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Faculteit Revalidatiewetenschappen

master in de revalidatiewetenschappen en de kinesitherapie

Masterthesis

Subtyping tinnitus: important factors to keep in mind a prospective cohort study

**Fleur Ennekens
Paulien Smolders**

Scriptie ingediend tot het behalen van de graad van master in de revalidatiewetenschappen en de kinesitherapie, afstudeerrichting revalidatiewetenschappen en kinesitherapie bij musculoskeletale aandoeningen

PROMOTOR :

Prof. dr. Sarah MICHIELS

BEGELEIDER :

De heer Antonios CHALIMOURDAS



UHASSELT

KNOWLEDGE IN ACTION

www.uhasselt.be
Universiteit Hasselt
Campus Hasselt:
Martelarenlaan 42 | 3500 Hasselt
Campus Diepenbeek:
Agoralaan Gebouw D | 3590 Diepenbeek

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RESEARCH CONTEXT

The purpose of this study was to investigate the diagnostic value of a series of symptoms and questionnaires in the identification of the primary etiology of tinnitus in a tertiary population. The study is situated within the research context of the domain 'pain, fatigue, and somatically unexplained physical symptoms'. This study is covered by the central format.

This Master's Thesis is an independent study. The investigation was mainly done in the University Hospital in Antwerp, at the TINTRA tinnitus clinic.

There have been various studies investigating tinnitus, however, to our knowledge this is the first study that investigates different etiologies and their associated symptoms. Because of this, we consider our research very relevant. We hope that our findings can contribute to new and useful information regarding the associated symptoms of specific etiologies of tinnitus. However, further investigation is needed to confirm our findings and expand the knowledge regarding the associated symptoms of the specific etiologies of tinnitus.

The research question was established in agreement with the promotor, Sarah Michiels. The writing of this thesis happened under the supervision of Sarah Michiels and Antonios Chalimourdas, but was mainly independently designed by the two students, Fleur Ennekens and Paulien Smolders.

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SUBTYPING TINNITUS: IMPORTANT FACTORS TO KEEP IN MIND – A PROSPECTIVE COHORT STUDY

ABSTRACT

Goal: The purpose of this prospective cohort study was to investigate the diagnostic value of a series of symptoms and questionnaires in the identification of the primary etiology of tinnitus in a tertiary population.

Methods: Patients with a primary complaint of tinnitus, who visited the TINTRA tinnitus clinic at Antwerp University Hospital (UZA) for the first time, were included in the study.

Study participants were investigated by a multidisciplinary team of otorhinolaryngologists, audiologists, and physiotherapists using a structured medical history, otoscopy, standard hearing tests, and a set of questionnaires to investigate the tinnitus severity, presence of neck pain, temporomandibular disorders (TMD), anxiety, depression, and hyperacusis. After the multidisciplinary assessment, a score between 0 and 3 was given to each of the potential contributing factors in tinnitus etiology. A factor was scored 0 if the team considered this factor had no influence and 3 in case this factor was considered the primary etiology of a patient's tinnitus. Scores 1 and 2 were given depending on the strength of the influence of this factor on the patient's tinnitus. The different contributing factors in the etiology of tinnitus, included in this study were: hearing loss related, transmission, noise, cervical dysfunction, temporomandibular disorder (TMD), psychological, neurological, noise trauma, idiopathic, post-operative, Meniere's disease (MD), and vascular cause.

Data were analyzed using logistic regression analysis.

Results: In total, 414 patients with a mean age of 47.70 years old (SD= 14.388) were included in the study. A hearing loss-related problem as primary tinnitus etiology can be predicted by Pure Tone Audiogram-Left (PTA-Le), (OR=1.113, CI 95%=1.083-1.145, p<0.001), Pure Tone Audiogram-

Right (PTA-Ri), (OR=1.102, CI 95%=1.073-1.131, $p<0,001$), Pure Tone Audiogram high-Left (PTAhigh-Le), (OR=1.149, CI 95%=1.116-1.183, $p<0.001$), and Pure Tone Audiogram high-Right (PTAhigh-Ri) (OR=1.140, CI 95%=1.108-1.173, $p<0.001$). TMD as primary tinnitus etiology can be predicted by TMD pain (OR=54.762, CI 95%=18.183-164.931, $p<0.001$) and a positive score (a score ≥ 3 in a 0-7 range) on the TMD pain screener (OR=15.408, CI 95%=6.661-35.641, $p<0,001$). Finally, a cervicogenic problem, as primary tinnitus etiology, can be predicted by cervical spine modulation (OR=24.731, CI 95%=9.908-61.734, $p<0.001$). Other causes of tinnitus examined in this study showed no moderate to very strong correlation (Pearson $r \geq 0.4$). Because of this, no further statistical analysis was performed on these etiologies.

Conclusions: Three etiologies of tinnitus can be predicted by looking at associated symptoms and questionnaires in a tertiary population. A hearing loss-related problem as primary tinnitus etiology, can be predicted by PTA and PTAhigh, both on the left and right ear. A TMD as primary tinnitus etiology, can be predicted by TMD pain and a positive score on the TMD pain screener. Finally, a cervicogenic problem as primary tinnitus etiology, can be predicted by cervical spine modulation (CSM). To the best of our knowledge, this is the first study investigating different etiologies and their associated symptoms. Further investigation is needed to confirm these results.

