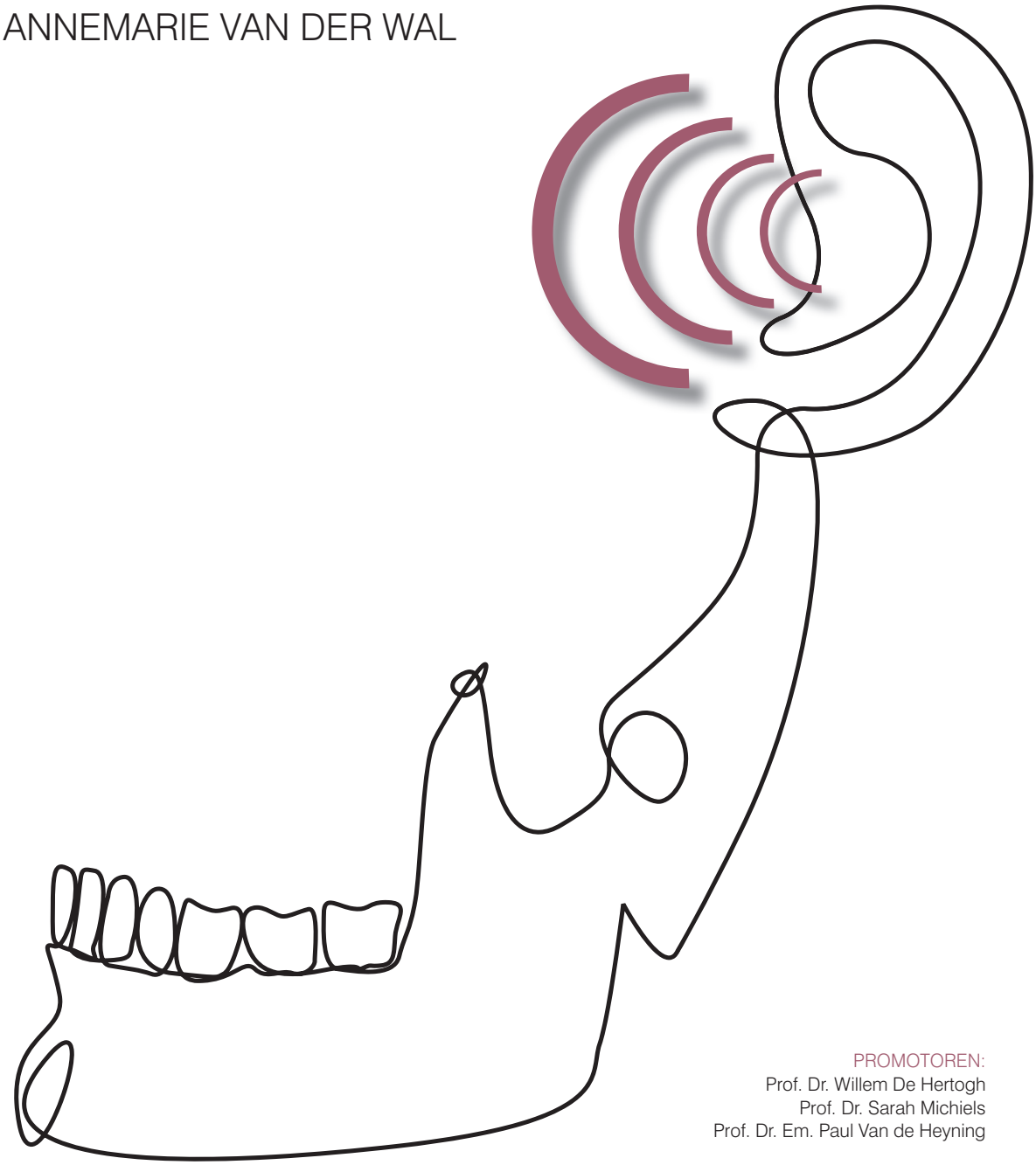
TINNITUS AND TEMPOROMANDIBULAR DISORDERS

A STUDY ON THE EFFECTIVENESS OF CONSERVATIVE TEMPOROMANDIBULAR TREATMENT ON TINNITUS

ANNEMARIE VAN DER WAL



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Tinnitus en temporomandibulaire disfunctie

Een studie naar de effectiviteit van conservatieve temporomandibulaire behandeling bij tinnitus

Proefschrift voorgelegd tot het behalen van de graad van Doctor in de Medische Wetenschappen aan de Universiteit Antwerpen te verdedigen

door

Annemarie van der Wal

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SYNOPSIS

Tinnitus, also known as “ringing in the ears”, is the conscious perception of a sound in the absence of a corresponding external stimulus. The prevalence of tinnitus in an adult population ranges from 5.1% to 42.7%. Tinnitus can be very bothersome and largely affect a patient's quality of life. Tinnitus can cause participation problems on work and is often accompanied by sleep disturbances. One specific subtype of tinnitus, that is particularly interesting for physical therapists and dentists, is somatic tinnitus (ST). In patients with ST, the intensity and character of the tinnitus can be altered by influences from the neck and jaw area. For example, increased muscle tension of the neck or jaw musculature or forceful muscle contractions (e.g. by clenching or grinding the teeth) can change the loudness or pitch of an existing tinnitus or, in some rare cases, can cause tinnitus. The connection between the somatic system and the auditory system might explain the higher prevalence of tinnitus in patients with pain or dysfunction in the masticatory muscles and temporomandibular joint, in medical terms called temporomandibular disorders (TMD). Currently, the most effective treatment for TMD is a multidisciplinary treatment comprising orofacial physical therapy and occlusal splint application.

This thesis focuses on TMD related ST. We assume that normalization of somatosensory input from the jaw area by orofacial therapy, can also reduce tinnitus. Therefore, **part 1** of our study investigates the effect of orofacial therapy on tinnitus complaints in patients with TMD related ST. In addition, we want to explore to what extent a decrease in TMD pain contributes to a reduction in tinnitus severity.

To measure the effect of orofacial therapy on patients with TMD related ST, a Randomized Controlled Trial (RCT) with delayed treatment design was performed. This means that patients were at random divided in two groups: a group that immediately starts with the therapy (the “direct” group) and a group with a waiting period for 9 weeks before starting with the same therapy (the “delayed” group). All patients received orofacial treatment for 9 weeks. The evolution of the tinnitus was measured at week 9, 18 and 27 with the Tinnitus Functional Index (TFI) which is a questionnaire that evaluates the tinnitus severity. After 9 weeks, the tinnitus severity was significantly decreased in the direct group compared with the delayed group. Specifically, the direct group decreased 13.8 points compared with 5.0 points of the delayed group which did not receive treatment yet. After completion of the treatment in the delayed group there was an equivalent reduction of 12.2 points on TFI score. Finally, a clinically relevant improvement was found in 61% of the patients after orofacial therapy.

Afterwards, based on the data from the RCT we analyzed to what extent the reduction in TMD pain can explain the improvement of tinnitus severity as measured by the TFI. Our analyses showed that 35% of the decrease on TFI score can be explained by the reduction in TMD pain. Future studies are needed to explain the remaining 65% .

In **Part 2** we investigated potential prognostic indicators for a positive treatment outcome in tinnitus severity after orofacial therapy.

As potential prognostic indicators we used a series of patient characteristics such as: age, gender, and duration of the tinnitus. Our analyses showed that young female patients and patients with a shorter duration of the tinnitus and lower pain pressure thresholds on the temporomandibular joint and the sternocleidomastoideus had a higher chance to benefit from orofacial therapy.

Finally, in **part 3** we explored the impact of tinnitus on a patient's daily functioning, using the International Classification of Functioning, Disability and Health (ICF). The ICF is an international classification system that is developed to indicate the functioning of people and the possible problems they perceive to structure, register and encode. Patient with ST turned out to have specifically problems in the domains 'mental functions', 'sensory functions and pain' and 'sleep functions'. Additionally, they perceived restrictions in 'focusing attention'.

In conclusion, in this thesis we found that orofacial therapy can reduce tinnitus severity in patients with TMD related ST. Specifically, young female patients with a shorter duration of their tinnitus have the best prognosis. Patients in our sample perceived several problems in daily living, but particularly in the categories 'onset of sleep' and 'sound detection'.

SAMENVATTING

Tinnitus, in de volksmond ook wel oorsuizen genoemd, is de auditieve perceptie van geluid in de afwezigheid van een externe geluidsbron. Het komt voor bij 5.1% tot 42.7% van de volwassenen en kan een belangrijke impact op de kwaliteit van leven hebben. Tinnitus kan onder andere zorgen voor participatieproblemen op het werk en gaat vaak gepaard met slaapstoornissen. Een specifieke vorm van tinnitus die interessant is voor kinesitherapeuten en tandartsen, is somatische tinnitus (ST). Bij patiënten met ST kan de intensiteit of het karakter van de tinnitus veranderd worden door invloeden vanuit de nek- en kaak regio. Zo kan een verhoogde spierspanning van nek- en kaakmusculatuur of het frequent aanspannen van kaakspieren (door bijvoorbeeld te klemmen of knarsen) zorgen voor een verandering in de luidheid of geluidsfrequentie van een bestaande tinnitus en in enkele gevallen kan dit zelfs een tinnitus veroorzaken. De verbindingen tussen het somatische systeem en het auditieve systeem zou mogelijk ook kunnen verklaren dat tinnitus veel vaker voor komt bij patiënten met aandoeningen aan de kaakspieren en kaakgewrichten, in medische terminologie temporomandibulaire dysfunctie (TMD) genoemd. De huidige literatuur wijst uit dat een multidisciplinaire behandeling voor TMD het meest effectief is. Afhankelijk van de oorzaak, bestaat deze behandeling uit orofaciale fysiotherapie (ook wel kaakfysiotherapie genoemd) en het dragen van een opbeetplaat die gemaakt wordt door de tandarts.

In deze thesis ligt de focus op ST gerelateerd aan TMD. We veronderstellen dat het normaliseren van de sensorische informatie vanuit de kaakregio naar het centrale zenuwstelsel, door orofaciale therapie, ook de tinnitus zou moeten verminderen. **Deel 1** van onze studie is daarom gericht op het onderzoeken van het effect van een kaakbehandeling op tinnitus klachten bij patiënten met TMD gerelateerde ST. Daarnaast willen we weten in welke mate de afname van TMD pijn verklarend is voor de vermindering in ernst van de tinnitus.

Om het effect van orofaciale therapie te meten bij patiënten met TMD gerelateerde ST werd een gerandomiseerde gecontrolleerde studie (Randomized Controlled Trial, RCT) opgezet. Daarin werd een *delayed treatment design* gebruikt. Dit wil zeggen dat patiënten die kunnen deelnemen aan de studie door het lot in twee groepen worden ingedeeld: een groep die direct met de therapie startte (de 'directe groep') en een groep die pas na een wachtperiode van 9 weken dezelfde therapie kreeg als de directe groep (de "vertraagde of *delayed* groep"). De therapie werd gegeven gedurende 9 weken. Vervolgens wordt de evolutie van de tinnitus na 9, 18 en 27 weken gemeten. Dat gebeurde onder andere met de Tinnitus Functional Index (TFI), een vragenlijst die de ernst van een patiënt zijn of haar tinnitus meet. Na 9 weken was de ernst van de tinnitus meer afgenomen in de directe groep dan in de *delayed* groep. Dit verschil was ook statistisch significant. Zo daalde de TFI score van de directe groep gemiddeld 13.8 punten. Bij de *delayed* groep was dit gemiddeld slechts 5.0 punten. Zodra de *delayed* groep ook de therapie volgde, was er een gelijkaardige daling in de TFI score te zien, namelijk gemiddeld 12.2 punten. Uiteindelijk was er bij 61% van de totale groep een klinisch relevant verschil na het volgen van de therapie.

Vervolgens gingen we na in hoeverre de daling in TMD pijn verklarend is voor de verbetering in ernst van de tinnitus, zoals gemeten met de TFI. Onze analyse toonde aan dat 35% van de daling in TFI score verklaard wordt door de afname van de TMD pijn. Dit betekent dat 35% van de daling van de ernst van de tinnitus uitsluitend kan worden toegeschreven aan de daling van TMD pijn. Wat de verklaring is van de resterende 65% van de daling, dient in de toekomst verder onderzocht te worden.

In **deel 2** onderzoeken we of er factoren zijn die een positief effect van de orofaciale therapie op de ernst van de tinnitus klachten kunnen voorspellen en of geslacht een rol speelt op de uitkomst van verschillende tinnitus behandelingen.

Als potentiële voorspellende factoren werden een reeks patiënt karakteristieken gebruikt, zoals: leeftijd, geslacht en duur van de tinnitus. De analyse van de verschillende karakteristieken apart toonde dat vrouwen, jongere patiënten, patiënten met een kortere duur van de tinnitus en patiënten met lagere drukpijndrempels ter hoogte van het temporomandibulaire gewricht en de sternocleidomastoïdeus meer kans hadden om te verbeteren na orofaciale therapie.

Tenslotte wordt in **deel 3** onderzocht wat de impact van tinnitus is op het dagelijks functioneren van een patiënt. Om dit in kaart te brengen hebben we de Internationale Classificatie voor het menselijke Functioneren (ICF) gebruikt. Dit is een internationaal classificatie systeem dat ontwikkeld is om het functioneren van mensen en de problemen die zij mogelijk ondervinden, te structureren, te registreren en te coderen. Patiënten met somatische tinnitus bleken in het dagelijks leven vooral problemen te ervaren in de domeinen ‘mentale functies’, ‘sensorische functies en pijn’ en ‘slaap functies’. Daarnaast ondervonden patiënten beperkingen met het ‘richten van hun aandacht’.

Uit deze thesis is naar voren gekomen dat orofaciale therapie de ernst van de tinnitus kan verminderen bij patiënten met TMD gerelateerde ST. In deze groep hebben jonge vrouwen met een kortere duur van de tinnitus de beste prognose. Onze groep tinnitus patiënten ervaren in het dagelijks leven allerlei problemen, maar met name op het gebied van slapen en het detecteren van geluid.

