 6** gebruikt. In deze studie werd gekeken naar verschillen op enkele domeinen, namelijk op het vlak van demografie, tinnitus-specifieke karakteristieken, algemene & psychische gezondheid karakteristieken, psychische gezondheid, gehoor specifieke karakteristieken en middelen- en lawaai misbruik. 34% van de deelnemers met oorsuizen konden geclassificeerd worden als hulp-zoekers. Verschillen tussen mensen die wel of geen hulp zochten werden met name geïdentificeerd in tinnitus specifieke en gehoor specifieke karakteristieken. Deze studie dient als een basis voor verder onderzoek naar de heterogeniteit in tinnitus.

In **hoofdstuk 5** onderzochten we het verschil in zorggebruik in de eerste lijn tussen patiënten met tinnitus en mensen zonder tinnitus. Wij maakten gebruik van de Nivel Zorgregistraties Eerste Lijn database. Hierin hebben we de data van 963,880 mensen geanalyseerd, waarvan 8050 een open tinnitus episode hadden. Deze werden gedefinieerd als tinnitus patiënten. Patiënten met tinnitus hadden meer eerste lijn consulten in vergelijking met mensen zonder tinnitus. Ook werden zij vaker verwezen naar de tweede lijn en werden er vaker medicijnen voorgeschreven.

Hoofdstukken 6, 7 en **8** richten zich op het voorspellen van oorsuizen en de ervaren last. In hoofdstuk 6 maakten we gebruik van dezelfde database als in hoofdstuk 3 en 4. Ditmaal onderzochten we associaties tussen verschillende variabelen en de

Tinnitus Functional Index (TFI). De TFI is een vragenlijst waarmee de impact van het oorsuizen op het dagelijks leven wordt gemeten. Associaties werden gezocht tussen de TFI en demografische-, tinnitus specifieke-, gehoor specifieke-, algemene gezondheid- en psychische gezondheid karakteristieken. Wij concludeerden dat de gehoor specifieke karakteristieken, zoals problemen met het gehoor en hyperacusis de grootste associatie hadden met de TFI.

In **hoofdstuk 7** hebben we een literatuuroverzicht gemaakt van de beschikbare studies over predictie modellen naar tinnitus én tinnitus last. We identificeerden 21 geschikte studies die aan onze inclusiecriteria voldeden. Deze 21 studies beschreven samen 31 verschillende predictie modellen. Van deze studies beschreven 17 studies predictie modellen voor tinnitus last, 3 voor het ervaren van tinnitus, en 1 beschreef één van beide. De meest gebruikte voorspellers in tinnitus last modellen waren depressie of angst geassocieerde variabelen, voor het ervaren van tinnitus waren dit demografische factoren. Echter waren alle studies slecht gerapporteerd en vonden wij bij alle studies een hoog risico op bias.

In **hoofdstuk 8** ontwikkelden wij zelf een predictie model. Hiervoor gebruikte wij de Lifelines database, waarin wij gebruik maakten van data van 122,884 deelnemers. 7965 (6.5%) ervaarden tinnitus. Wij gebruikten 24 kandidaat voorspellers in verschillende domeinen om het ervaren van tinnitus te voorspellen middels een elastic net logistische regressie. Het model werd intern gevalideerd. Negen variabelen eindigden in het definitieve model. Dit waren geslacht, het gebruik van gehoorapparaten, gehoorproblemen, arteriële bloeddruk, kwaliteit van slaap, persoonlijke indruk van algemene gezondheid, somatische klachten, cardiovasculaire risico factoren en leeftijd. Deze studie benadrukt het onderzoeken van co-morbiditeiten voor het voorspellen van tinnitus.

In **hoofdstuk 9** wordt een samenvatting van de studies beschreven. Daarnaast worden de uitkomsten van dit proefschrift bediscussieerd en ideeën voor toekomstig onderzoek besproken.

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Dankwoord

Het proefschrift is af! Op deze plaats wil ik iedereen bedanken die op zijn/haar manier een bijdrage heeft geleverd aan de totstandkoming van dit proefschrift.

Te beginnen met mijn copromotoren, Dr. I. Stegeman & Dr. A.L. Smit, Lieve Inge en Diane, I&D, het dynamische duo. Dank voor jullie niet aflatende steun en enthousiasme de afgelopen paar jaar. Ik herinner me nog als de dag van gister dat jullie mij op de KNO vergadering vroegen of ik onderzoek wilde komen doen. Nu, zoveel jaar verder, is dit boek het eindresultaat.

Jullie hebben mij meegenomen in de wondere wereld der wetenschap. Met verschillende soorten projecten, van (talloze) reviews tot een discrete keuze experiment, hebben jullie mij allerlei verschillende vaardigheden bijgebracht. Van statistiek tot sterk verbeterde wetenschappelijke schrijfvaardigheid, maar met name het kritische denken. Kritisch op de wetenschap in het algemeen, maar ook kritisch op elkaars en eigen werk. Dat leidde tussen jullie tot bevlogen discussies over tal van onderwerpen, zoals de vraag of je een gordel om moet in Dubai.