INTRODUCTION

Tinnitus, also called ringing in the ears, is one of the most common otological symptoms. Overall, up to 10-15% of adults worldwide report experiencing this phenomenon (Tunkel et al., 2014). It can be defined as: 'an auditory perception in the absence of an auditory stimulus' (Henry, 2016). The ringing in the ears can cause distress to patients and affect their ability to function physically, emotionally, or socially (Ciminelli et al., 2018). Previous studies found that 1.6% of people experience tinnitus as bothersome (Baguley et al., 2013).

There are several known causes of tinnitus, which can be classified as subjective or objective tinnitus. Subjective tinnitus can be defined as an auditory perception, which is experienced in the absence of any external or internal auditory stimuli, where no definite organic lesions are observed after an examination (Chen et al., 2022). In objective tinnitus, the sound is detectable by a clinician. Objective tinnitus is reported in less than 1% of patients with tinnitus, and is caused by noise generated from structures near the ear (e.g. myoclonic contractions of the tensor tympani muscle or altered blood flow in vessels near the ear). This often indicates a treatable underlying medical condition (e.g. arteriovenous fistulas) (Hofmann et al., 2013).

Tinnitus often has a multifactorial origin with several influencing factors maintaining the tinnitus percept. Often tinnitus is related to hearing loss, which can be age-related or related to noise exposure, or a noise trauma. Noise trauma meaning the patient was exposed to excessively loud noise (e.g. an explosion)(Baguley et al., 2013b). In some people, a specific disease, such as Meniere's disease (MD) is causing tinnitus.

Additionally, tinnitus can be influenced by somatic disorders, such as cervical spine dysfunction or temporomandibular disorder (TMD). In this case, changes in the somatosensory input from the lower cranial nerves and upper cervical nerves cause alterations in tinnitus pitch and loudness (Michiels et al., 2021).

Furthermore, psychological disorders, such as excessive stress, anxiety disorder, and depression can cause or influence existing tinnitus (Molnàr et al., 2022).

In pulsatile tinnitus, patients hear a throbbing sound that can often be objectively detected through auscultation. This type of tinnitus is often caused by vascular abnormalities (e.g. neurovascular conflict). In pulsatile tinnitus, the auditory perception is repetitively synchronous

with the patient's heartbeat. It can be detected in <10% of patients with tinnitus. All other auditory perceptions are considered non-pulsatile (Pegge et al., 2017).

Surgery can also be the source of tinnitus. It can induce or worsen tinnitus. A study done by K. S. Mikkelsen et al. found that 12.1% of patients without prior tinnitus developed tinnitus following cochlear implantation. In addition, 25% of the patients affected by pre-operative tinnitus experienced aggravation of existing tinnitus (Mikkelsen et al., 2017).

Finally, a neurological etiology (e.g. traumatic brain injury, acoustic neuroma, or intracranial tumors) can cause tinnitus (Dalrymple et al., 2021).

Apart from influencing factors that can cause or worsen a patient's tinnitus, a whole series of symptoms can be associated with the presence of tinnitus. People with tinnitus often suffer from sleeping problems (difficulties getting to sleep or staying asleep) and have trouble concentrating. Sometimes people also complain about headaches or dizziness as accompanying symptoms. It is not clear to what extent different influencing factors and accompanying symptoms co-exist. Therefore, this study aims to investigate if specific etiologies of tinnitus are associated with specific symptoms.

METHODS

PATIENTS AND STUDY DESIGN

A prospective cohort study was conducted to investigate the correlation between specific etiologies or influencing factors of tinnitus and possible associated symptoms.

Between 2017 and 2022 all patients, who presented themselves for the first time at the TINTRA tinnitus clinic of the Antwerp University Hospital with a primary complaint of tinnitus, were included in the study.

Prior to the study enrollment, all subjects provided informed consent.

ASSESSMENTS AND DATA COLLECTION

The investigation was done by a multidisciplinary team of otorhinolaryngologists, audiologists, and physiotherapists. All the patients underwent a standard procedure at UZA, meaning a structured medical history, otoscopy, standard hearing tests, and a set of questionnaires to investigate the tinnitus severity, presence of neck pain, temporomandibular disorders, anxiety, depression, and hyperacusis.

SYMPTOMS AND MEASUREMENT TOOLS

SYMPTOMS

The following symptoms were included in the dataset: date of birth, age, tinnitus etiology, cervicalgia, TMD pain, clenching, grinding, pulsatile, headache, vertigo, sleep disorder, cervical spine modulation (CSM), and temporomandibular joint (TMJ) modulation. CSM and TMJ modulation means a possible modulation of tinnitus with respectively neck and jaw movements.

MEASUREMENT TOOLS

The measurement tools which were used, are the Tinnitus Functional Index (TFI), Neck Bournemouth Questionnaire (NBQ), Temporomandibular Disorder pain screener (TMD-pain screener), Hyperacusis Questionnaire (HQ), Hospital Anxiety and Depression Scale - fear (HADS-fear), Hospital Anxiety and Depression Scale - depression (HADS - depression), Visual Analog Scale - tinnitus left (VAS-tinnitus left), Visual Analog Scale - tinnitus right (VAS - tinnitus right), Pure Tone

Audiogram - Left (PTA-Le), Pure Tone Audiogram - Right (PTA-Ri), Pure Tone Audiogram high - Left (PTAhigh-Le) and Pure Tone Audiogram high - Right (PTAhigh-right).