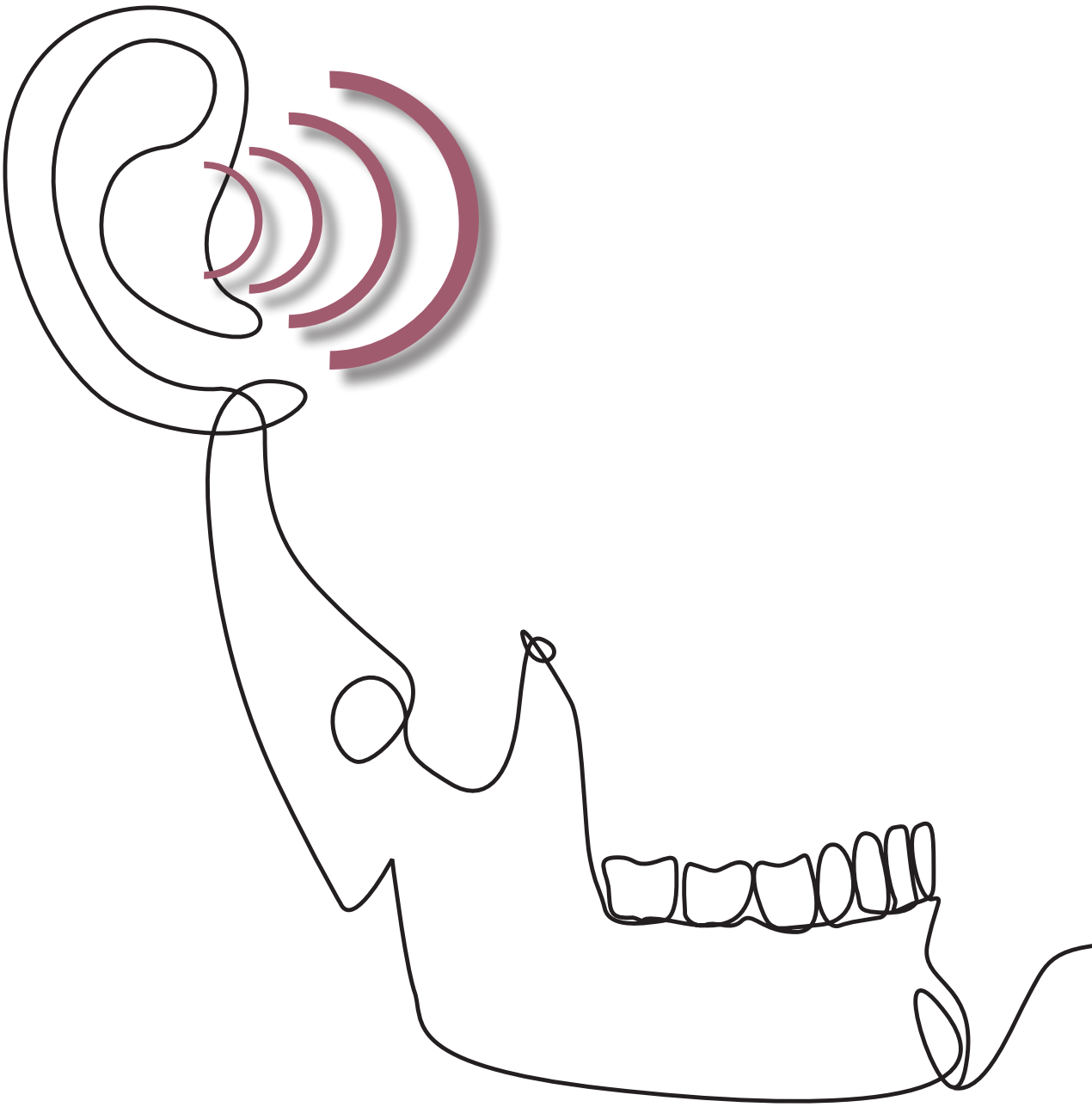
CONTENT

List of figures

List of Tables

ABBREVIATIONS

CBT:	Cognitive Behavioral Therapy
TRT:	Tinnitus Retraining Therapy
tDCS:	Transcranial Direct Current Stimulation
rTMS :	repetitive Transcranial Magnetic Stimulation
ST:	Somatic or Somatosensory Tinnitus
CN:	Cochlear Nucleus
DCN:	Dorsal Cochlear Nucleus
TMD:	Temporomandibular Disorders
TMJ:	Temporomandibular Joint
TCN:	Trigeminal Nucleus Complex
DC-TMD:	Diagnostic Criteria for Temporomandibular Disorders
ICF:	International Classification of Functioning, Disability and Health
TQ:	Tinnitus Questionnaire
TFI:	Tinnitus Functional Index
RCT:	Randomized Controlled trial
ENT:	Ear-Nose-Throat
HADS:	Hospital Anxiety and Depression Scale
HQ:	Hyperacusis Questionnaire
VAS:	Visual Analogue Scale
NBQ:	Neck Bournemouth Questionnaire
SRT:	Speech Reception Threshold
SPIN:	Speech in noise
SPIN:	Leuven Intelligibility Sentence Test
PPT:	Pain Pressure Threshold
dBHL:	Decibels Hearing Level
dBSL:	Decibels sensation level
TINTRA:	Tinnitus Treatment and Research centre Antwerp
EMDR:	Eye Movement Desensitisation and Reprocessing therapy
HDtDCS:	High-Definition transcranial Direct Current Stimulation
LIST:	Leuven Intelligibility Sentence Test
PTA:	Pure Tone Average
WHO:	World Health Organization
COMIT:	Core Outcome Measures in Tinnitus



CHAPTER 1

General Introduction

1.1 TINNITUS

1.1.1 Definition and prevalence

Tinnitus can be defined as the conscious perception of a sound in the absence of a corresponding external stimulus. It is a common medical symptom with a prevalence ranging from 5.1% to 42.7% in the adult population [1, 2]. Derived from the originally Latin verb “tinnire” (which means “to ring”), tinnitus is colloquially known as “ringing in the ears”. Instead of ringing, there can be many other sounds experienced by the patient such as whistling, sizzling, buzzing, chirping or a combination of these sounds [1]. Furthermore, tinnitus can be located unilaterally, bilaterally or centrally (i.e. in the head) and can occur occasionally or permanently. Tinnitus is called chronic when it is present for more than three months [3].

1.1.2 The impact of tinnitus

Tinnitus can be very debilitating and approximately 5% of the tinnitus patients is affected in their quality of life [2]. Common problems in daily living are sleep disturbances and cognitive difficulties (specifically with attention), but tinnitus can also interfere with relationships or have impact on work [4]. Apart from these problems, patients can experience psychological complaints, such as stress, depression or anxiety, that can worsen the burden of the tinnitus.

Moreover, tinnitus is associated with significant healthcare costs. For example, in a cost of illness study in the Netherlands the total tinnitus-related costs were € 5315 per patient [5]. These costs were subdivided in direct costs (€ 1544), indirect costs (€ 3702) and out-of-pocket costs (€ 69). The direct costs in this study included health care costs of the patient such as consultation costs of the general practitioner, medical specialist in the hospital or other health care professionals (e.g. clinical physicist in audiology). The indirect costs were based on the loss of productivity due to the tinnitus. On average, patients reported to have been absent from their job for 15.41 days. The out-of-pockets costs were the expenses from the patients on headphones, ear protection or sound-isolation materials for walls and ceilings. All abovementioned costs varied widely from patient-to-patient, but the out-of-pocket costs fluctuated most from € 0 to € 6832 [5].

1.1.3 Subjective and objective tinnitus

In general, tinnitus can be divided in objective and subjective tinnitus [6]. Tinnitus is called ‘objective’ in case an existing sound source within the patient’s body causes the tinnitus percept, for example sounds provoked by myoclonic contractions of the tensor tympani muscle or pulsating sounds originating from blood vessels. Subjective tinnitus, on the other hand, is far more prevalent and is defined as the perception of a sensory experience in the absence of a physical sound source stimulus [7].

Various underlying diseases and conditions have been described that might influence or trigger subjective tinnitus. The main risk factor is hearing loss, but other risk factors such as noise trauma,

alcohol consumption and smoking have been reported as well. Furthermore, otologic diseases (for example acoustic neurinoma, Meniere's disease, otosclerosis) and various ototoxic medications can trigger tinnitus. Other factors that can influence tinnitus are depression and anxiety disorders and dysfunctions from the cervical spine and temporomandibular area [8]. Table 1.1 shows a summary of the most important known influencing factors, diseases and malfunctions for subjective tinnitus [9].

Table 1.1: known influencing factors, diseases or malfunctions for subjective tinnitus.

Otologic	Hearing loss, noise trauma, otosclerosis, Meniere's disease, acoustic neuroma [8, 9]
Ototoxic medications	Analgesics, antibiotics, antineoplastic drugs, corticosteroids, diuretics, immunosuppressive drugs, non-steroidal anti-inflammatory drugs, steroidal anti-inflammatory drugs [10]
Neurologic	Multiple sclerosis, meningitis, migraine, epilepsy [8]
Traumatic	Head or neck injury [11]
Psychogenic	Depression or anxiety disorder, excessive stress [9, 12]
Somatogenic	Temporomandibular disorders, cervical spine disorders, bruxism, dental diseases, rheumatic diseases [11, 13, 14]

Overall, subjective tinnitus is a very complex phenomenon with many different influencing factors and mechanisms that play a role in the generation and continuation of a patient's tinnitus. To objectify all these factors for the individual tinnitus patient, a multidisciplinary collaboration between otologists, neurologists, audiologists, psychologists, physical therapists, dentists etc. is necessary.

1.1.4 Pathophysiology

To date, the pathophysiology of subjective tinnitus is still not fully understood. A wide range of explanatory models have been proposed in the literature [15]. Although cochlear abnormalities are considered to be the initial source of tinnitus, neural changes in the central auditory pathway are more likely to maintain the tinnitus percept [8].

The normal pathway to an auditory percept is from the cochlea, via the cochlear nerve and the spiral ganglion into the brainstem and thalamic nuclei to the central auditory nervous system (CANS) (including the primary and secondary auditory cortex) and the limbic system. However, when a signal arrives at the auditory cortex and the limbic system, it is not necessarily noticed [16, 17]. For the conscious perception of a sound, the signal has to be perceived by the awareness network and brought into our attention in the brain. On the whole, there are many peripheral and central areas involved in the perception of a sound that can also play a role in the perception of tinnitus.

One proposed explanatory model for tinnitus is the theory of the "phantom percept" wherein the similarity between phantom pain and phantom sound is described [16, 18]. Map reorganization in the auditory cortex after hearing loss has also been compared to map reorganization in somatosensory

cortex after amputation. It is known that an auditory perception is possible in the absence of an auditory input (like in phantom pain) due to spontaneous activity in the auditory pathway. For instance, about 83% of a population without tinnitus perceive phantom sounds when placed in a silence room [19].

From this hypothesis of "phantom percept", different places for the generation of the neural signs have been described. Several authors point out the role of the dorsal cochlear nucleus as the possible source for the initial tinnitus-generated signals [20-23]. According to their theory, spontaneous activity in the dorsal cochlear nucleus (due to for example cochlear destruction through excessive sound exposure) can initiate tinnitus. Another source for the generation of tinnitus can be an increased temporal synchrony in the firing pattern across neurons in the primary auditory cortex. These changes in neural activity in the auditory pathway was found after acoustic trauma in cats [24, 25]. Similarly as the somatosensory cortex, the auditory cortex has also the ability to reorganize in response of peripheral or central disruptions, called cortical map plasticity [26].

However, as described above, the perception of tinnitus is only generated if the primary cortex is connected to other cortical parts of the brain involving frontal, parietal and limbic areas [16]. Thus, the phantom sound might be elicited by maladaptive plastic changes at several levels of the cortical network, but it ends up in the awareness network of the brain. So, for the generation of tinnitus, it is also important to know how the sensory information is interpreted in the brain and which cognitions (i.e. thoughts/beliefs) and emotions are linked to the sound.

The fact that especially the auditory-limbic interactions play an important role in patients with chronic tinnitus is also pointed out in the explanatory model of Leaver et al [27]. According to Leaver and colleagues, dysregulation of the auditory system by specific structures of the limbic system maintains tinnitus and might be the reason that subjective tinnitus can become chronic.

Overall, many influencing factors are pointed out that can generate or influence tinnitus. These factors were divided by Van de Heyning et al [28] in bottom-up influences and top-down influences. Bottom-up influences are all the sensory information that projects to the awareness network of the brain. So, it includes all sensory information from the cochlea, brainstem, CANS and limbic system. Top-down influences, on the other hand, are the cognition and emotion that are connected to the sound. It is believed that both bottom-up and top-down influences must be present for the perception of tinnitus [17] (figure 1.1).

1.1.5 Management of tinnitus in general

Regarding the symptomatic treatments, cognitive behavioral therapy (CBT) and tinnitus retraining therapy (TRT) are mostly supported by literature. Both therapies have proven to be effective in reducing the negative impact of subjective tinnitus [29-31].

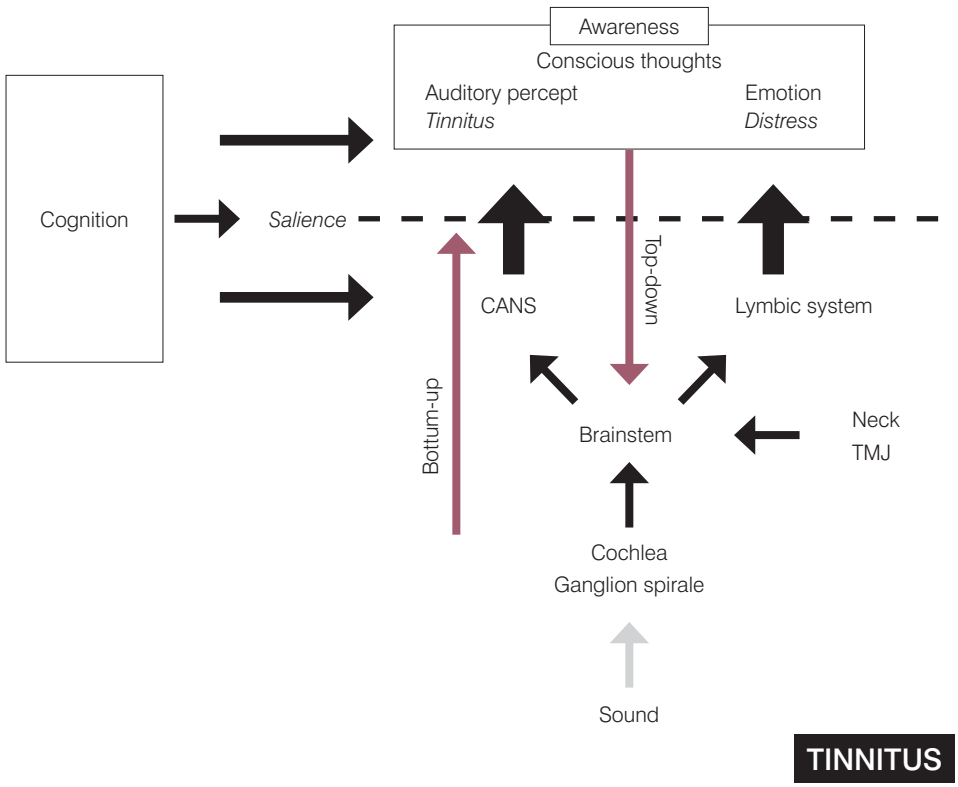


Figure 1.1: figure partly retrieved from Van de Heyning et al. [28]. Diagram of the auditory perception with tinnitus.

CBT is a behavioral therapy that is commonly used by psychotherapists to treat psychiatric disorders such as generalized anxiety disorder and unipolar depression [32]. The purpose of the therapy is to change a patient's irrational cognitions. In tinnitus, it is used to reduce negative thoughts, emotions and behaviors based on the idea that the way tinnitus influences daily life depends on the meaning that is given to the sound and the thoughts that are associated with the tinnitus. Apart from using techniques to reduce the negative association with tinnitus, also mindfulness and relaxation techniques are added to this therapy [33].

TRT, on the other hand, is a habituation technique based on a neurophysiological model of tinnitus. TRT focusses on improving the patient's quality of life by using a combination of education, counselling and sound therapy. During habituation therapy the patient learns to give secondary attention to the tinnitus sensation itself. The aim is to reduce the response on tinnitus and decrease the sensations of the patient by influencing the limbic, autonomic and auditory systems. Therefore, this treatment method should reduce a patient's annoyance by the tinnitus, even when still perceived [34, 35].