Ik denk terug aan een prachtige onderzoek tijd met als hoogtepunten de corona werk sessies bij Inge thuis (ongelooflijk dat jij op ieder moment in het jaar minstens 10 onaangeroerde Tony repen hebt liggen), de heerlijke chocolaatjes van de bakkerij Verhoeff, reis naar Regensburg waar Diane zonder problemen vijf uur lang aan een stuk doorreed, terwijl Inge bij hoog en laag beef volhouden dat we er “bijna” waren ook al was het nog vijf uur rijden…, de reis naar Nottingham en als kers op de taart het congres in Dubai. Met Jan als onze beschermheer hebben we een fantastische week gehad in de woestijn. De need for speed van Jan is goed getemd tijdens het Dune Bashen in de woestijn, helaas dat Inge het iets minder leuk vond. Het sandboarding, de ijsbeer tijdens het congres diner en de “legendarische” kamelenrit maakte het af. Niet te vergeten zijn de M.I.D. (Maaike, Inge, Diane) overlegsessies met thee uit Inge’s thermoskan of colaatjes zero. Met jullie passie voor de wetenschap (en het KNO-artsen bestaan) zijn jullie een ongelooflijk groot voorbeeld voor mij, Ik ben onwijs dankbaar dat ik zoveel van jullie heb mogen leren.

Mijn promotor, prof. Dr. R.J. Stokroos, Beste Robert, bedankt voor de begeleiding tijdens dit project. Ik waardeer het vertrouwen dat je in mij had om dit project tot een goed einde te brengen.

Leden van de beoordelingscommissie, prof. dr. P. van Dijk, prof. dr. J.H. de Boer, prof. dr. A.J.W.P. Rosenberg, prof. dr. N.J. de Wit, & prof. dr. R.L.A.W. Bleys, graag wil ik jullie bedanken voor de kritische en deskundige beoordeling van dit proefschrift.

Lieve clubgenootjes, al sinds 2011 zoveel plezier en gezelligheid. Lieve Carolijn, Sanne en Merula als Utrechtse zorgcollega's begrijpen we elkaar precies en hebben we aan een half woord genoeg. Dank voor jullie vriendschap. Carolijn, hopelijk nog vele jaren samen fietsen of rijden naar werk en daar cappuccino's drinken. Lieve Hoeckers, speciaal over de afgelopen jaren denk ik aan alle corona lunch wandelingen met Thalita, alle etentjes en borrels met Caat & de heerlijke vakantie in Toscane en zeilend door Kroatië met Ines.

Lieve Chimaids & Kooka's, vrienden sinds (voor) de middelbare school. Zo dierbaar dat wij elkaar nog regelmatig spreken op onder andere de jaarlijkse weekenden en kerstdiners. In het bijzonder Ber, Fleur, Caat, Steph, Juul & JW. Lieve Wichert, dank voor je eeuwige vriendschap en gekwebbel. Eén belletje met jou zorgt ervoor dat ik weer helemaal afgeleid ben en op de hoogte van iedereen die wij kennen!

Lieve Emilie, al sinds de eerste dag van mijn leven zijn we vriendinnen. Wat geweldig dat we nu weer zo dicht bij elkaar wonen!

Lieve wetenschapscollega's, jullie hebben mijn onderzoek jaren tot een waanzinnig leuke tijd gemaakt! Ik kijk met heel veel plezier terug op de eeuwige koffie treinen, de donderdag koffie, de koffiekoning(in), de BBQ's en de COVID zoom borrels. Mijn tijd op de H02 begon met Jan, die altijd zo genoot van de donderdag koffie. Ik zal de reis naar de alpen en het formule 1 hotel samen met Jan & (R/K)utger nooit vergeten. Lieve Laura, als kamergenoot hebben we het heel gezellig gehad met zijn tweeën, jij zonderde je altijd lekker af met de noise cancelling headphones omdat ik altijd pratend zat te werken. Super gezellig dat we nu praktisch buren zijn! Lieve Kelly bedankt voor alle Franse lessen. Dank voor alle gezelligheid Sambal Saad, Viking Henk (R-held), Dyan, Natalia, Huib, Maartje (Bla bla bla chocoladevla), Dominique, Anouk & Emma. Seb, Jägermeijers, als mede auteur aan twee never ending systematic reviews verdien je een extra bedankje. Na de eerste hadden we gezworen nooit aan een tweede te beginnen, maar helaas hebben we ons toch laten overtuigen. Lieve Esther, we begonnen samen als wetenschapsstudenten en nu zijn we samen AIOS, wat een feest!