Tinnitus Functional Index

The TFI is an internationally recognized tool, which offers insight into tinnitus severity and the potential negative impact on a patient.

The TFI consists of 25 items with eight subscales: 'intrusive', 'sense of control', 'cognitive, sleep', 'auditory', 'relaxation', 'quality of life', and 'emotional', which address important domains of negative tinnitus impact. Each item is scored on a 0-10 scale, with a possible maximum score of 250. To calculate the overall TFI score, the sum of all valid answers is divided by the number of questions for which the respondent provided valid answers. This number is multiplied by 10, which provides the overall TFI score within the 0-100 range. A higher score means a higher severity of tinnitus and a greater negative impact on everyday life.

Looking at the measurement properties of the TFI, Cronbach's alpha is 0.97. The test-retest reliability of the TFI is very good (0.78). Furthermore, the TFI appeared to have a very good sensitivity to treatment-related changes (Henry et al., 2016).

Neck Bournemouth Questionnaire

The NBQ is a modified version of the original Bournemouth Questionnaire (BQ) for lower back pain. The NBQ aims to assess biopsychosocial aspects of neck pain. The questionnaire consists of seven items that measure the affective and cognitive aspects of neck pain, in addition to pain and disability. It aims to assess pain intensity, disability in activities of daily life, disability in social activities, anxiety and depression, the cognitive aspects of fear avoidance, and pain locus of control. Each item is scored on an 11-point scale. The total score ranges from 0 to 70 points. A higher score indicates more pain and more limitations (Bolton and Breen, 1999; Bolton, 2004). According to this study, a score $\geq 14/70$ is considered a positive score (neck pain is relevant).

This study used the Dutch-language NBQ, originally made by Schmitt et al., in 2009. The reliability of the NBQ is excellent (ICC = 0.92). No floor or ceiling effects have been detected (Schellingerhout et al., 2011).

Hospital anxiety depression scale

The HADS is a tool to measure the potential presence of anxiety and depression disorders. The scale is based on feelings over the last four weeks and consists of 14 items, divided into two subgroups: a depression scale (7 items) and an anxiety scale (7 items).

Scoring for each item is done on a 4-point Likert scale (0-3). The wording of the questions and response options is positive (0-3) for 6 items and negative (3-0) for 8 items. Scoring for each subscale is done on a 22-point scale (0-21). The score of the anxiety scale is the sum of the points of the odd-numbered questions. The depression scale score is the sum of the points of the even questions. A score from zero to seven indicates 'no anxiety disorder or depression', a score from eight to ten indicates a 'possible anxiety disorder or depression' and a score from eleven to twenty-one indicates a 'suspected anxiety disorder or depression' (Zigmond AS, Snaith RP; 1983, 1992, 1994).

The methodologic quality of the original tool was investigated in a study by Bjelland, et al. (2002). It concluded that the concurrent validity of the HADS is good to very good.

The HADS (Zigmond AS, Snaith RP; 1983, 1992, 1994), has been translated into different languages. This study used the Dutch version (Pouwer F, Snoek FJ, van der Ploeg HM, 1997). Cronbach's alpha for the total scale and both subscales (range 0.71 to 0.90) are satisfactory to good. Test-retest reliability of the total scale and the subscales were good (Spinoven et al., 1997).

Visual Analogue Scale - tinnitus

The VAS (Freyd M, 1923), is a non-specific ordinal measuring instrument that was used to measure tinnitus loudness. It consists of a horizontal or vertical line, the length of which is usually 100 millimeters (mm). The score ranges from 0 to 100, with 0 being 'inaudible tinnitus' and 100 being 'extremely loud tinnitus'. A higher score indicates louder tinnitus. The patient should indicate perpendicularly to the line the degree corresponding to the requested sensation. In this case, the loudness of the tinnitus on the left or right side respectively VAS-Left or VAS-Right. The number of millimeters between the beginning of the line (0mm) and the self-designated line is the score on the VAS.

In general, the VAS is a reliable, valid, responsive, and frequently used pain outcome measure (Raj-Koziak et al., 2018).

A study by Adamchic, I., Langguth, B., Hauptmann, C., & Tass, P. A. (2012), investigated the measurement properties of the VAS in the assessment of patients with chronic tinnitus. VAS loudness showed good test-retest reliability of 0.8. In terms of convergent validity, VAS loudness correlated well with the tinnitus questionnaire at all clinical visits (max $r = .67$, $p < 0.05$). It concluded that VAS loudness is a valid and effective measurement tool for capturing reductions in tinnitus severity in patients with chronic tinnitus.

The study of Raj-Koziak et al. (2018) supports these findings. For VAS-loudness, a test-retest of 0.95 was found, which shows high reliability. The study adds that there is a reproducibility of 0.95 when the test was taken twice over the course of three days. It concludes that VAS scales are valid and reliable brief screening tools, which make it possible to obtain quick information about tinnitus at the patient's first intake.

TMD pain screener

The TMD pain screener is a six-item questionnaire, which allows the identification of patients with painful Temporomandibular conditions or TMJ Pain (Karegeannes, 2022).