Additionally, patients in which the tinnitus is the result of acquired, profound to severe hearing loss may benefit from a cochlear implant [36, 37]. Furthermore, transcranial Direct Current Stimulation (tDCS) and repetitive Transcranial Magnetic Stimulation (rTMS) are promising experimental treatments, but need further research before general use can be recommended [33, 38-40]. Apart from these treatments, prescription of medications is described for tinnitus cases with psychiatric comorbidities needing drug treatment [9]. Overall, there is need for other treatments focusing on the underlying pathophysiology in the individual tinnitus patient.

1.1.6 Personalized care

Due to the great heterogeneity of tinnitus, several authors noted that it is not reasonable to expect that a single cause or single pathophysiology can be responsible for all forms of subjective tinnitus [6, 8, 14, 41]. Therefore one uniform effective treatment for all subjective tinnitus patients seems unlikely and a personalized approach is necessary [28].

A model for personalized care with various influencing factors is proposed by Van de Heyning at al. [28] (figure 1.1). Treatment can be directed to the influencing factor that is suspected to play a major role in the tinnitus percept. For instance, when cognition (i.e. thoughts/beliefs) and emotion are the major influencing factors, CBT seems to be the most appropriate treatment. Likewise, when the somatosensory system has a significant contribution, treatment of the cervical spine and/or temporomandibular area might be able to alter the intensity and character of the tinnitus.

One specific subtype of subjective tinnitus is somatosensory or somatic tinnitus (ST). A patient's tinnitus is called somatic, when the somatosensory system is one of the major influencing factors. All studies performed in the context of this PhD focus on temporomandibular related ST.

1.2 SOMATIC TINNITUS AND THE TEMPOROMANDIBULAR AREA

1.2.1 Somatic tinnitus

In 1999, Levine first described the possible influence of the somatosensory system in patients with tinnitus and introduced the term somatic or somatosensory tinnitus (ST) to describe this specific subtype [42]. According to his theory, tinnitus could be elicited by the somatosensory system of the cervical spine and temporomandibular area. The fact that tinnitus and the somatosensory system are in a complex way related with each other is noticed in several ways. Clinical observations show that about two-third of tinnitus patients can modulate the loudness or pitch of their tinnitus by mandibular movements, or pressure applied on the temporomandibular joint or masticatory muscles [43] [44]. Also, movements of the neck can elicit tinnitus [42, 45]. The fact that movements of the jaw and neck can modulate the psychoacoustic attributes of the tinnitus raises the question: How are the somatosensory system and the auditory system neurophysiologically intertwined? [45].

1.2.2 Pathophysiology of somatic tinnitus

The somatosensory system is a complex system where specialized sensory receptors in the skin, muscles and joints transform mechanical stimuli into electrical discharges. This somatosensory information is then conveyed by peripheral afferent nerves, past their cell bodies in the dorsal root and cranial nerve ganglia [46]. Somatosensory information from temporomandibular area (specifically the trigeminal nerve) is conveyed by afferent fibers, the cell bodies of which are located in the trigeminal ganglion (figure 1.2). From the trigeminal ganglion the somatosensory information enters the brainstem in the trigeminal nucleus complex (TCN).

The anatomical relationship between the somatosensory system and the auditory system can be found in the brainstem and upper cervical spinal cord [46-49]. Animal studies demonstrated that axons of the trigeminal ganglia (figure 1.2, number 1) and dorsal root ganglia (figure 1.2, number 2) end in the ventral and dorsal cochlear nucleus (CN) which are second-order auditory nuclei in the brainstem. Also, secondary sensory neurons of the medullary somatosensory nuclei (specifically the spinal trigeminal nucleus and dorsal column nuclei) project to the dorsal cochlear nucleus (DCN) (figure 1.2, number 3)[42, 46-48].

Human neuroimaging studies found an increased neural activity in the brainstem (i.e. in the CN and inferior colliculus) in patients that can modulate their tinnitus by jaw protrusion in comparison with the healthy control group [49]. The fact that the auditory system responds on a non-auditory stimulus, implies also connections between the somatosensory system and auditory system.

Since it has been hypothesized that the tinnitus percept may originate from hyperactivity from the DCN, systems that are connected to the DCN might influence tinnitus [50]. Thus, afferent somatosensory information conveyed by fibers of the dorsal root and trigeminal ganglia projects on the DCN and can, in this way, influence the auditory system by altering the spontaneous rates (not driven by auditory stimuli). Due to this mechanism, changes in somatosensory afference can change the tinnitus loudness of a patient [42, 45-48]. Furthermore, increased activity from the somatosensory neurons affects the synchrony of firing among neurons in the CN, inferior colliculus or auditory cortex which can change the tinnitus pitch [46-48]. Hence, tinnitus can be evoked or modulated by inputs from the somatosensory system through increased muscle tension from the cervical spine or masticatory muscles or pressure on myofascial trigger points or pressure on the temporomandibular joint.

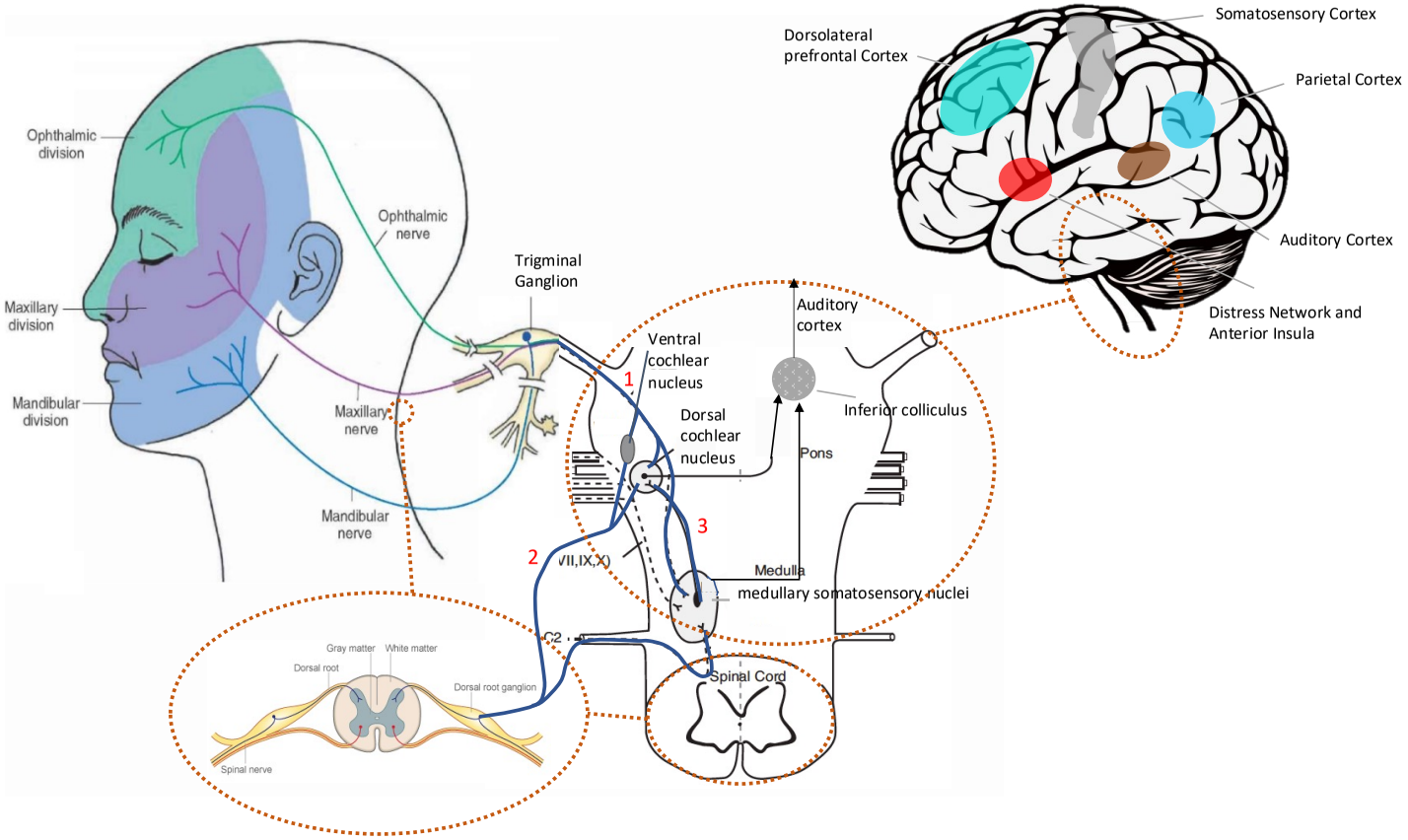


Figure 1.2: (partly retrieved from Levine, 1999 [42] and De Ridder [16]). Somatosensory information from the trigeminal nerve and the dorsal root ganglia end in the cochlear nucleus. Furthermore, connecting fibers between the spinal trigeminal nucleus and somatosensory nucleus.

1.2.4 Diagnostic criteria for somatic tinnitus

Over the last 15 years, a wide range of diagnostic criteria of ST is mentioned in the literature. Some authors suggest that somatosensory modulation through movements or resistance tests should be one of the major criteria, while other authors attach great importance on the appearance or increase of both pain in the neck and/or jaw and tinnitus [51-53]. Also, extensive grinding or clenching the teeth during the night and recurrent pain episodes in head, neck or shoulder girdle is mentioned [51]. This wide variance in diagnostic criteria in ST might explain the differences in prevalence in the literature which range between 12% to 43% [54-57]. Due to the lack of an agreed standard for clinical assessment, a group of experts in ST conducted a two-round Delphi survey and a face-to-face meeting to reach consensus on diagnostic criteria for ST. They developed a set of 16 items that strongly suggest somatosensory influence on tinnitus (Table 1.2: Diagnostic criteria for somatosensory tinnitus according to the Delphi study of Michiels et al. [55].

A subdivision is herein made in criteria on modulation, tinnitus characteristics and accompanying symptoms. Looking closer to these 16 items, it must be noted that 5 of these items are related to TMD or bruxism. So, if tinnitus can be triggered by TMD or bruxism, conservative orofacial treatment (which is currently the evidence-based treatment for TMD) might decrease tinnitus severity.

Table 1.2: Diagnostic criteria for somatosensory tinnitus according to the Delphi study of Michiels et al. [55].

Criteria on tinnitus modulation
• The patient is able to modulate the tinnitus by voluntary movement of the head, neck, jaw or eyes
• The patient is able to modulate the tinnitus by somatic maneuvers
• Tinnitus is modulated by pressure on myofascial triggerpoints
Tinnitus Characteristics
• Tinnitus and neck or jaw complaints appeared simultaneously
• Tinnitus and neck/jaw pain symptoms aggravate simultaneously
• Tinnitus is preceded by a head or neck trauma
• Tinnitus increases during bad postures
• Tinnitus pitch, loudness and/or location are reported to vary
• In case of unilateral tinnitus, the audiogram does not account for unilateral tinnitus
Accompanying symptoms
• Tinnitus is accompanied by frequent pain in the cervical spine, head or shoulder girdle
• Tinnitus is accompanied by the presence of pressure tender myofascial triggerpoints
• Tinnitus is accompanied by increased muscle tension in the suboccipital muscles
• Tinnitus is accompanied by increased muscle tension in the extensor muscles of the cervical spine
• Tinnitus is accompanied by temporomandibular disorders
• Tinnitus is accompanied by teeth clenching or bruxism
• Tinnitus is accompanied by dental diseases

1.2.5 Tinnitus and temporomandibular disorders

Altered somatosensory input can originate from temporomandibular disorders (TMD). The relationship between TMD and tinnitus is frequently mentioned in the literature and the fact that patients with TMD often report the co-existence of tinnitus suggests that both conditions are intertwined. For instance, Manfredini et al [58] found a tinnitus prevalence of 30.4% in patients with TMD and Tuz et al [59] found a prevalence of 59.1% in patients with myofascial pain and dysfunction of the cervical and temporomandibular area [58, 59]. However, the fact that patients have both tinnitus and TMD, does not necessarily imply a causal relationship. Therefore, an extensive tinnitus assessment covering all the possible influencing factors and taking into account the diagnostic criteria for ST is necessary.

1.3 TEMPOROMANDIBULAR DISORDERS AND BRUXISM

1.3.1 Definition and prevalence

TMD is defined as a subgroup of craniofacial pain problems that involve the temporomandibular joint, masticatory muscles and associated head and neck musculoskeletal structures [60]. Common symptoms are jaw pain, limited mandibular motion, earache and temporomandibular joint sounds. With a prevalence ranging from 5% to 12% in the adult population, TMD is the second most common musculoskeletal condition [61]. The peak prevalence occurs in the group between 20 and 40 years old and it occurs twice as much in women than in men [62]. A variety of possible etiological factors have been studied over the years such as occlusion, stress, depression and anxiety [63-65]. Currently, a multifactorial origin with influence of biological, behavioral, environmental, social, emotional and cognitive factors is suggested [60].

One of the major risk factors for developing a temporomandibular disorder is bruxism which is generally known as clenching or grinding the teeth [66]. However, bruxism involves more than only tooth clenching or movement of the jaw. To date, bruxism is seen as a complex phenomenon where sleep and awake bruxism are considered as different behaviors with a separate definition [67]:

1. Sleep bruxism is “a masticatory muscle activity during sleep that is characterized as rhythmic (phasic) or non-rhythmic (tonic) and is not a movement disorder or a sleep disorder in otherwise healthy individuals.”
2. Awake bruxism is “a masticatory muscle activity during wakefulness that is characterized by repetitive or sustained tooth contact and/or by bracing or thrusting of the mandible and is not a movement disorder in otherwise healthy individuals”.

The etiology of bruxism is still unclear, but nowadays experts hypothesize that both sleep and awake bruxism are mainly regulated centrally and not caused by anatomical factors (e.g. dental occlusion or articulation) [68]. In addition, influencing factors for bruxism are smoking, alcohol, drugs, diseases, trauma and stress [68].

1.3.2 The impact of temporomandibular disorders

Despite the high prevalence of TMD, only 5% to 12% of the patients experiences high disability that requires treatment [60, 69]. Especially painful TMD can impact the patient's daily activities (e.g. with biting, chewing, kissing), psychosocial functioning and quality of life [61]. TMD can be accompanied by significant healthcare costs. In a British study of adults with persistent orofacial pain, the total health care costs varied from £321 to £519 per patient per 6-month period [70]. The average direct costs in this study (e.g. consultation costs) were £334 per person. As a result of this loss of productivity at work the indirect costs averaged £905 per person. Since TMD complaints were sometimes not recognized by dentists and general practitioners, most costs were caused by disorganized care pathways. Therefore, the number of consultations required for a diagnosis or treatment was relatively high [70].

1.3.3 Subtypes

In the past 20 years, different classification systems have been described for subtyping orofacial complaints [71]. Currently, the most commonly applied classification is the Diagnostic Criteria for Temporomandibular Disorders (DC-TMD) [61] which is appropriate for use in both clinical and research settings [61]. The DC-TMD is an updated version from the original Research Diagnostic Criteria for TMD (RDC-TMD)[72] and is divided in two-axis protocols. Axis I defines 38 different types of TMD and consists of a standardized questionnaire for detecting pain-related TMD, a symptom questionnaire, demographics, an examination protocol, a decision tree and a diagnostic criteria table. The diagnostic decision tree differentiates between pain-related TMD (sensitivity $\geq$ 0.86, specificity $\geq$ 0.98) and the most common intra-articular joint disorders (sensitivity 0.80 and specificity 0.97). Figure 1.3 describes the diagnosis "myalgia" which is the most common pain-related temporomandibular disorder. Myalgia can further be divided into three subtypes; local myalgia, myofascial pain and myofascial pain with referral. The diagnosis "arthralgia" is given when replication of joint pain occurs with provocation testing of the temporomandibular joint (TMJ) (figure 1.3).