Lieve (oud) AIOS, dank voor alle gezelligheid op en naast de werkvloer. Het hitje van Hol, de vrijdagmiddagborrels in het AIOS hok, de ski vakanties met de legendarische jas van Martijn, mijn fashion-twin Anne, & de KNOhesie weekenden maken het helemaal af. Emmy, het is weer hoog tijd dat we onze wekelijkse sportsessie in de tuin nieuw leven inblazen!

Lieve Juliette en Katherine, ik ben ongelooflijk blij dat jullie als paranimfen naast mij staan. Lieve Juliette, de cirkel is helemaal rond. We bewandelen al jaren dezelfde paden, zo leerden wij elkaar kennen bij de organisatie van het Nationaal Coassistenten Congres in 2015 en waren wij daarna kortstondig huisgenoten. Vervolgens begonnen we samen aan het KNO-traject, eerst als onderzoeker en nu als AIOS, jij in Leiden en ik in Utrecht. Fantastisch dat je dit moment samen met mij wil vieren!

Lieve Kat, sinds de eerste dag als jaargenoten zijn wij dikke vriendinnen, samen met Nina begonnen wij met zijn drieën als jaarband haarband 2022. Altijd lachen met alle afko's (valiga & SpoCo) waar we menig (voornamelijk ouder, mannelijk) collega de kast op jagen. Ik kan mij de opleiding zonder jou niet voorstellen. Ik heb ontzettend veel steun aan jou dankzij alle belletjes en etentjes om even de dag te bespreken (en te klagen). Bedankt dat je naast mij wil staan!

Lieve (modern) schoonfamilie, wat bof ik met zo'n liefdevolle schoonfamilie. Dank voor alle gezellige momenten samen. Lieve Mara, Isis, Hanna, Sam & Doris jullie zijn stuk voor stuk schatjes en ik ben dolgelukkig dat ik jullie tante mag zijn.

Lieve Jochem, Lies en Emmeline, ik prijs mij erg gelukkig hoe leuk en gezellig wij het met elkaar hebben, mede dankzij de vele vakanties in de bergen. Ik hoop dat er nog veel van zullen volgen.

Lieve papa en mama, dank voor alle onvoorwaardelijke steun, liefde en vertrouwen die jullie mij iedere dag geven. Ik waardeer ontzettend hoe jullie in het leven staan; met humor, interesse in éénieder en met onuitputtelijke energie. Jullie zijn geweldig!

Lieve Daan, je was vanaf moment één bij dit project betrokken. Zonder jou had het eindresultaat waarschijnlijk nog even op zich laten wachten, maar dankzij de (letterlijke) steun in de rug (uit bed op zondagochtend…) is het er nu. Ik ben ontzettend gelukkig met jou; jij haalt het beste in mij naar boven! Ik hou van jou en kan niet wachten op de rest van ons leven!

About the author | Curriculum Vitae

Maaike Maartje Rademaker was born on November 5th 1992 in The Hague, the Netherlands. She grew up with her parents, brother and sister. She received her gymnasium diploma from the Rijnlands Lyceum Wassenaar in 2011.

Afterwards she moved to Utrecht to study Medicine at Utrecht University. In 2017 she visited the Queen Elizabeth Hospital in Blantyre, Malawi for a public health internship.

During her studies she joined several committees. Among others, she joined the board of the national interns congress (Nationaal Co-assistenten Congres) from 2015 – 2017, where she co-organised a biannual congress for medical interns in the Netherlands.

In her final year of medical school she did her senior- and scientific internships at the department of Otorhinolaryngology and Head & Neck Surgery at the University Medical Center Utrecht (UMCU).

After obtaining her Master's degree in 2018, she started to work as a PhD student at the Department of Otorhinolaryngology and Head & Neck Surgery in the UMC Utrecht (under supervision of dr. A.L. Smit, dr. I. Stegeman and prof. dr. R.J. Stokroos). In spring 2021 she participated in a junior consulting project for stichting Medical Business. Afterwards she set up the regional board of Medical Business Projects in Utrecht.

In October 2021 she started as a resident not in training at the department of Otorhinolaryngology and Head & Neck Surgery at the UMC Utrecht for two months. In January 2022 she enrolled in the residency program of Otorhinolaryngology at the same department under supervision of drs. I. Ligtenberg – van der Drift and prof. dr. R.J. Stokroos. She completed part of her training at the St. Antonius hospital in Nieuwegein and Utrecht Leidsche Rijn (supervised by dr. M.P. Copper).

Maaike lives together with Daan Wilhelmus in Utrecht, the Netherlands.

Hoe spreek ik Tinnitus uit?
Is het tie-nnie-tus? *(ti.ni.təs)* Of juist ti-nni-tus? (tɪnɪtəs)

Ti-nai-tis *(tɪna.ⁱtəs)* of tiny-tis? *(ta.ⁱni.təs?)*
Of toch tiny-tits? *(ta.ⁱni.tɪts?)*

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ISBN 978-94-6419-863-8