Patients who score ≥ 3 points on the TMD pain screener (0-7 range) are anticipated to have a painful TMD based on the Diagnostic Criteria for Temporomandibular Disorders (DC/TMD) (Van Der Meer et al., 2021).

It is a simple, reliable, and valid self-report instrument, which can be used as a 'short screener'. It has a sensitivity and specificity of ≥ 0.95 for TMD diagnosis (Schiffman et al., 2014).

Hyperacusis Questionnaire

The HQ is a frequently used measurement tool for screening patients with signs of hyperacusis. The measurement consists of 2 parts. The first part asks for general information about hearing impairment and noise exposure. The second part consists of 14 items to be scored on a 4-point scale: "No" (0 points), "Yes, a little" (1 point), "Yes, quite a lot" (2 points), and "Yes, a lot" (3 points). The total individual scores are added up to a total score of 42 points. A global score of >28 indicates hyperacusis. Items related to the three subscales can also be summed to provide subscale scores (Khalifa et al., 2002).

The HQ has a satisfactory internal consistency reliability (0.66 for subscale 'attentional', 0.68 for the subscale 'social', and 0.67 for the subscale 'emotional') according to Cronbach's alpha values, and factorial validity (Khalifa et al., 2002).

In 2015, a study by Fackrell et al. was conducted in the UK to evaluate the validity and reliability of the HQ for use as a measurement tool in a specific tinnitus research population. Internal consistency was measured as Cronbach's alpha with estimates $\alpha > 0.7$ and $\alpha < 0.9$ to indicate acceptable internal consistency. The correlations were ranging from 0.06 to 0.72, indicating very low to moderate internal consistency. In contrast, Cronbach's alpha estimates for the HQ global score were high ($\alpha = 0.88$) and subscale scores were all above the specified criteria ($\alpha > 0.7$). Furthermore, the HQ demonstrates acceptable discriminant validity.

PROCEDURE - STATISTICAL ANALYSIS

To determine the presence of an etiology, the etiologies were originally scored from 0-3, meaning 0: etiology is not present, 1: the etiology is not primarily present, 2: the etiology has a significant influence, and 3: the etiology is the primary cause.

To examine relationships between the cause of tinnitus and possible associated symptoms, patients were divided into groups, according to the etiology of their tinnitus (e.g. transmission, noise, cervicogenic, TMD, psychological, hearing loss related, neurological, traumatic, idiopathic, post-operative, MD and vascular). For this statistical analysis, SPSS (version 28.0.1.1) was used. Due to the large sample size, parametric tests were used.

First, a correlation table was made. The Pearson correlation analysis was used to search for correlations between the different etiologies and data obtained from the standard protocol, to examine the likelihood of having a certain tinnitus etiology. When at least a moderately significant correlation (Pearson $r = \geq 0.40$) was found, it was considered relevant for further analysis (p -values < 0.05) (Schober et al., 2018).

All factors that were found potentially relevant and significant ($p > 0.05$), were afterward inserted in a logistic regression analysis. The significance level of the Odds Ratio (OR) in a 95% confidence interval (CI) was examined. Values that were considered statistically significant ($p < 0.05$), were included in the results.

RESULTS

GENERAL

First, each etiology was dichotomized, meaning they were assigned a score of 0 (etiology not present) or 1 (etiology present). Each etiology was originally scored from 0-3, meaning 0: etiology is not present, 1: the etiology is not primarily present, 2: the etiology has a significant influence, 3: the etiology is the primary cause. A score of 0 or 1 on an etiology was converted to 0, and a score of 2 or 3 was converted to 1. The TMD pain screener was also dichotomized. It has originally a range of 0-7, where a score >3 means a painful TMJ. A score <3 was converted to 0 (no TMJ pain), and a score >3 was converted to 1 (painful TMJ), as can be seen in Table 1.

TABLE 1. Scoring used for data analysis

Scoring and interpretation	
E-perception	0 = not present or small influence, 1 = obvious influence or main cause
E-transmission	0 = not present or small influence, 1 = obvious influence or main cause
E-noise	0 = not present or small influence, 1 = obvious influence or main cause
E-cervicogenic	0 = not present or small influence, 1 = obvious influence or main cause
E-TMD	0 = not present or small influence, 1 = obvious influence or main cause
E-psychological	0 = not present or small influence, 1 = obvious influence or main cause
E-neurological	0 = not present or small influence, 1 = obvious influence or main cause
E-trauma	0 = not present or small influence, 1 = obvious influence or main cause
E-idiopathic	0 = not present or small influence, 1 = obvious influence or main cause
E-post operative	0 = not present or small influence, 1 = obvious influence or main cause
E-vascular	0 = not present or small influence, 1 = obvious influence or main cause
E-MD	0 = not present or small influence, 1 = obvious influence or main cause
Cervicalgia	0 = symptom not present, 1 = symptom present
TMD-pain	0 = symptom not present, 1 = symptom present
CSM	0 = symptom not present, 1 = symptom present
TMJ modulation	0 = symptom not present, 1 = symptom present
Clenching	0 = symptom not present, 1 = symptom present
Grinding	0 = symptom not present, 1 = symptom present
Pulsatile	0 = symptom not present, 1 = symptom present
Headache	0 = symptom not present, 1 = symptom present
Vertigo	0 = symptom not present, 1 = symptom present
Sleeping problems	0 = symptom not present, 1 = symptom present
TFI	Range: 0-100 A higher score means a higher severity of tinnitus and a greater negative impact on everyday life
NBQ	Range: 0-70 A higher score indicates more pain and more limitations.
TMD-pain screener	≥14/70 = neck pain relevant 0 = no (painful) TMJ 1 = painful TMJ
HQ	Range: 0-42
HADS-fear	>28/42 = hyperacusis Range: 0-21
HADS-depression	0-7 = no anxiety disorder or depression, 8-10 = possible anxiety disorder or depression, 11-21 = suspected anxiety disorder or depression Range: 0-21
VAS-tinnitus-Le	0-7 = no depression, 8-10 = possible depression, 11-21 = suspected depression Range: 0-100 mm The higher the score, the higher the perception of the requested sensation.
VAS-tinnitus-Ri	Range: 0-100 mm The higher the score, the higher the perception of the requested sensation.
PTA-Le	Scoring in dB
PTA-Ri	Scoring in dB
PTAhigh-Le	Scoring in dB, high tone
PTAhigh-Ri	Scoring in dB, high tone