Intra-articular joint disorders can be divided in four subtypes; disc displacement with reduction, disc displacement with reduction with intermittent locking, disc displacement without reduction with limited opening, disc displacement without reduction without limited opening. Finally, the diagnose degenerative joint disorder is described and can be diagnosed when crepitus in the TMJ is detected by the examiner. The axis II consists of screening and comprehensive self-reported instrument sets to assess information about the patient's psychological status.

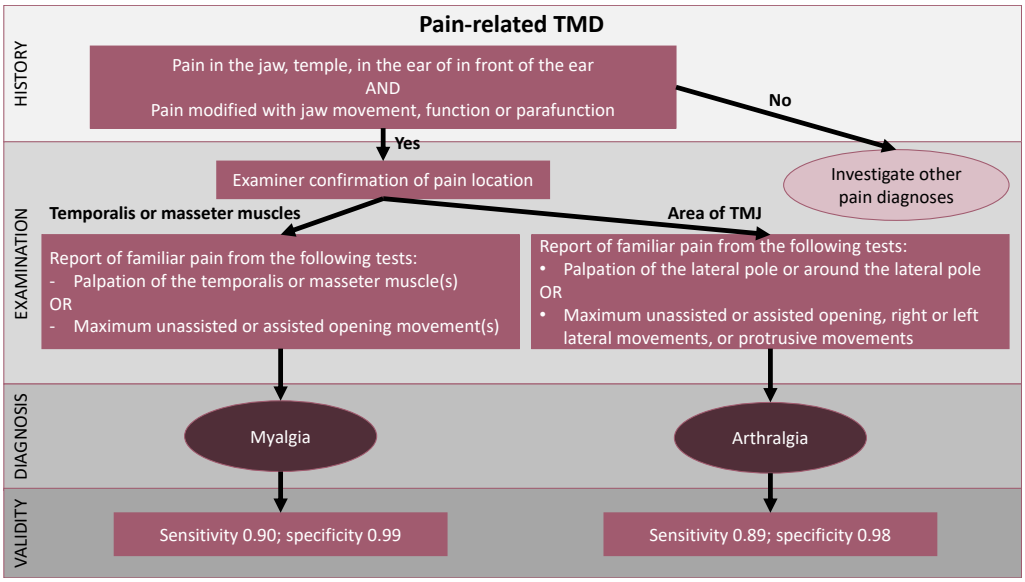


Figure 1.3: Decision tree for pain-related TMD. Adapted from the Diagnostic Criteria for TMD [61]. In our study, we diagnosed only patients with myalgia or arthralgia. For this reason, we eliminated the intra articular joint disorders.

1.3.4 Treatment for temporomandibular disorders and bruxism

Since biological, psychological and social factors may play a role in the etiology and continuation of TMD, a multidisciplinary approach is often recommended [73]. Currently, the evidence-based conservative treatment for TMD consists of counseling regarding mouth habit reversal, sleep hygiene, lifestyle advice, biofeedback, stretching exercises, massage of the masticatory muscles and occlusal splints [61, 74]. This multimodal therapy is often applied in a cooperation between a dentist and a physical therapist.

Additionally, the treatment should be individually tailored depending on the possible causes and influencing factors of TMD. For example, if a patient awakes with TMD pain that last for a few hours, this might suggest that nocturnal factors, such as sleep bruxism, contribute to the TMD pain. Then, the treatment should focus on relaxation techniques prior to sleep, improve sleep positions and wearing an occlusal splint at night [75]. On the other hand, if a patient awakes without symptoms and the TMD complaints develop during the day, it might suggest that influencing factors during daytime, such as clenching habits or other parafunctions which are often stress related, are more prominent. In such case, relaxation and stress management techniques such as learning to relax the masticatory muscles, learning coping skills for life's irritations, are required [75]. When psychological factors play an important role, a multidisciplinary approach, comprising treatment of a physical therapist, dentist, psychologist or even a psychiatrist, is recommended. Although the etiology of TMD is complex and

multi-factorial, between 75% and 90% of the patients with TMD respond well to conservative orofacial treatment [76].

In this thesis, we use the term "TMD treatment" for a multidisciplinary conservative orofacial treatment which is provided by dentists and physical therapists.

For the management of bruxism alone, the 'multiple-P' approach is currently the best strategy which comprises of a combination of occlusal splints ('plates'), counseling/behavioral techniques ('pep talk'), 'physiotherapy', 'psychology' and pharmacological interventions ('pills') [77-79]. In general, the different strategies are combined to get the best results and a personalized care is necessary to determine which combination of treatment modalities is most suitable for the patient [79]. However, the preference in clinical practice is to start with the least invasive intervention(s) [78]. Therefore, counseling is recommended as first approach, since it is safe and non-harmful and patients should be aware that they clench or grind their teeth. In most cases, counseling is combined with physical therapy and oral appliances. Psychology and pharmacological strategies are less frequently used, but should be considered if psychological factors play an important role [78, 79].

1.3.5 Orofacial treatment for patients with somatic tinnitus

The fact that tinnitus can be triggered by altered somatosensory input from the temporomandibular area suggests that the treatment of TMD or bruxism might decrease tinnitus severity. Several studies have found a positive effect of orofacial treatment on tinnitus loudness and severity [80-84]. The treatments consisted of counseling (to make the patient aware of oral parafunctions), splint-therapy, heat treatment, massage of the masticatory muscles, self-monitoring of clenching habits, exercise therapy (i.e. massage exercises and stretching exercises) and biofeedback training. However, a high risk of bias is present in these studies due to the lack of comparison between groups, incomplete presentation of data and selective reporting. In addition, there was also lack of information concerning blinding of the subjects, therapist and researchers [85, 86]. Furthermore, most studies used a sample where TMD was the primary complaint, not tinnitus.

In conclusion, due to the low level of evidence in these studies, information about the effect of TMD treatment in patients with ST is still lacking. Moreover, due to the heterogeneity of tinnitus it is not known which patients benefit most from orofacial treatment for their tinnitus complaints. Finally, the health status and perceived disability in patients with ST should also be described in terms of the International Classification of Functioning, Disability and Health (ICF).

1.4 RESEARCH OBJECTIVES

The main objective of the current thesis is to improve the quality of care for patients with ST attributed to TMD. To achieve this objective a clinical study to investigate the effect of TMD treatment on ST is conducted with an analysis of prognostic indicators. Furthermore, the impact of tinnitus on patients functioning is studied.

In accordance, the following research questions are put forward:

1. What is the effect of multidisciplinary orofacial treatment on somatic tinnitus complaints in patients with ST?
2. To what extent does a decrease in TMD pain contribute to the overall reduction of tinnitus severity after multidisciplinary orofacial treatment?
3. Which prognostic indicators predict a positive outcome after multidisciplinary orofacial treatment?
4. What is the impact of tinnitus on patients in their functioning and disability in terms of the International Classification of Functioning, Disability and Health (ICF)?

1.5 OUTLINE OF THE DISSERTATION

The present dissertation consists of three main parts covering the research objectives. Part one concerns TMD treatment and covers the studies that investigate the effect of orofacial treatment in patients with ST. It consists of a study protocol, a randomized controlled trial and a mediation analysis. Part two presents prognostic indicators that predict a positive outcome after TMD treatment and explores gender differences in the outcome of different tinnitus treatments. Part three concerns the impact of tinnitus on patients functioning and disability in terms of the ICF. It investigates which domains of the ICF are covered by the Tinnitus Questionnaire (TQ) and Tinnitus Functional index (TFI) and describes the health status and perceived disability of patients with ST in terms of the ICF.

1.5.1 Part 1: the effect of TMD treatment in patients with somatic tinnitus

First, the study protocol for a randomized controlled trial with a delayed treatment design is presented (**chapter 2**). The protocol describes the tinnitus assessment, the design of the study, the randomization procedure, outcome measures and intervention.

Next, the results of the randomized controlled trial are reported (**chapter 3**). The effect of TMD treatment on tinnitus annoyance and tinnitus severity in patients with ST is discussed. The randomized controlled trial differs from earlier studies, because data was collected from patients with chronic ST in a tertiary tinnitus clinic. By using a multidisciplinary team with otorhinolaryngologists, audiologists, physical therapists and dentists for the assessment, all influencing factors and/or objective causes for the tinnitus were identified. Only when the somatosensory system was one of the major influencing factors, patients were included in the study. Evaluation for tinnitus annoyance and severity, measured by the TQ and TFI, took place at baseline, at the start of therapy, 9 weeks after therapy and at follow-up.

Furthermore, a mediation analysis is described (**chapter 4**) in which we calculate to what extent a decrease in TMD pain contributes to the overall reduction of tinnitus severity. A mediation analysis is an indirect way to investigate underlying mechanisms of a therapy. Although orofacial treatment is primarily aimed at decreasing TMD complaints, it can also have other effects. In this study, we investigated how much the actual decrease in TMD pain contributes to the patient's tinnitus improvement.

1.5.2 Part 2: prognostic indicators for a positive treatment outcome

In part 2 we identified prognostic indicators that can predict a positive outcome after TMD treatment (**chapter 5**). By identifying predicting factors for an individual outcome, the clinical success rates can be improved and unnecessary other trajectories could be avoided.

Moreover, the effects of gender on the outcomes of the distinct tinnitus therapies (i.e. Tinnitus Retraining Therapy (TRT)/Cognitive Behavioral Therapy (CBT) or TRT/Eye Movement Desensitization

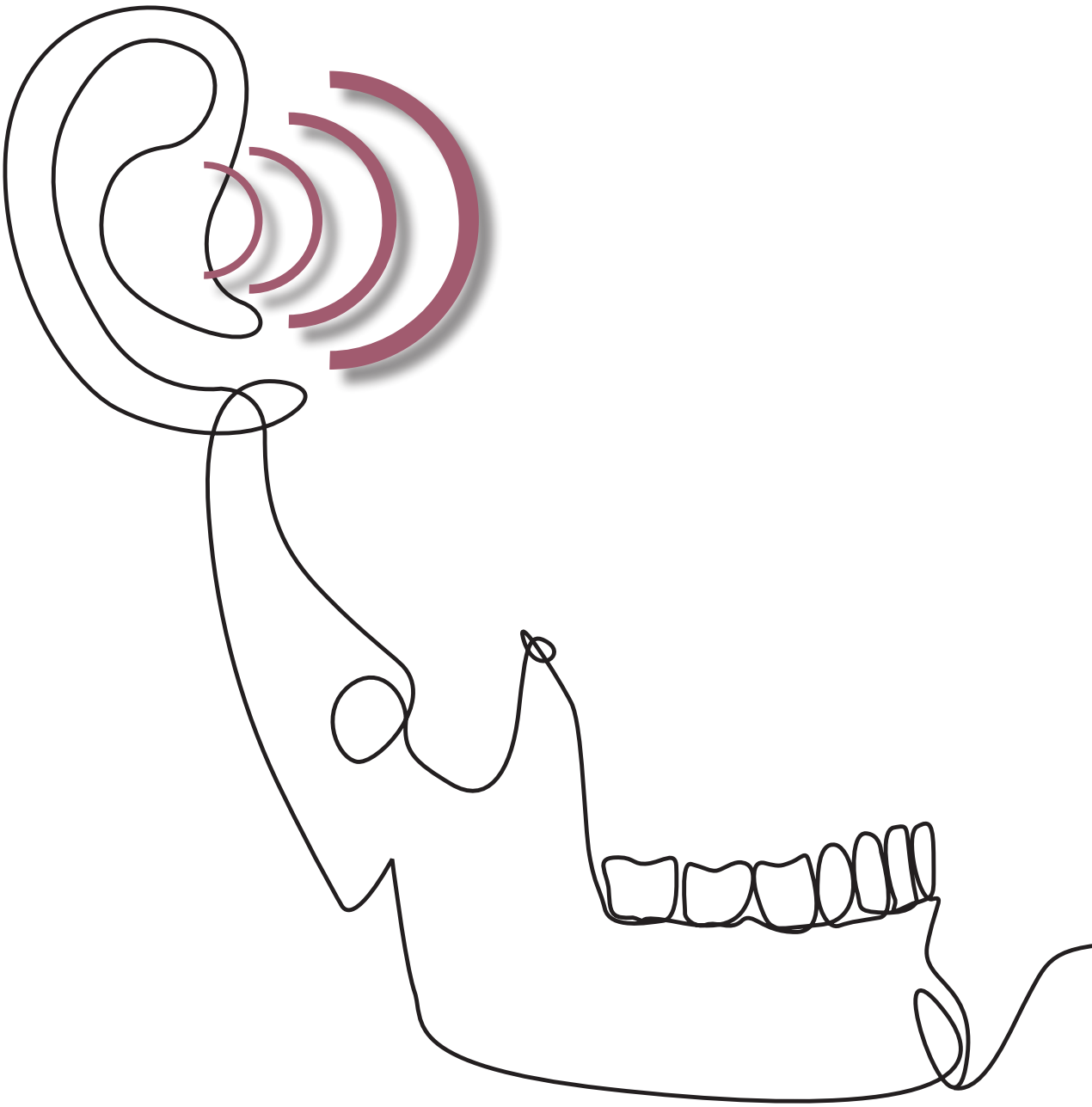
and Reprocessing therapy (EMDR), high-definition transcranial direct current stimulation (HDtDCS), and TMD treatment) in Tinnitus Treatment and Research Centre Antwerp are reported (**chapter 6**). If male and female tinnitus patients seem to react differently to different therapy options, caregivers should take these gender differences into account.

1.5.3 Part 3: health status and perceived disability of patients with somatic tinnitus

Problems in daily life and the impact on the quality of life between tinnitus patients varies largely. Questionnaires such as the TFI and TQ are designed to objectify the patient's functioning and disability in daily living. However, it is unknown if these questionnaires cover various domains of the ICF. Furthermore, it is unclear which domain has the greatest impact on a tinnitus patient's life. To close the knowledge gap, a cross-sectional study was conducted (**chapter 7**) to objectify firstly which domains of the ICF are measured by the TQ and TFI and secondly to describe the health status and perceived disability of patients with ST in terms of the ICF. In order to understand the health of populations in an international context and the impact of a health condition on a person's quality of life, the World Health Organization (WHO) developed the ICF as a conceptual framework for disability and health [87]. To compare which domains, chapters and categories are covered by the TQ and TFI, their questions were linked to the ICF model via the linking rules procedure described by Cieza et al. [88]. Additionally, a detailed overview of an individual's perceived health and disability in patients with ST is presented.

PART 1

THE EFFECT OF TMD TREATMENT IN PATIENTS WITH SOMATIC TINNITUS



CHAPTER 2

Conservative therapy for the treatment of patients with somatic tinnitus attributed to temporomandibular dysfunction: Study protocol of a randomised controlled trial

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2.1 ABSTRACT

Background

Tinnitus is a highly prevalent symptom affecting 10 to 15% of the adult population. It often affects patients' quality of life and frequently causes distress. When subjective tinnitus can be elicited by the somatosensory system of the cervical spine or temporomandibular area it is called somatic tinnitus. The first aim of the current study is to investigate the effect of the best evidence conservative temporomandibular disorder (TMD) treatment on tinnitus in patients with co-existence of tinnitus and TMD or oral parafunctions compared to no treatment. The second aim is to identify a subgroup of patients with tinnitus that benefits from the conservative TMJ treatment.