Note: the table shows an overview of the scoring used for data analysis which is slightly different from the primary scoring.

E = etiology, TMD = temporomandibular dysfunction, MD = Meniere Disease, TMJ = temporomandibular joint, TFI = tinnitus functional index, NBQ = Neck Bournement Questionnaire, HQ = hyperacusis questionnaire, HADS-fear = hospital anxiety depression scale for fear, HADS-depression = hospital anxiety depression scale for depression, VAS-tinnitus-Le = visual analogue scale for tinnitus on the left side, VAS-tinnitus-Ri = visual analogue scale for tinnitus on the right side, mm = millimeter, PTA-Le = pure tone average on the left side, PTA-Ri = pure tone average on the right side, dB = decibel, PTAhigh-Le = Pure Tone Average for high tones on the left side, PTAhigh-Ri = Pure Tone Average for high tones on the right side.

DEMOGRAPHICS

In total, 414 subjects (mean age = 47.70, SD= 14.388) were included in this study of which 129 were females and 285 were males. Out of the 414 persons, 44.9% (N= 186) had the etiology perception, 26.6% (N= 110) etiology noise, 24.4% (N= 101) psychological etiology, 7.2% (N=30) etiology TMD, 6.8% (N= 28) etiology cervicogenic, 5.8% (N=24) etiology idiopathic, 3.6% (N=15) etiology neurological, 3.4% (N= 14) etiology transmission, 2.4% (N= 10) etiology trauma, 0.5% (N=2) etiology post-operative, 0.2% (N= 1) etiology MD, and 0.2% (N= 1) etiology vascular. Table 2 shows these demographic features.

TABLE 2. Demographic features

	<i>Prevalence in % and N</i>
Gender	Women 31% (N=129) Men 69% (N=285)
Mean age	47.70 (SD 14.388)
Etiologies	E-perception 44.9% (N=186) E-noise 26.6% (N=110) E-Psychological 24.4% (N=101) E-TMD 7.2% (N=30) E-Cervicogenic 6.8% (N=28) E-Idiopathic 5.8% (N=24) E-Neurological 3.6% (N=15) E-Transmission 3.4% (N=14) E-Trauma 2.4% (N=10) E-Post operative 0.5% (N=2) E-MD 0.2% (N=1) E-Vascular 0.2% (N=1)

Note: E = etiology, N = number, SD = Standard Deviation, TMD = Temporomandibular Dysfunction, MD = Meniere Disease.

Table 3 shows the prevalence of associated symptoms that come with experiencing Tinnitus. 40.1% experience sleeping problems, 31.9% cervicgia, 16.9% vertigo, 15.9% temporomandibular pain, 15.0% CSM, 14.7% grinding, 13.0% clamping, 11.0% TMJ-modulation, 8.0% headache, and 5.3% pulsatile. For those who completed the questionnaires: 12.3% scored a positive result (≥ 3) on the TMD-pain screener (mean= 0.81, SD= 1.472). On the TFI: 22.2% scored <25, 39.6% scored 25-50, and 34.3% scored >50 (mean = 41.787, SD= 19.943). On the HADS-fear: 58.2% scored between 0-7, 20.3% scored between 8-10, and 16.9% scored between 11-21 (mean= 7.09, SD=3.965). On the HQ: 6.5% scored a positive, and 88.9% scored negative (mean= 16.57, SD= 7.757). On the HADS-depression questionnaire: 70.8% scored between 0-7, 13.0% scored between 8-10, and 11.6% scored between 11-21 (mean= 5.11, SD= 4.145). On the NBQ: 41.1% scored $\geq 14/70$ (mean= 14.85, SD= 13.045).

TABLE 3. Associated symptoms and questionnaires

<i>Prevalence in % and N</i>		
Symptoms (yes/no)	Sleeping problems 40.1% (N=166)	
	Cervicalgia 31.9% (N=132)	
	Vertigo 16.9% (N=70)	
	TMD pain 15.9% (N=66)	
	CSM 15.0% (N=62)	
	Grinding 14.7% (N=61)	
	Clamping 13.0% (N=53)	
	TMJ modulation 11.0% (N=45)	
	Headache 8.0% (N=33)	
	Pulsatile 5.3% (N=22)	
	Questionnaires	TMD pain screener 12.3% (N=51)
		TFI
		<25 22.2% (N=92)
		25-50 39.6% (N=164)
>50 34.3% (N=142)		
HADS-fear		
0-7 58.2% (N=241)		
8-10 20.3% (N=84)		
11-21 16.9% (N=70)		
HADS-depression		
0-7 70.8% (N=293)		
8-10 13.0% (N=54)		
11-21 11.6% (N=48)		
HQ		
6.5% (N=27)		
NBQ		
41.1% (N=170)		
VAS-Le		
Mean 43.30mm (SD 26.381)		
VAS-Ri		
Mean 45.09mm (SD 26.000)		
PTAhigh-Le		
Mean 16.67dB (SD 13.256)		
PTAhigh-Ri		
Mean 16.32dB (SD 12.347)		
PTA-Le		
Mean 12.57dB (SD 11.928)		
PTA-Ri		
Mean 12.67dB (SD 10.880)		

*Note: Percentage (%) and numbers (N) are shown of those who have the specific symptom or score positive on the questionnaires.
E = etiology, N = number, SD = Standard Deviation, TMD pain = Temporomandibular dysfunction pain, CSM = Cervical Spine Modulation, TMJ modulation = Temporomandibular Joint modulation, TMD pain screener = Temporomandibular dysfunction pain screener, TFI = Tinnitus Functional Index, HADS-fear = Hospital Anxiety and Depression scale – fear, HADS-depression = Hospital Anxiety and Depression scale – depression, HQ = Hyperacusis Questionnaire, NBQ = Neck Bournemouth Questionnaire, VAS-Le = Visual Analogue Scale – Left, VAS-Ri = Visual Analogue Scale – Right, PTAhigh-Le = Pure Tone Average for a high tones – Left, PTAhigh-Ri = Pure Tone Average for a high tones – Right, PTA-Le = Pure Tone Average – Left, PTA-Ri = Pure Tone Average – Ri, mm = millimeter, dB = Decibel.*

For the VAS-Left 43.30mm was the mean score, with a SD of 26.381. The mean score on the VAS-Right was 45.09mm, with a SD of 26.00.

For the hearing tests, the following mean scores were found: 16.67 decibels (dB) on the PTAhigh-left (SD 13.256), 16.32dB (SD 12.347) on the PTAhigh-right, 12.57dB (SD 11.928) on the PTA-left, and 12.67 dB (SD 10.880) on the PTA-right.

In this study, there was only 1 person with MD and 1 person with a vascular etiology as the cause of tinnitus. For MD this was a 39-year-old woman with cervicalgia, TMD pain, CWK modulations, grinding, and vertigo present. On the TFI she obtained 15.6/100, on the NBQ 4/70, on the HQ 16/42, on the HADS fear 4/21, on the HADS depression 3/21, a tinnitus VAS-Left score of 43mm and Right 45mm, a PTA-Left score of 20 dB and Right 17 dB and finally a PTAhigh-Left score of 17 dB and Right 18 dB. Since there is only 1 person with MD included in the study, it is not possible to generalize these data.

For vascular etiology, this was a 64-year-old woman with CSM. On the completed questionnaires the scores were TFI 29.2/100, NBQ 4/70, HQ 22/42, HADS-fear 5/21, HADS-depression 4/21, VAS-Left 33mm, VAS-Right 34mm, PTA Left 7 dB, PTA-Right 5 dB, PTAhigh-Left 15 dB, PTAhigh-Right 13 dB.

CORRELATION AND REGRESSION ANALYSIS

RESULTS PER ETIOLOGY

Hearing loss-related etiology

Table 4 shows an overview of the significance level, OR, and 95% upper and lower CI. The analysis revealed that patients with a higher PTA-Le (OR=1.113, CI 95%=1.083-1.145, $p < 0.001$), PTA-Ri (OR=1.102, CI 95%=1.073-1.131, $p < 0.001$), PTAhigh-left (OR=1.149, CI 95%=1.116-1.183, $p < 0.001$), and PTAhigh-Ri (OR=1.140, CI 95%=1.108-1.173, $p < 0.001$) were more likely to have hearing loss related tinnitus.

TABLE 4. Hearing loss related etiology

Test/symptom	Sig.	OR	95% CI lower (OR)	95% CI upper (OR)
PTAhigh-Le	<0.001	1,149	1,116	1,183
PTAhigh-Ri	<0.001	1,140	1,108	1,173
PTA-Le	<0.001	1,113	1,083	1,145
PTA-Ri	<0.001	1,102	1,073	1,131

Note: Sig = significance level (p -value < 0.05), OR = Odds Ratio, CI = confidence interval, PTAhigh-Le = Pure Tone Average for high tones on the left side, PTAhigh-Ri = Pure Tone Average for high tones on the right side, PTA-Le = pure tone average on the left side, PTA-Ri = pure tone average on the right side

Etiology TMD

Table 5 shows an overview of the significance level, OR, and 95% upper and lower CI. The analysis revealed that patients with TMD pain (OR=54.762, CI 95%=18.183-164.931, $p < 0.001$) were 55 times more likely to have TMD tinnitus. Patients with a positive TMD pain screener were 15 times more likely to have TMD tinnitus (OR=15.408, CI 95%=6.661-35.641, $p < 0.001$).