Methods and design

This study is designed as a randomised controlled trial with delayed treatment design. Patients with a temporomandibular dysfunction (TMD pain screener ≥ 3 points) or oral parafunctions (such as clenching and bruxism), which are suffering from moderate to severe subjective tinnitus (Tinnitus Functional Index (TFI) between 25 and 90 points), will be recruited from the tertiary tinnitus clinic of the University Hospital of Antwerp (Edegem, Belgium).

Patients will be excluded in case of clear otological or neurological causes of the tinnitus, progressive middle ear pathology, intracranial pathology, traumatic cervical spine or temporomandibular injury in the past 6 months, severe depression as diagnosed by a psychologist, tumors, previous surgery in the orofacial area, substance abuse that may affect the outcome measures, any contra-indication for physical therapy treatment directed to the orofacial area or when they received TMD treatment in the past 2 months.

After screening for eligibility, baseline data among which scores on the TFI, tinnitus questionnaire (TQ), mean tinnitus loudness as measured with visual analogue scale (VAS), TMD pain screener, and a set of temporomandibular joint tests will be collected.

Patients will be randomized in an early-start group and in a delayed-start group of therapy by 9 weeks. Patients will receive conservative TMD treatment with a maximum of 18 sessions within 9 weeks. At baseline (week 0), at the start of therapy (weeks 0 or 9), 9 weeks after therapy (weeks 9 or 18), and at follow-up (weeks 18 or 27) data from the TFI, TQ, VAS mean tinnitus loudness and the TMD pain screener will be collected.

Discussion

In this study we aim to improve the quality of care for patients with tinnitus attributed to TMD or oral parafunctions. By evaluating the effect of state of the art TMD treatment on tinnitus complaints, we can investigate the usefulness of TMD treatment in patients with somatic tinnitus.

Keywords

Occlusal splints – Temporomandibular disorders – Physical therapy modalities – Somatic Tinnitus - Somatosensory

2.2 BACKGROUND

Tinnitus is a common symptom that occurs in 10-15% of the adult population, often affecting patients' quality of life and frequently causing distress [8, 89]. In the absence of any acoustic stimulus (internal nor external) it is called subjective tinnitus, which is the most common form of tinnitus [8]. Besides hearing loss or noise trauma, tinnitus can also be attributed to the somatic system of the cervical spine or temporomandibular area [8, 13, 90]. This type of tinnitus is called somatic or somatosensory tinnitus and has been described in 36-43% of a population with subjective tinnitus [91, 92]. The frequent co-existence of tinnitus and temporomandibular disorders (TMD) has been shown by several studies [93, 94]. Manfredini et al.[58] investigated patients with TMD and found a tinnitus prevalence of 30.4%. Furthermore, Lam et al.[95] found that 64% of patients with tinnitus suffered from TMD and Buergers et al. demonstrated that tinnitus is 8 times more prevalent in patients with TMD, compared to patients without TMD and that the tinnitus perception can often be altered by forceful clenching of the teeth[96].

A physiological explanation for the frequent co-existence is delivered by several animal studies, which have found connections between the somatosensory system of the cervical spine and temporomandibular area on one hand and the cochlear nuclei (CN) on the other hand[97, 98]. Cervical and temporomandibular somatosensory information is conveyed to the brain, by afferent fibres, of which the cell bodies are located in the dorsal root ganglia or the trigeminal ganglion. Some of these afferent fibres also project to the central auditory system and more specifically to the dorsal CN [99]. This makes the somatosensory system able to influence the auditory system by altering the spontaneous rates (i.e. not driven by auditory stimuli) or the synchrony of firing among neurons in the CN, inferior colliculus or auditory cortex. In this way, the somatosensory system is able to alter the intensity and the character of the tinnitus by, for instance, forceful muscle contractions of the neck or jaw musculature or by increased muscle tension in the tensor tympani muscle [46]. These findings have led to the assumption that appropriate treatment of TMD can also alleviate the perceived tinnitus.

An evidence based conservative management of TMD should be based on the multifactorial aetiology of TMD. Since biological, psychological as well as social factors may play a role in the aetiology and continuation of TMD, the treatment of TMD should also be based on a multidisciplinary approach [100]. Furthermore, the first line management in all patients with TMD should be to encourage self-management through patient education [76]. Patients should be educated regarding the possible causes of TMD and it is important that they understand their own central role in the management of TMD [76, 101-103]. Depending on the diagnosis and aetiology, the therapy should be individually tailored. Both dentists and physical therapists may play a role in the conservative, individual and multimodal management of such patients [104, 105].

The primary aim of this study is to investigate the effect of a state of the art conservative TMD treatment, as described above, on tinnitus complaints, compared to no treatment. Secondary, this study aims to identify mediating factors, i.e. factors that contribute to the therapeutic effect. To help clinicians in their clinical process, we will identify prognostic indicators, i.e. factors that predict a positive or negative outcome of TMD treatment.

2.3 METHODS

2.3.1 Patients

Patients will be recruited from the Antwerp University Hospital (UZA, Edegem, Belgium) by otolaryngologists at their tertiary tinnitus clinic. During this consult, patients are thoroughly tested to exclude any objective causes of the tinnitus.

All patients will be investigated by means of medical history, Ear-Nose-Throat (ENT) examination with micro-otoscopy, brain MRI (Magnetic Resonance Imaging) to exclude vascular compression or tumoural processes like acoustic neurinoma, audiometry (pure tone audiometry, tinnitus pitch and loudness matching and speech in noise test), tinnitus assessment comprising tinnitus loudness using a Visual Analogue Scale (VAS), tinnitus annoyance using the Tinnitus Questionnaire (TQ) and tinnitus severity using the Tinnitus Functional Index (TFI). Complementary, all the patients will undergo an electroencephalogram (EEG) in which the auditory event-related potentials (ERP) will be measured to investigate the alteration in processing of sound before and after TMJ treatment in an objective way [17].

Patients will be included when suffering from chronic somatic tinnitus, attributed to TMD or oral parafunctions, which has been stable for at least 3 months. This diagnosis will be made, by the ENT surgeon based on the abovementioned clinical process and using the diagnostic criteria for tinnitus attributed to TMD [51]. According to these criteria, tinnitus can be attributed to TMD or oral parafunctions when one of the following criteria are present: tinnitus association with manipulation of the teeth or jaw, temporal coincidence of onset or increase of both TMD pain and tinnitus, increase of tinnitus during inadequate postures during rest, walking, working or sleeping, or intense bruxism and/or clenching periods during the day or night.

Additional evaluations in the context of this study involve temporomandibular investigation. During anamnesis, patients are questioned about the presence of bruxism and clenching. Furthermore, patients are screened on the presence of a painful TMD by the TMD pain screener [106]. In case a patient scores positive on at least three out of six questions of the TMD pain screener, the patient is suspected to suffer from a painful TMD (sensitivity 0.99 and specificity 0.95-0.98, respectively). The patient is then referred to the dentist, who will perform a clinical investigation according to the internationally recognized classification system for TMD [61].

Patients will be excluded in case of clear otological or neurological causes of the tinnitus such as Menière's disease, severe depression (diagnosed by a psychiatrist), progressive middle ear pathology, intracranial pathology, traumatic cervical spine or temporomandibular injury in the past 6 months, tumours, previous surgery in the orofacial area, substance abuse which may affect the outcome measures or in case physical therapy treatment directed to the orofacial area is contra-indicated. Given the treatment that is studied, patients will also be excluded if they received TMD treatment in the past 2 months.

Inclusion	Exclusion
Subjective tinnitus > 3 months	Clear otological or neurological causes of the tinnitus
AND one of the following present:	Severe depression
• Tinnitus association with manipulation of the teeth or jaw	Progressive middle ear pathology
• Temporal coincidence of onset or increase of both TMD pain and tinnitus	Intracranial pathology
• Increase of tinnitus during inadequate postures during rest, walking, working or sleeping	Traumatic cervical spine or temporomandibular injury in the past 6 months
• Intense bruxism and/or clenching periods during the day or night	Tumors
	Previous surgery in the orofacial area
	Substance abuse which may affect the outcome measures
	TMD treatment is contra-indicated
	Already received TMD treatment in past 2 months

2.3.2 Study design

This study is designed as a randomised controlled trial with a delayed treatment design (Figure 2.1). At baseline, patients are randomly assigned by an independent researcher to the early-start group or to the delayed-start group. In part 1, the early-start group receives the TMD treatment for 9 weeks. The delayed-start group receives the standard information and advice about tinnitus, but no treatment in the first 9 weeks. In part 2, the patients in the delayed-start group receive TMJ treatment for the next 9 weeks. The early-start group now enters a follow-up period. In part 3, all patients enter a follow-up period. Follow-up data are collected after 18 and 27 weeks. This is in line with previous studies about somatic tinnitus of our research group [56, 92]

The results of the trial will be reported according to the CONSORT guidelines.

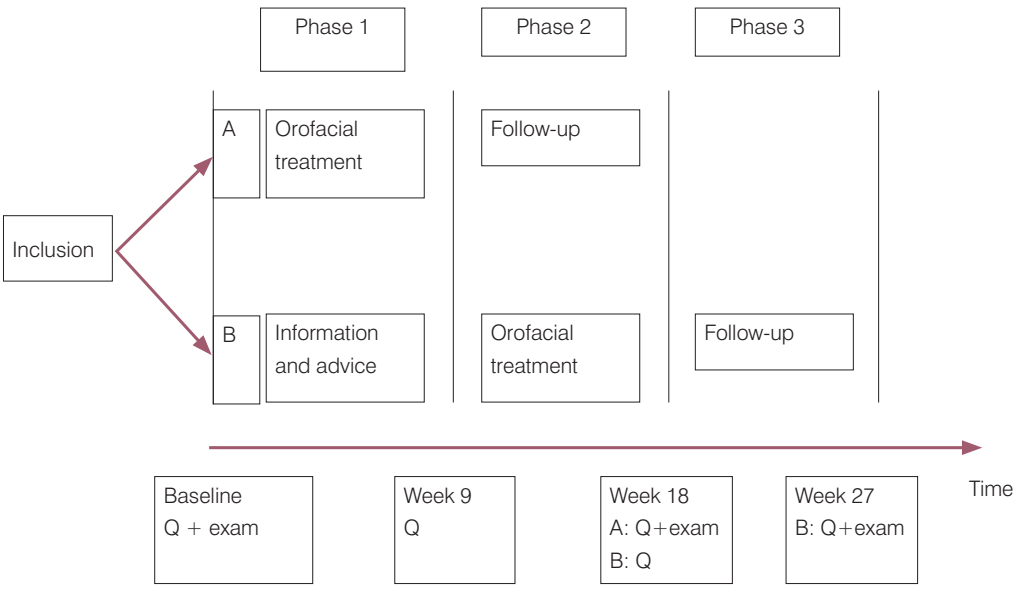


Figure 2.1: Delayed-start design; (A: early-start group; B: delayed-start group; Q: Questionnaires; Exam.: full examination)

2.3.3 Randomisation procedure

Patients will be randomised into the early-start group or into the delayed-start group in a 1:1 ratio insuring an even distribution based on gender and age. The randomised list will be generated by an independent researcher using QMinim Online Minimisation®[107]. The assessor, performing the clinical tests, is blinded to the allocation of the patients in the direct-start or delayed-start group. This is possible because all patients are investigated 18 weeks after the start of their therapy (figure 1). The extra measurements in the delayed-start group, in week 18 of the study, are questionnaires that are completed via an online tool. The patient cannot be blinded in this protocol.

2.3.4 Outcome measures

1. Primary outcome measure

The primary outcome measure is change in tinnitus related distress, measured using the Dutch version of the **TQ**, validated in 2007 [108, 109]. The TQ consists of 52 questions of which 40 are used for calculating the total score and 2 are counted double (items 5 and 20). The questions are answered on a 3-point scale, ranging from 'true' (scoring 0), 'partly true' (scoring 1) to 'not true' (scoring 2). The total score on the TQ ranges from 0 to 84. Higher scores correspond with higher tinnitus related distress. The TQ shows high internal consistency (Cronbach's alpha: 0.95) and a good correlation with the Tinnitus Handicap Inventory and Tinnitus Impairment Questionnaire (0.83 – 0.90) [110]. A decrease of 8.72 points is considered as clinically relevant (Standardised Response Mean: 1.04) [110].

2. Secondary outcome measures

Various secondary outcome measures will be measured, these will be used to describe the population and identify possible mediating factors, i.e. factors that contribute to the therapeutic effect. An overview is presented in table 2.1.

a. Temporomandibular outcome measures

The **TMD pain screener** is a 6-item questionnaire regarding pain complaints from the orofacial region, and their dependency on functions, like opening wide or chewing. Internal consistency of the questionnaire is excellent, with coefficient α value of 0.93, reliability is acceptable (ICC: 0.79), and it has excellent sensitivity and specificity (0.99 and 0.95-0.98, respectively) [106]. Apart from the questionnaire, a set of **clinical TMD tests** are performed to investigate the presence of a painful TMD. This examination includes:

- the assessment of pain on active movements of the mandible, palpation of the jaw muscles and temporomandibular joint, and measuring of the mouth opening. This will be performed according to the standardised protocol of the DC/TMD [61]. Based on this examination the presence of the specific TMD-pain diagnosis will be assessed: myalgia (sensitivity: 0.90, specificity: 0.99) and/or arthralgia (sensitivity: 0.89, specificity: 0.98).
- pressure pain thresholds (PPT's) will be measured using a hand-held algometer (Somedic AB, Farsta, Sweden). The PPT's will be measured on the temple, the masseter, and the sternocleidomastoid muscles and on the temporomandibular joint (TMJ). The tibialis anterior muscle will be used as a reference point. The PPT's are expressed in kPa. The average of three measurements will be used for further calculations. For the measurement of PPT's, the pressure is progressively increased. Subjects have to report when the feeling of pressure changes into a feeling of pressure and pain by pressing a patient controlled switch. Measuring pressure pain thresholds on masticatory muscles and the temporomandibular joint has been shown to be accurate and reliable [111].

b. Audiological outcome measures

The **TFI [112]** assesses tinnitus severity focusing on eight different domains: the unpleasantness of the tinnitus, reduced sense of control, cognitive interference, sleep disturbance, auditory difficulties attributed to the tinnitus, interference with relaxation, reduction in quality of life and emotional distress. The test-retest reliability of the TFI is good (r: 0.78). The convergent validity with the Tinnitus Handicap Inventory (r: 0.86) and VAS (r: 0.75) is good, as well as the discriminant validity with the Beck Depression Inventory-Primary Care (r: 0.56). A reduction of 13 points is considered to be clinically relevant. This questionnaire will be used to obtain a detailed view on the patients' subjective tinnitus complaints.

The subjective loudness of the tinnitus is rated using a **VAS**. The patient is asked to indicate the average loudness of his or her tinnitus on a 10cm horizontal line. On this line, the left end indicates 'no tinnitus' and the right end indicates 'as loud as you can imagine'.

The **Hospital Anxiety and Depression Scale (HADS)** is a self-assessment scale and was developed to identify the possibility and probability of the presence of anxiety and depression among patients in nonpsychiatric hospital clinics [113]. It exists of two subscales, an Anxiety subscale (HADS-A) and a Depression subscale (HADS-D), both containing seven intermingled items. All symptoms of anxiety or depression relating also to physical disorder, such as dizziness, headaches, insomnia, anergia and fatigue, are excluded to prevent intrusion from somatic disorders on the scores. Since symptoms relating to serious mental disorders were less common in patients attending a nonpsychiatric hospital clinic, these symptoms are also excluded [113, 114]. The HADS is found to be a reliable instrument for detecting states of depression and anxiety in the setting of an hospital medical outpatient clinic [113].

Hyperacusis is quantified and characterized using the Dutch version of the **Hyperacusis Questionnaire (HQ)** [36]. This questionnaire consists of 14 questions that are answered on a 4-point scale, ranging from 'No' (scoring 0 points), 'Yes, a little' (scoring 1 point), 'Yes, quite a lot' (scoring 2 points to 'Yes, a lot' (scoring 3 points). Scores on the HQ consequently range from 0 to 42 and the cut-off value for hyperaccusis is 28 points [115]. The HQ is used to investigate the presence of hyperaccusis.

In addition to the questionnaires, a set of audiological parameters will be performed, comprising pure tone audiometry, tinnitus analysis and speech in noise test.

- **Pure tone audiometry**, the key hearing test used to identify hearing threshold levels, will be measured according to the current clinical standards (ISO 8253-1, 1989), using a two-channel Interacoustics AC-40 audiometer in a soundproof booth. Air conduction thresholds will be measured at 125 Hz, 250 Hz, 500 Hz, 1 kHz, 2 kHz, 3 kHz, 4 kHz, 6 kHz and 8 kHz. This test is used to identify the presence and level of hearing loss. When the level of hearing loss, corresponds to the tinnitus pitch, a causal relation can be expected [116].
- The **tinnitus analysis** starts with identifying the type of tinnitus, by asking whether one perceives a pulsatile or non-pulsatile tinnitus, whether the tinnitus is perceived constantly or not and whether the tinnitus sound is a pure tone, a noise or a mixture of different sounds (polyphonic). Then the tinnitus pitch is assessed. The pitch is the psychoacoustic equivalent of the physical parameter frequency. The tinnitus pitch is obtained by use of a pitch matching technique that is the quantitative and qualitative description of the spectral characteristics of the tinnitus. For this technique a two-alternative forced choice procedure is used using the contralateral ear as the reference ear. In cases where tinnitus is perceived bilaterally, the choice of ear is arbitrarily. By this technique, an attempt is made to identify the centre pitch of the tinnitus. When multiple tinnitus sounds are perceived, it is suggested to concentrate on the most troublesome tinnitus sound. Each time a pair of pure tones, or noises in case of noise-like tinnitus, differing by one or more octaves, are presented to the subject who has to indicate which of the tones resembles the tinnitus the most. This procedure is repeated and finer adjustments are made to obtain a match of tinnitus pitch as exact as possible. Afterwards, a tinnitus loudness matching is performed. Loudness is the perceptual correlate of the sound intensity. The tone (or noise) defined as the pitch math

is presented to the ipsilateral ear when appropriate and a loudness match is made by use of an alternating procedure. Because of compressed dynamic range frequently present at the tinnitus frequency, final loudness measurements are made with 1 dB steps. This measures the absolute level of tinnitus loudness expressed in dB hearing level (dB HL). In addition, a calculation is made to provide a measurement of relative loudness expressed in dB sensation level (dB SL) that is the level of the loudness match minus the auditory threshold at tinnitus frequency. The tinnitus analysis provides an objective image of the perceived sound [116].

- **Speech in noise tests** are performed to investigate whether or not patients with somatic tinnitus attributed to TMD, in whom no hearing loss is assumed, perform worse on speech in noise tests. The Leuven Intelligibility Sentence Test (LIST) [117], a Dutch sentence test, will be applied. The LIST consists of 35 lists of 10 sentences that are a reflection of daily communication and are of equivalent difficulty. An adaptive procedure is used with the noise at a fixed level of 65 dB sound pressure level (SPL). The procedure starts at a signal-to-noise ratio (SNR) of 0 dB meaning that speech and noise are presented equally loud (65 dB SPL). Subsequently, the intensity level within a list of sentences is varied in steps of 2 dB adaptively in a 1-down (when the keywords in the sentence are correctly repeated), 1-up (when the keywords in the sentence are incorrectly repeated) procedure to determine the 50% correct identification point which is called the speech reception threshold (SRT), expressed in dB SNR. Before starting the actual procedure, one list will be performed as a training list for both left and right ear.

Complementary, all the patients will undergo an electroencephalogram (EEG) in which the auditory event-related potentials (ERP) will be measured to investigate the alteration in processing of sound before and after TMJ treatment in an objective way [17]. This provides an objective outcome measure besides the subjective outcome measures.

Finally, the information from medical history taking by an ENT doctor, who is part of the standard tinnitus assessment, is used to gain insight in the duration of the complaints. Questions referring to the diagnostic criteria of somatic tinnitus are also included in the anamnesis: duration of the complaints, localisation of the tinnitus (unilateral, bilateral or central), tinnitus association with some manipulation of the teeth or jaw, temporal coincidence of appearance or increase of both pain and tinnitus, increase of tinnitus during inadequate postures during rest, walking, working or sleeping, bruxism and/or clenching periods during day or night. In table 2.1, an overview of the primary and secondary outcome measures is presented.

Table 2.1: Overview of primary and secondary outcome measures.

	Baseline	Follow-up	Measuring tool	Completed by
Primary outcome measure				
Tinnitus related distress	X	X	Tinnitus Questionnaire	Patient
Secondary outcome measure				
TMJ pain	X	X	TMD pain screener	Patient
Myalgia	X	X	DC/TMD	Researcher
Arthralgia	X	X	DC/ TMD	Researcher
Pressure sensitivity	X	X	Pressure algometer (Somedic), kPa	Researcher
Mouth opening	X	X	Ruler, cm	Researcher
Hearing loss	X		Pure Tone audiometry Speech in noise test	Audiologist
Psychoacoustic tinnitus analysis	X	X	Type of tinnitus, tinnitus pitch and tinnitus loudness	Audiologist
Tinnitus severity	X		Tinnitus Functional Index	Patient
Subjective tinnitus loudness	X	X	Visual Analogue Scale (0-100mm)	Patient
State of anxiety and depression	X		Hospital anxiety and depression scale	Patient
Hyperacusis	X		Hyperacusis questionnaire	Patient
Auditory event-related potential	X	X	Auditory event-related potential	Researcher
General tinnitus characteristics such as duration of the complaints, localization (Unilateral, bilateral, central), somatic modulation, temporal relation with TMD, bruxism periods.	X		Medical history	ENT

2.3.5 Intervention

TMD treatment is multifactorial, and is provided by dentists and physical therapists. It consists of patient education on normal jaw function, avoidance of overuse in oral 'bad habits' such as nail biting and tooth clenching. In case of grinding, night time use of stabilisation splints can be applied. Bothersome malocclusions will be addressed, e.g. by providing stabilization splints. Patients are encouraged to relax their masticatory muscles, and relaxation of the muscles will be trained. Painful muscles will be stretched. Stretching techniques will be instructed to the patients so they can continue these exercises at home. During every physical therapy session, these exercises will be boosted to enhance patients' compliance[118]. In total, the treatment period can last up to 9 weeks. This is longer than the traditional 6 weeks. It is however based on our previous trial concerning cervicogenic somatic tinnitus, where an increase of complaints was observed after 6 weeks of therapy [92]. We therefore provide 3 additional weeks where the patient can be followed-up by the treating health care professional. Depending on the needs, up to 18 physical therapy sessions can be scheduled over a

period of 9 weeks; 2 sessions per week for the first 3 weeks, 1 session per week for the next 6 weeks, and optional additional sessions to monitor the patients compliance.
Trained clinicians will provide treatment. All participating clinicians are trained in the treatment protocol by the researchers. Patients with tinnitus attributed to a TMD will be referred to the trained clinicians for TMD treatment (guided referral).

2.3.6 Sample size and power

The primary outcome measure, the TQ, will be used to investigate differences between the direct-start group and delayed-start group in week 9 of the study. We plan to include patients in both groups in a 1 to 1 ratio. Based on literature data [110], we expect a minimal significant decrease in TQ score of 8.72 points (SD 13.72). To be able to reject the null hypothesis that the population means of the direct-start group and delayed-start group in week 9 are equal with probability (power) of 0.8, we will need to study 37 patients in each group. The Type I error probability associated with this test of this null hypothesis is 0.05.

This sample size will be refined after a pilot study containing 2x5 patients. Taking into account the possibility of dropouts and the later analysis of prognostic indicators and mediation analysis, we aim to recruit 2x100 patients.

The primary analysis population is the intention-to-treat population. This population includes all randomized patients who provided baseline data, regardless of whether or not they adhere to the complete protocol.

2.3.7 Statistics

Our null hypothesis is that the change in TQ at week 9 is equal in both groups (early-start and delayed-start):

H_0: Change in TQ-baseline to TQ-9 weeks (early start) = Change in TQ-baseline to TQ-9 weeks (delayed start)

The primary outcome is a change in the scores on the TQ after 9 weeks treatment. The mean change in TQ score between baseline and 9-weeks (post treatment) scores will be calculated. This mean change in TQ of the early start group will be compared to the mean change in TQ of the delayed-start group that received no treatment yet at this point. A difference between both groups will be defined as statistically significant when $p < 0.05$.

A repeated measures ANOVA and post-hoc tests will be used to compare the mean changes of the early-start group and delayed-start group at 9 weeks, and secondary at baseline, 18, and 27 weeks follow-up. The same cut-off point of $p < 0.05$ will be used here.

For the mediation analysis, the protocol described by Baron and Kenny [119] will be used to calculate the role of potential contributing factors in the obtained output. This implies the execution of three regression analysis. A first analyses the relation between the applied therapy (independent variable) and the outcome (dependent variable). A second analyses the relation between the applied therapy (independent) and a mediating factor. This to confirm that the applied treatment significantly affects the mediator. A third analysis is used to confirm that the mediator significantly predicts the treatment outcome (dependent variable), while controlling for the applied treatment (independent variable). Again, a cut-off point of $p < 0.05$ will be used.

Bootstrapping will be performed to avoid overestimation of the mediation effect. As potential mediating factors, all secondary outcome measures will be used.

2.4 DISCUSSION

The aim of this study is to investigate the effect of a conservative TMJ treatment on several tinnitus and TMJ-related parameters. Currently, the studies that investigated the effect of TMJ therapy on somatic tinnitus have a high risk of bias, mainly due to lack of statistical analyses between groups and before-after treatment, incomplete presentation of the data and selective reporting [86]. Additionally, risk of bias is present due to lack of information about the blinding process of the subjects, therapists and investigators. Blinding of the subjects and therapists is always a hurdle in studies investigating therapy treatment and is hard to overcome. Therefore, blinding of the assessor, who performs the follow-up measurements and data processing, is even more crucial. In this study, a high quality methodological design will be used by performing a prospective comparative delayed design and with blinded evaluator for baseline, end of therapy, and 9 and 18 weeks after therapy.

Furthermore, earlier studies that investigated the effect of conservative TMJ treatment on somatic tinnitus did not always match the evidence-based practice for TMJ treatment. In patients with tinnitus as well as TMD or oral parafunctions, it is thought that tinnitus improvement can be obtained by improving the TMJ complaints. Therefore, it is necessary to use the best available TMJ treatment option in order to gain maximal improvement in tinnitus complaints. For example, Bösel et al.[82], applied self-therapy next to splint therapy, although Tuncer et al.[120]found that physiotherapy performed by a therapist in combination with home physical therapy was more effective in terms of TMD pain and pain-free maximal mouth opening, than home physical therapy alone.

Additionally, the multifactorial aetiology of TMD should be taken into account. Studies have proven that TMD patients show increased somatisation, stress, anxiety and depression, compared to healthy individuals [121, 122]. Therefore, there is a need for multimodal therapies, incorporating behavioural and educational approaches, which seem to offer more benefit than a single-treatment program in patients with high psychological distress [123].

In this respect, we decided to use a multimodal treatment in the current study, which is provided by dentists and physical therapists. All physical therapists are trained in the treatment protocol by the researchers (guided referral) and will adjust the treatment modalities to the needs of the individual patient.

Currently, the clinical evaluation of somatic tinnitus is based on a generally accepted set of anamnestic criteria [51]. According to these criteria, somatic tinnitus is suspected when the tinnitus is associated with an evident history of head or neck trauma, some manipulation of the teeth, jaw or cervical spine, recurrent pain episodes in head, neck or shoulder girdle, temporal coincidence of onset or increase of both pain and tinnitus, increase of tinnitus during inadequate postures during rest, walking, working or sleeping or intense bruxism periods during the day or night. These criteria imply a temporal and mechanical association between TMJ or cervical spine dysfunction, and tinnitus complaints. If one of the abovementioned criteria is present, somatic tinnitus is suspected and further evaluation is warranted. Other studies have described the presence of modulation of tinnitus during forceful contractions of the neck and jaw musculature [91, 124]. These tests however also elicit a sound perception in 65% of an asymptomatic control group without tinnitus complaints. Therefore, modulation tests are not very useful for diagnosing somatic tinnitus. Therefore, we apply a combination of thorough ENT, audiological and temporomandibular investigations combined with the abovementioned diagnostic criteria for diagnosing somatic tinnitus. While all objective causes of tinnitus are excluded, we aim to include patients with a co-existence of severe subjective tinnitus and temporomandibular complaints in order to include patients who can potentially benefit from the treatment.

To obtain a detailed view on the patients' subjective tinnitus complaints, the TFI will be used [112]. Since the responsiveness of this questionnaire is limited due to important floor effects on more than half of the questions this questionnaire will not be used to evaluate treatment effect [125].