In addition, TMJ modulation showed a weak correlation, Pearson $r = 0.320$ ($p < 0.001$). Also, grinding and clamping showed a weak correlation, respectively Pearson $r = 0.303$ ($p < 0.001$) and Pearson $r = 0.394$ ($p < 0.001$), and are therefore not included in the logistic regression.

TABLE 5. Etiology TMD

Test/symptom	Sig.	OR	95% CI lower (OR)	95% CI upper (OR)
TMD pain	<0,001	54,762	18,183	164,931
TMD pain screener	<0,001	15,408	6,661	35,641

Note: Sig = significance level (p -value < 0.05), OR = Odds Ratio, CI = confidence interval, TMD pain = temporomandibular disorder pain, TMD pain screener = temporomandibular disorder pain screener

Etiology cervicogenic

Table 6 shows an overview of the significance level, OR, and 95% upper and lower CI. The analysis revealed that patients with CSM were 25 times more likely to have cervicogenic tinnitus (OR=24.731, CI 95%=9.908-61.734, $p < 0.001$).

In addition, cervicalgia and NBQ showed a weak correlation, respectively Pearson $r = 0.372$ ($p < 0.001$) and Pearson $r = 0.332$ ($p < 0.001$) and are therefore not included in the logistic regression analysis.

TABLE 6. Etiology cervicogenic

Test/symptom	Sig.	OR	95% CI lower (OR)	95% CI upper (OR)
CSM	<0,001	24,731	9,908	61,734

Note: Sig = significance level (p -value < 0.05), OR = Odds Ratio, CI = confidence interval, CSM = cervical spine modulation

Other etiologies of Tinnitus:

The results showed no moderate to very strong correlations between associated symptoms from the UZA standard protocol and noise etiology, psychological etiology, idiopathic etiology, neurological etiology, transmission etiology, trauma etiology, post-operative etiology, MD etiology, and vascular etiology of tinnitus. Because of this, no further statistical analysis was conducted.

DISCUSSION

The purpose of this cross-sectional study was to investigate the diagnostic value of a series of symptoms and questionnaires in the identification of the primary etiology of tinnitus in a tertiary population.

Because of the multifactorial cause of tinnitus, it is necessary to get an overview of the various influencing factors since it is important to offer a 'patient-tailored' treatment.

In this study, 414 persons were included, of which 129 were females and 285 were males. Since tinnitus is equally prevalent in men and women, we consider this division illogical. Previous research showed that women experience more bothersome tinnitus, so we would expect women to be more likely to sign up for treatment.

In addition, previous research showed that the prevalence of tinnitus varies across different age categories. A systematic review and meta-analysis by Jarach et al. (2022), found that an increased prevalence was associated with age, 9.7% among adults aged 18-44 years, 13.7% among those aged 45-64 years, and 23.6% among those aged >65 years. The mean age of our study participants is 47.70 years. Since 44 out of 414 participants were >65 this may be less representative of the tinnitus population in general.

Only patients new to the department (referred or voluntary consultation) were included in the study. It is a tertiary center, so most of these patients were referred. Thereby most subjects, included in this study, will have chronic Tinnitus.

Looking at the results of this study, several significant correlations were found. Three etiologies in our study described a significant association with associated symptoms, namely cervicogenic, TMD, and hearing loss-related etiology. All of them showed a moderate correlation.

Even though 414 people were included in the study, there were only 14 individuals with transmission etiology, 10 individuals with trauma etiology, 2 individuals with post-operative etiology, 1 individual with MD etiology, and 1 individual with vascular etiology. Since these sample sizes are so small, we are unable to generalize these results. Previous research by Tunkel et al. (2014) suggests that objective tinnitus is rare (<1%), since vascular tinnitus is a form of objective tinnitus, we consider this small sample size logical. According to a study by Langguth et al. (2013),

noise trauma is a common cause of tinnitus, so this number of individuals included is rather illogical. Based on previous research, there is no consensus about the prevalence of the other specific etiologies. The sample sizes may be coincidental, according to the patients who visited UZA in this period.

The symptom of sleeping problems is the most prevalent in our database. We consider this logical since sleep impairment is common among patients with tinnitus (Gu et al., 2022). On the other hand, although sleeping problems are reported frequently in tinnitus patients, our study was not able to link it to a specific pathology. In addition, a study by Folmer & Griest (2000) showed that insomnia is associated with greater perceived loudness and severity of tinnitus. It is therefore important to better understand this link and the possible associated etiologies. Further research is indicated.

Looking at the results of the correlation table in etiology psychological, no relevant correlations were found. We expected to find moderate correlations between sleeping problems, a positive score on HADS-depression, and HADS-fear with a psychological etiology of tinnitus since psychological causes of tinnitus include stress, anxiety, and depression. Numerous studies show that impairments in chronic tinnitus are closely connected with psychosomatic symptoms. A study by Mazurek et al. (2023) investigates tinnitus-related distress. It states that tinnitus-related distress emerges against a background of pre-existing medical, psychological, or social vulnerability and can manifest itself in a variety of functional phenomena, such as (1) other functional hearing disorders (e. g. hyperacusis), or (2) anxiety and depression cycles, which, in turn, may involve (a) sleep or concentration difficulties, (b) cognitive difficulties, or (c) mood volatility. By this, a correlation with anxiety, depression, and sleeping problems, in the etiology psychological, seems logical.

This study did not find a moderate to very strong correlation (pearson= >0.4) between etiology cervicogenic and cervicalgia, and the NBQ score. In both cases, significant values were found, but the correlations were weak (respectively Pearson $r = 0.372$ and Pearson $r = 0.332$). Therefore, this was not included in further statistical analysis. This finding does not correspond to previous research. According to Oostendorp et al. (2016), cervicogenic tinnitus is a subgroup of patients with (chronic) somatosensory tinnitus, in which tinnitus is related to changes in anatomical structures and physiological functions of the cervical region. Based on several (animal) studies, the existence of neural connections between the cervical region and the auditory system can be

assumed. In addition, a study by Michiels et al. (2015) investigated the diagnostic value of clinical cervical spine tests, including the NBQ, in people with cervicogenic somatic tinnitus (CST). It concluded that the diagnosis of CST becomes less likely with NBQ scores of <14/70 (sensitivity of 80%, likelihood ratio [LR] of 0.3, and posttest probability of 19%). This in combination with the absence of trigger points can help to exclude CST. So, previous research did find correlations between cervicalgia, the NBQ-score, and cervicogenic tinnitus, while our study did not. This may be due to the relatively small sample size of patients with a cervicogenic etiology (6.8%) in our database.

The results of the etiology TMD revealed that patients with TMD pain were 55 times more likely to have TMD tinnitus and patients with a positive TMD pain screener were 15 times more likely to have TMD tinnitus. These findings correspond to previous research. The frequent co-existence of tinnitus and TMD has been shown in several studies. Manfredini et al. (2015) investigated patients with TMD and found a tinnitus prevalence of 30.4%. Furthermore, Lam et al. (2001) found that 64% of patients with tinnitus suffered from TMD.

In addition, our study showed a weak correlation between etiology TMD and grinding and clamping. Therefore, these symptoms were not included in the logistic regression. This is in contrast with findings from a study by Buergers et al. (2014), which demonstrated that tinnitus is eight times more prevalent in patients with TMD, compared to patients without, and that the tinnitus perception can often be altered by forceful clenching of the teeth. These findings in combination with other hypotheses, have led to the assumption that appropriate treatment of TMD can also alleviate the perceived tinnitus (Michiels et al., 2018).

For the results of the hearing loss-related etiology, our study found that patients with a higher PTA-Le, PTA-Ri, PTAhigh-left, and PTAhigh-Right were more likely to have hearing loss-related tinnitus. This is a logical finding because this indicates a direct correlation between hearing impairment and hearing loss-related tinnitus. According to a Clinical Practice Guideline by Tunkel et al. (2014), hearing loss is the most common cause of tinnitus. A study, investigating tinnitus and hearing loss, showed tinnitus is often related to hearing loss and can occur in any type. The perceived severity of the tinnitus may not correlate to the degree of hearing loss. It occurs due to poorly understood mechanisms in the brain in response to hearing loss. Therefore, it is important to better understand the underlying causes and the associated symptoms (Shapiro et al., 2021).

STRENGTHS AND WEAKNESSES

A limited number of participants with etiologies transmission (N=14), trauma (N=10), post-operative (N=2), MD (N=1), and vascular (N=1), were included in the study. Because of this, it is difficult to generalize results concerning these etiologies.

For the statistical analysis, the TMD pain screener (originally ranging from 0-7) was dichotomized (0-1). For the execution of the statistical analysis in SPSS, this was not necessary. This may have a small influence on the results and is not necessary for future studies.

Besides these study limitations, several strengths were also present. Our study has a large sample size (N = 414), enabling it to be more representative of the general tinnitus population. Many associated symptoms and different etiologies were considered. Tests and measurement tools, included in this study, showed good validity and reliability.

FUTURE PERSPECTIVES

Our findings contribute new and useful information regarding associated symptoms of specific etiologies of tinnitus. However, further investigation is needed to confirm our findings and expand the knowledge regarding the associated symptoms of the specific etiologies of tinnitus.

As discussed above for certain etiologies, a small sample size was used. Thus, further investigation is needed. Follow-up studies may for example focus on one specific etiology, to obtain more extensive information, which is easier to generalize.

Regarding the generalization of study findings, future research may take age categories into account. This may influence possible findings since tinnitus is more prevalent in certain age categories (e.g. >65 years).

CONCLUSION

The goal of this study was to investigate the diagnostic value of a series of symptoms and questionnaires in the identification of the primary etiology of tinnitus in a tertiary population.

For three etiologies, significant values were found in the logistic regression. A hearing loss-related problem as primary tinnitus etiology can be predicted by PTA and PTA_{high}, both on the left and right ear. A TMD problem as primary tinnitus etiology can be predicted by TMD pain and a positive score on the TMD pain screener. Finally, a cervicogenic problem as primary tinnitus etiology can be predicted by CSM. To the best of our knowledge, this is the first study investigating different etiologies and their associated symptoms. Further investigation is needed to confirm these results.

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