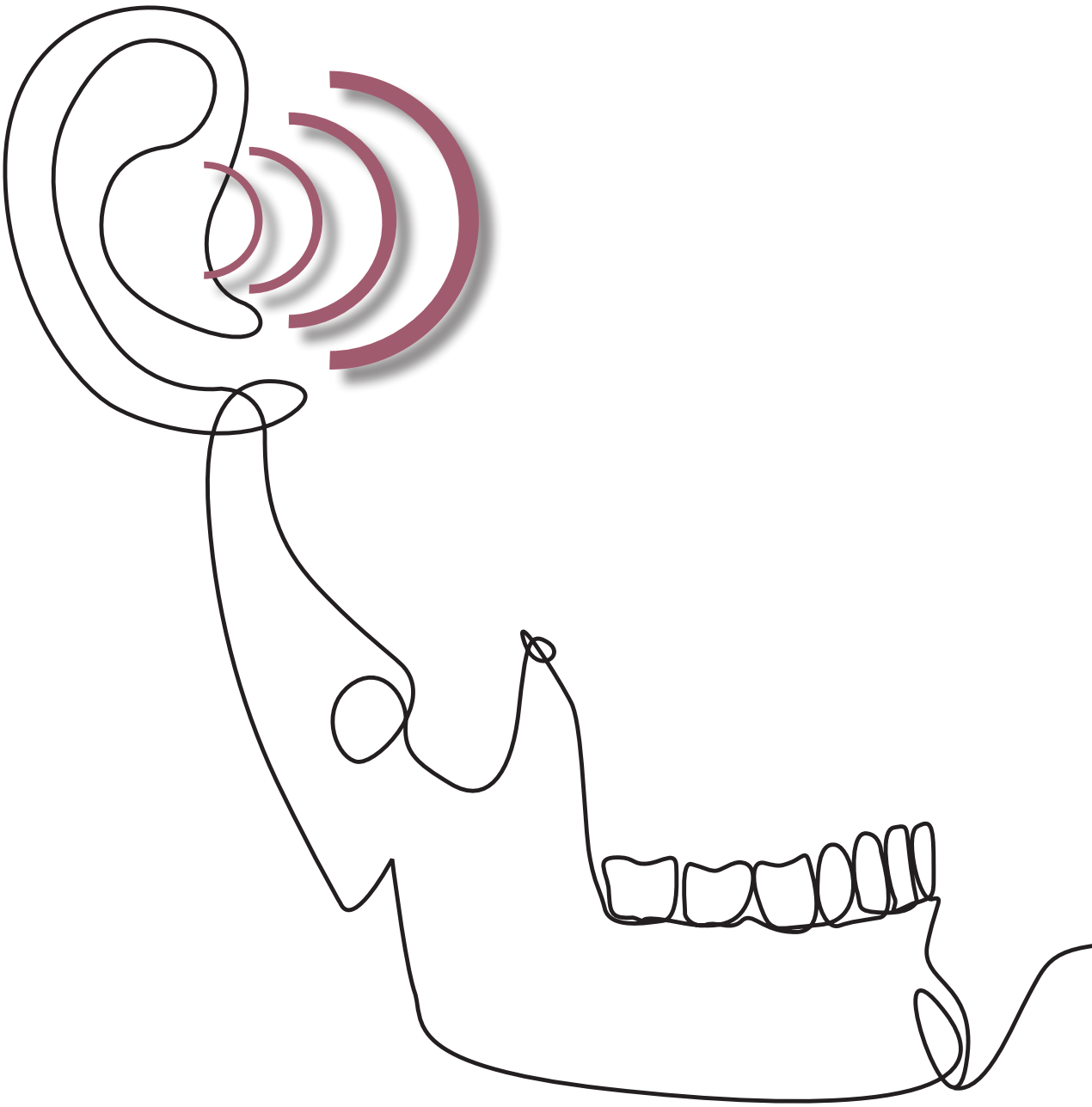
To improve the quality of patient care, it is important that clinicians are able to identify who has high chance for a positive treatment effect and who is at risk for poor recovery. Therefore we aim to identify prognostic indicators, to provide arguments why someone might benefit from TMJ treatment or not. This can reduce the current trial and error strategy of patients and thus avoid patient frustration and unnecessary reimbursement of unsuccessful therapies. To date, no prognostic indicators are available for the effect of TMD treatment on tinnitus. An earlier study in cervicogenic somatic tinnitus however, showed that patients with low-pitched tinnitus, that co-varies with the neck complaints and increases during inadequate postures, have the best prognosis after cervical spine treatment [126]. Rollman et al. [127] studied a variety of prognostic indicators for TMD pain in general. They found that a longer duration of the TMD-pain complaint, a higher number of attended care practitioners and higher degree of hindrance on function negatively predicted 6-month improvement. It is unclear to what extent these prognostic indicators can be transferred to our population of patients with tinnitus as main complaint; consequently we aim to identify prognostic indicators for the effect of TMJ treatment on tinnitus.

To understand the working mechanism behind TMJ treatment for somatic tinnitus it is necessary to identify variables that have an effect on the main outcome variable (TQ). Knowing that a treatment is beneficial for patients is important, but knowing how it works adds to the understanding and acceptance of the findings among clinicians. Therefore we also aim to identify possible mediating factors, i.e. factors that contribute to the therapeutic effect. The underlying idea is that TMJ contributes to somatic tinnitus. Consequently, variables that measure TMJ parameters are used as potential mediators. These are TMJ pain via the TMD pain screener, pain sensitivity as measured via PPT and mouth opening.

Since patients are recruited in a tertiary centre with long waiting lists, it would be unethical to include patients in a placebo group, receiving no treatment at all. Therefore, this study is designed as a randomised controlled trial with a delayed treatment design. In this type of design, one group of patients will receive 9 weeks of treatment immediately, while the delayed-start group will receive the standard information and advice about tinnitus. After 9 weeks, the delayed-start group will also receive the TMD therapy.

To date, the inclusion of the pilot study is completed. The follow-up results are expected by the end of December 2017. Afterwards, a sample size recalculation will be performed.

This study is the first to investigate the effect of a state of the art conservative TMJ treatment protocol on patients with somatic tinnitus using a prospective comparative delayed design and blinded evaluator for baseline, end of therapy, and 18 and 27 weeks after therapy.



Chapter 3

Treatment of somatosensory tinnitus: A randomized controlled trial studying the effect of orofacial treatment as part of a multidisciplinary program

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3.1 ABSTRACT

Background

Tinnitus, or ringing in the ears, is a perception of sound in the absence of overt acoustic stimulation. In some cases tinnitus can be influenced by temporomandibular somatosensory input, then called temporomandibular somatosensory tinnitus (TST). It is however, not entirely known if orofacial treatment can decrease the tinnitus severity. The purpose of the study was to evaluate the effect of orofacial treatment on tinnitus complaints in patients with TST.

Methods

Adult patients with TST were included and all received information and advice about tinnitus and conservative orofacial treatment consisting of physical therapy and, in case of grinding, occlusal splints were applied. Included patients were randomly assigned to an early-start group and a delayed-start group according to our delayed-treatment design.

Results

In total 40 patients were included in each group. The treatment effect on tinnitus severity was investigated using the Tinnitus Questionnaire (TQ) and Tinnitus Functional Index (TFI). On TQ-score, no clinically relevant reductions were observed, and no significant differences in decrease were observed between the early-start group and the delayed-start group. Contrarily, a significantly higher percentage of patients showed a decrease in TQ-degree in the early-start group compared to the delayed-start group (30.0% versus 2.8%, $p=0.006$). The TFI-score did show a significantly greater and clinically relevant reduction in the early-start group compared to the delayed-start group ($p=0.042$).

Conclusions

A multidisciplinary non-invasive orofacial treatment was able to reduce tinnitus severity in patients with temporomandibular related somatosensory tinnitus.

Trial registration

clinicaltrials.gov: NCT03209297

Keywords

tinnitus; temporomandibular disorders; occlusal splints

3.2 INTRODUCTION

Tinnitus, or ringing in the ears, is a perception of sound in the absence of overt acoustic stimulation. It occurs in 10 to 15% [8] of the adult population and is generally described as hissing, sizzling or ringing and can be constant or intermittent, located in one or both ears or centrally located inside the head [8].

The international tinnitus guidelines distinguish between two forms of tinnitus, namely objective and subjective tinnitus [9]. Tinnitus is "objective" in case the tinnitus sound originates from an internal source within the patient's body, such as turbulences in the blood flow [8]. In case of subjective tinnitus, on the other hand, no source (externally or internally) can be found for the perceived tinnitus [8]. Subjective tinnitus can have many different aetiologies and often has a multifactorial origin with several influencing factors. Common influencing factors are hearing loss, noise trauma or psychological factors, such as stress, depression and anxiety disorders. Additionally, altered somatosensory input from the cervical spine or temporomandibular area can also influence the tinnitus percept [8, 13, 90]. When this somatosensory influence is one of the major influencing factors, a patient's tinnitus is called somatic or somatosensory tinnitus (ST). This type of tinnitus is present in 12 to 43% of tinnitus patients, depending on the setting (primary care, tertiary care, open population) and diagnostic criteria for ST [54-56, 128].

Physiologically, ST is explained by the presence of connecting fibres between the somatosensory system of the cervical spine and temporomandibular area and the dorsal cochlear nucleus (DCN). Through these fibres, afferent somatosensory information from the cervical spine or temporomandibular area can alter the spontaneous firing rates and synchrony of firing among neurons in the DCN, inferior colliculus and auditory cortex. In this way, the somatosensory system is able to alter the pitch or loudness of an existing tinnitus or in rare cases it can also cause the tinnitus [99].

One reason for altered somatosensory input, is the presence of temporomandibular disorders (TMD) or oral parafunctions [55]. TMD comprises various conditions where pain and dysfunction of the masticatory muscles or the temporomandibular joint (TMJ) are involved [61]. Oral parafunctions (e.g. bruxism, excessive gum chewing, lip or fingernail biting) are often related to TMD [129, 130]. The fact that prevalence studies show that tinnitus occurs in 30% to 64% [58, 95] of patients with TMD, suggests that TMD and tinnitus are intertwined. Additionally, TMD and oral parafunctions are related to 5 out of 16 criteria that are part of the internationally agreed set of diagnostic criteria for ST [131].

Previous studies [80-82] showed that TMD treatment can positively affect tinnitus loudness and severity, but a high risk of bias is present in these studies. The main methodologic limitations in these studies were related to lack of statistical analysis between groups, incomplete presentation of the data, and selective reporting [86]. Furthermore, lack of blinding of subjects, therapists and investigators caused a high risk of bias [85]. On the other hand, previous studies often used a primary

TMD population to investigate the effect of TMD treatment on concomitant tinnitus complaints. Therefore, more high quality research, with limited risk of bias and in a primary tinnitus population is necessary. Thus, the aim of this study was to investigate the effect of an evidence based conservative orofacial treatment on subjective tinnitus complaints in patients with TMD related ST, while limiting the risk of bias.

3.3 METHODS

3.3.1 Patients

Patients were recruited by the multidisciplinary team of the tertiary tinnitus clinic of the Antwerp University Hospital in Belgium. Patients were thoroughly assessed by the multidisciplinary team (with otorhinolaryngologists, audiologists, physical therapists and dentists) to identify the influencing factors of their tinnitus and to exclude any objective causes [28]. Patients were included in the study when suffering from a combination of moderate to severe chronic subjective tinnitus, defined as a Tinnitus Functional Index (TFI) score between 25 and 90 [112], that had been stable for at least three months and TMD (diagnosed according to the Diagnostic Criteria for TMD[61]) and/or oral parafunctions. Patients suffering from otological or neurological causes of the tinnitus such as Menière's disease, progressive middle ear pathology, intracranial pathology, severe depression or anxiety disorders (diagnosed by a psychiatrist), traumatic cervical spine or temporomandibular injury in the past 6 months, tumours or previous surgery in the orofacial area were not considered for inclusion. Patients were also excluded if they had received TMD treatment in the past three months.

3.3.2 Intervention

3.3.2.1 Information and advice

In our clinic, all patients receive information and advice concerning their tinnitus prior to any other treatment suggestion. This information and advice is provided by experienced clinicians in tinnitus treatment.

3.3.2.2 Orofacial treatment

Orofacial treatment was provided by a team of dentists and physical therapists who were specifically trained to apply the required treatment prior to the start of the study. The intervention consisted of orofacial physical therapy, comprising counselling regarding mouth habit reversal, bruxism, sleep hygiene, lifestyle advice and biofeedback; massage of the masticatory muscles; stretching exercises and relaxation therapy. In case of grinding, the orofacial physical therapy was complemented with an occlusal splint by the dentist. In case the patient also suffered from cervical spine problems, which is highly prevalent in patients with TMD [132-134], additional cervical spine treatment (mobilisations and exercises) was added to the treatment. This type of multidisciplinary orofacial treatment is currently the evidence-based treatment for the conservative management of TMD [74, 135].

The treatment protocol provided a maximum of 18 orofacial physical therapy sessions during a 9-week treatment program as described in the published protocol [136].

The therapists adapted the used techniques and exercises to the patient's current dysfunction, as is the current best practice in orofacial treatment. No additional tinnitus treatments were allowed during the participation in the study.

3.3.3 Study design

The study was designed as a randomized controlled trial with a delayed treatment design to evaluate the effectiveness of a conservative orofacial treatment on tinnitus annoyance in patients suffering from temporomandibular related somatosensory tinnitus. The delayed treatment design allowed us to obtain data for a control group by creating a waiting list, since the use of a control group that receives no treatment at all, was not considered ethical in a tertiary centre population.

At baseline, patients were randomly assigned to receive immediate treatment (early-start group) or to be placed on the waiting list (delayed-start group). In phase 1 (weeks 0-9), the early-start group received the orofacial treatment for 9 weeks. The delayed-start group entered a wait-and-see period. In phase 2 (weeks 9-18), the patients in the delayed-start group started their 9 weeks orofacial treatment period, while the early-start group entered a 9-week follow-up period. In phase 3 (weeks 18-27) , the delayed-start group entered their 9-week follow-up period. The early-start group ended their participation to the study at the end of week 18.

3.3.4 Outcome measures

3.3.4.1 Primary outcome measure

The primary outcome measure for this study was the Tinnitus Questionnaire (TQ). The TQ is a validated and commonly used instrument for assessment of tinnitus annoyance. The TQ incorporates scales evaluating emotional and cognitive distress, intrusiveness, auditory perceptual differences, sleep disturbances and associated somatic complaints. The TQ consists of 52 questions that are answered on a 3-point scale, ranging from 'true' (scoring 0), 'partly true' (scoring 1) to 'not true' (scoring 2). The total score on the TQ ranges from 0 to 84. Additionally, the total score can be used to create four groups based on the degree of tinnitus related distress: degree 1 (slight) up to 30 points, degree 2 (mediocre) between 31-46 points, degree 3 (severe) between 47-59 points and degree 4 (extremely severe) between 60-84 points. The TQ showed a good correlation with the Tinnitus Handicap Inventory, Tinnitus Impairment Questionnaire and Tinnitus Functional Index (0.79 – 0.90) [110, 137]. A decrease of 8.72 points is considered clinically relevant [110].

3.3.4.2 Secondary outcome measures

The Tinnitus Functional Index (TFI) was used to measure change in tinnitus severity after treatment and follow-up. This questionnaire consists of 25 questions divided into eight subscales: intrusiveness, sense of control, cognitive, sleep, auditory, relaxation, quality of life and emotional. For each question

patients respond on a Likert scale of 0-10, allowing the detection of small changes over time. The global score ranges from 0 to 100, with higher scores denoting higher levels of handicap. The test-retest reliability of the TFI is good (r=0.78). The convergent validity with the Tinnitus Handicap Inventory (r= 0.86) and VAS (r=0.75) is good. A reduction of 13 points is considered clinically relevant [112].

All outcome measures were documented at baseline, after 9 weeks in the delayed-start group, immediately after the last treatment session (post-treatment) and after 9 weeks follow-up.

More information about the used baseline measures is provided in the published protocol [56].

3.3.5 Sample size and power

The sample size was calculated using Medcalc (Medcalc Software bvba). Sample size calculation was performed for the clinically relevant change of 8.72 points in TQ score (27). The sample size was calculated for the study to have 80% power to reject the null hypothesis. The type I error probability, associated with this test, is 0.05. To achieve 80% power, 37 patients were required in each study arm.

3.3.6 Randomization and blinding

After baseline measurements, patients were randomized into the early-start group or delayed-start group based on block-randomization 1: 1 with variable block lengths. A concealed randomization list was generated using Microsoft Excel® software by an independent researcher. Treating therapists were blinded at all times to whether a patient was included in the early-start or delayed-start group.

3.3.7 Ethical approval and consent

Ethical approval was obtained from the ethics committee of the Antwerp University Hospital (reference number B300201730825). Written informed consent was obtained for all patients prior to the start of the study. The study was registered at ClinicalTrials.gov (NCT03209297).

3.3.8 Statistics

An intention-to-treat analysis was performed on the study cohort. First, the normality of the data was investigated using a Kolmogorov-Smirnov test. Baseline comparability ($p > 0.05$) of both groups was analysed using descriptive statistics, Mann-Whitney U-tests for non-normally distributed data and the independent samples t-tests for normally distributed data. Chi-square tests were used to determine differences between dichotomous variables.

To answer our primary research question, differences in changes on TQ and TFI from baseline to week 9 of the study between the early-start and delayed-start groups, were calculated to investigate the effect of orofacial treatment. The data in week 18 of the study were analysed to investigate if a similar decrease in changes on TQ and TFI-score was present in the delayed start group after receiving orofacial treatment.

Before starting the actual analysis of the treatment effect, new variables were calculated, being the change in TQ-score, change in TQ degree and change in TFI-score from baseline to week 9 and from baseline to week 18. These parameters enabled us to compare the evolution of the TQ and TFI in both groups. Since the TQ-change was not normally distributed, differences between both groups was calculated using the Mann-Whitney U-test. Differences in the TFI-change was calculated using the independent samples t-test. Additionally, for each patient, the TQ-degree at baseline and at 9-weeks was determined according to the guidelines of Zeman et al [110]. The change in TQ-degree was calculated as the difference between the TQ-degree at baseline and the TQ-degree in week 9 of the study. This TQ-degree-change score was then dichotomized with 0 scored in case the patient showed no decrease or an increase in TQ-degree and scored 1 in case the patient decreased at least one degree. Differences between both groups in change in TQ-degree where then calculated using Chi-square test.

In a third stage of the analysis, the TQ and TFI-change scores were dichotomized, based on the clinically relevant change of 8.72 points for the TQ and 13 points for the TFI [110, 112]. Differences in the number of patients who perceived a clinically relevant change in both groups were calculated using chi square tests.

Additionally, within-group differences from baseline to posttreatment and follow-up were analyzed using paired samples tests. Hereby, we expected that the TQ-score and TFI-score in the early-start group would decrease from baseline to week 9, while the delayed-start group would stay stable or have a slight decrease (because only the early-start group received orofacial treatment). At the end of phase 2, these differences between the two groups would become smaller, because the delayed-start group also received orofacial treatment in that period and de early-start group ended the treatment.

3.4 RESULTS

3.4.1 Patients

In total, 80 patients were included in the study in a period of 2 years: 40 patients were randomly assigned to the early-start group and 40 patients to the delayed-start group. In the early-start group, all 40 allocated patients received orofacial treatment. Three of them were lost to follow-up after the 9-weeks follow-up period. In the delayed start group, 35 patients received orofacial therapy after 9 weeks wait-and-see. Reasons for drop-out are specified in figure 3.1. Two of the treated patients were lost to follow-up after the 9-weeks follow-up period. An overview of the enrolment is shown in figure 3.1. In addition to the physical therapy, 52% of the patients (n = 39) received an occlusal splint. These patients were equally distributed over both groups.

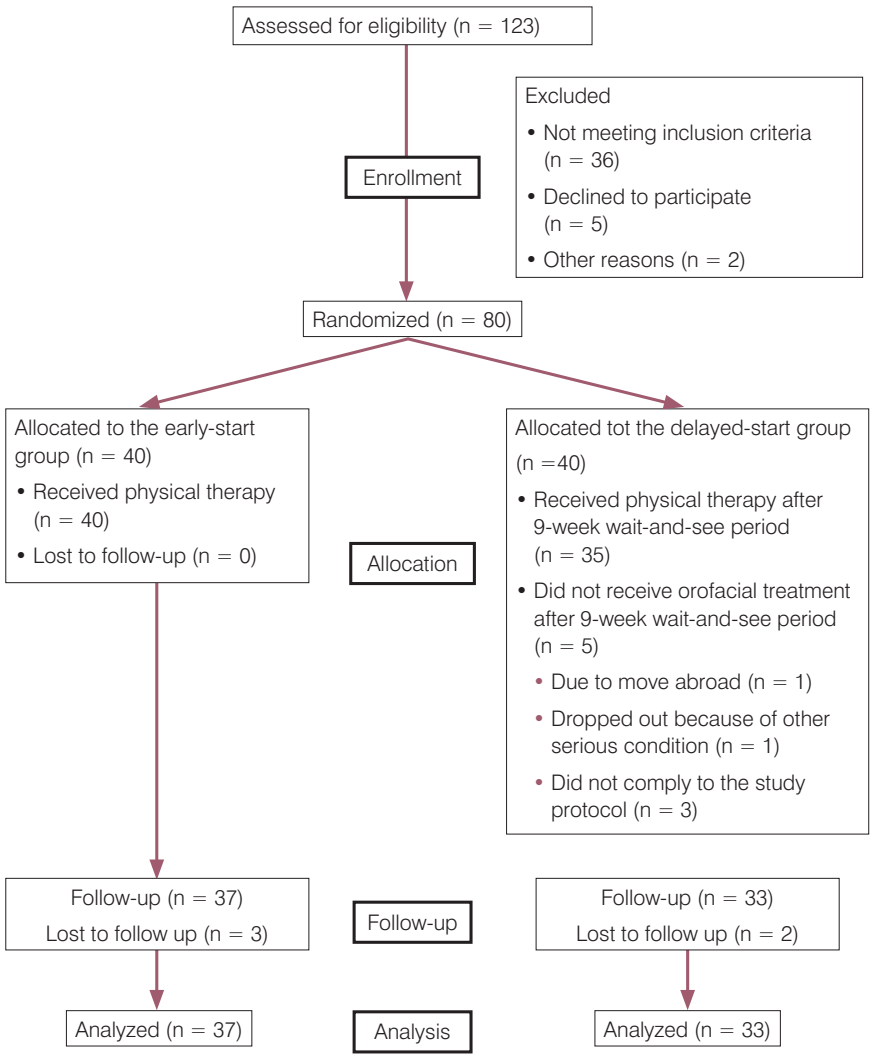


Figure 3.1: Flow chart of participation of the patients through the study.

The baseline characteristics of the patients in the two groups are presented in Table 3.1. Both groups were similar in terms of clinical and demographic characteristics. More specifically, no significant differences in baseline characteristics (TFI score, age and gender) were found between both groups (Table 3.1).

Table 3.1: Baseline characteristics of the early-start group and the delayed-start group.

Characteristic	Early-start group	Delayed-start group	Total	p-value	Statistic test	Value	DF
Number of subjects	40	40	80				
Gender male/female	18/22 (45%/55%)	24/16 (60%/40%)	42/38 (53%/47%)	0.168	Chi-square	1.805	1
Age in years (SD)	46 (13)	45 (15)	45 (14)	0.769	T-test	0.294	78
TQ (SD)	37 (16)	34 (15)	36 (16)	0.345	T-test	0.951	75
TFI (SD)	55 (17)	48(15)	52 (16)	0.086	T-test	1.741	78
TQ degree				0.376	Chi-square	3.105	3
% degree 1	30%	49%	39%				
% degree 2	40%	30%	35%				
% degree 3	15%	13%	14%				
% degree 4	15%	8%	12%				
VAS mean loudness tinnitus right ear (SD)	50 (30)	49 (25)	49 (27)	0.835	T-test	0.209	78
VAS mean loudness tinnitus left ear (SD)	46 (31)	45 (26)	45 (28)	0.858	T-test	0.180	78
TMD pain screener (percentage < 3/ percentage ≥ 3)	35%/65%	35%/65%	40%/60%	0.272	Chi-square	7.561	6
HQ (SD)	17 (8)	19 (9)	18 (8)	0.958	T-test	-0.053	76
HADS anxiety (SD)	9 (4)	8 (4)	9 (4)	0.076	T-test	1.695	77
HADS depression (SD)	7 (5)	5 (4)	6 (5)	0.257	T-test	1.429	75
Fletcher index left (SD)	13 (17)	11 (11)	13 (17)	0.725	T-test	0.135	78
Fletcher index right (SD)	11 (10)	13 (14)	11 (12)	0.359	T-test	-1.254	76

SD: standard deviation. TQ: Tinnitus Questionnaire. TFI: Tinnitus Functional Index. VAS: Visual Analogue Scale. TMD: Temporomandibular Disorder. HADS: Hospital Anxiety and Depression Scale. HQ: hyperacusis questionnaire.

3.4.2 TQ responses to treatment (primary outcome)

The TQ-score in week 9 of the study, showed a decrease of 4.1 points in the early-start group, compared to 0.2 in the delayed-start group. This difference in decrease between both groups however, was not statistically significant (p=0.099) nor clinically relevant (decrease < 8.72 points). A comparable decrease (6.0 points) was found after treatment in the delayed-start group (week 18). Both groups showed an additional decrease in TQ-score after follow-up: 2.0 points in the early-start and 1.2 points in the delayed-start group. Figure 3.2 shows the difference in evolution between the early-start and delayed-start group.

Looking at the within group analysis, the early-start group, shows a significant decrease in TQ-score from baseline to 9 weeks (p=0.033), whereas the delayed-start group remained stable (p=0.875). In week 18, after completion of the orofacial treatment in the delayed-start group, a significant decrease in TQ-score was found from baseline to 18 weeks in the delayed-start group (p=0.011). The decrease in both groups after follow-up did not reach the clinically relevant reduction of 8.72 points.

The TQ-degree in week 9 of the study did differ significantly (p = 0.006) between both groups. In the early-start group 30.0% of the patients showed a decrease of at least one degree on TQ, compared to 2.8% in the delayed-start group.

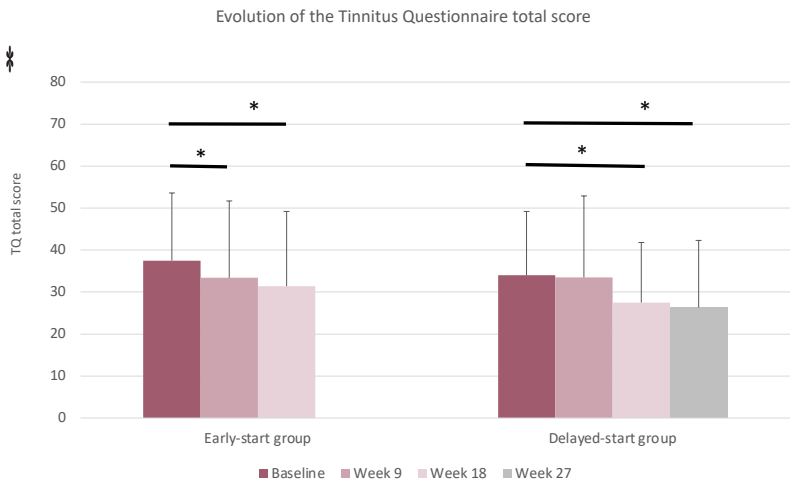


Figure 3.2: Evolution of the Tinnitus Questionnaire (TQ) scores in the early-start and delayed-start groups. (Error bars show the standard deviations, * p < 0.05)

3.4.3 TFI responses to treatment (secondary outcome)

The TFI-scores in week 9 showed a decrease of 13.8 points in the early-start group and 5.0 points in the delayed-start group. This difference in decrease was significantly different (p=0.042), indicating a significant effect of our treatment on tinnitus severity. This effect was bolstered by equivalent

decreases in TFI-score after completion of the treatment in the delayed-start group (12.2 points reduction).

Both groups showed an additional decrease in TFI-score after follow-up: 3.1 points in the early-start and 3.0 points in the delayed-start group. Figure 3.3 shows the evolution of TFI-scores over time between the early-start and delayed-start group. A clinically relevant reduction of 13 points was found after treatment in the early-start group and after follow-up in both groups. Figure 3.3 shows the difference in evolution between the early-start and delayed-start group.

Looking at the within group analysis, the early-start group showed a significant decrease in TFI-score from baseline to 9 weeks (p=0.000), while no such decrease was found in the delayed-start group (p=0.076). After the completion of the orofacial treatment in week 18 though, a significant decrease in TFI-score compared to baseline was found in the delayed-start group (p=0.001).

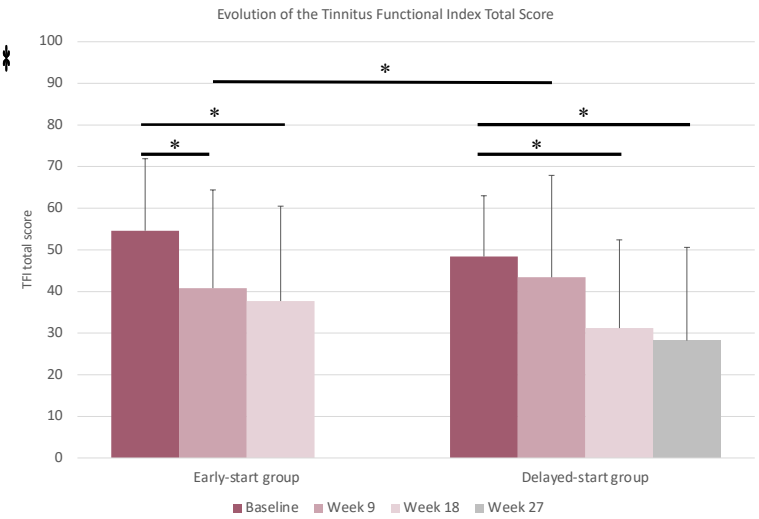


Figure 3.3: Evolution of the Tinnitus Functional Index (TFI) scores in the early-start and delayed-start groups. (error bars show the standard deviations, * $p < 0.05$)

3.4.4 Clinically relevant improvement

For the entire group, 34% of the patients showed a clinically relevant improvement of the TQ-score (cutoff score ≥ 8.72 points [110]) immediately after treatment. Looking at the TFI-score, 41% of the patients had a clinically relevant improvement (cutoff score ≥ 13 points [112]). After the follow-up period, respectively 46% (TQ) and 61% (TFI) reached the level of clinically relevant improvement compared to baseline.

3.5 DISCUSSION

To investigate the effect of a non-invasive orofacial treatment on tinnitus annoyance, the current study was designed using a delayed treatment design. A significant difference in decrease in TQ-degree was found between the early-start and delayed-start group, as well as a significant decrease in TFI-score, indicating a positive effect of orofacial treatment on tinnitus severity. These results confirm the findings of previous RCTs by Bösel et al [82], Erlandsson et al. [80] and Tullberg et al. [81], that were assembled in a recent systematic review [85].

After receiving orofacial therapy, a clinically relevant change in TQ-score was found in 34% of patients immediately after treatment and in 46% after follow-up. On TFI, larger percentages of clinically relevant change were found: 41% and 61% of patients immediately after treatment and after follow-up respectively. This difference might be explained by differences in scoring and construct of both questionnaires. The TQ uses a 3-point scale to rate each question, while the TFI uses an 11-point Likert scale. This makes the TFI potentially more sensitive than the TQ for smaller differences in tinnitus severity. This difference in sensitivity to change was also pointed out by Jacquemin et al. [137]. On the other hand, the TQ is designed to measure tinnitus annoyance, where the TFI is used to measure tinnitus severity. Another reason for the differences in results between the TFI and TQ scores might be our inclusion criteria. Patients were included when they had a TFI score between 25 and 90 points, but some patients already had a rather low TQ score at baseline. Hence, to measure a TQ-change of more than 8.72 points might have been more difficult.

Regarding the potential risk of bias, we believe that our study has a lower risk than those included in the above-mentioned review, with only 'blinding of subjects' and 'blinding of therapists' that might have introduced a slight bias, but cannot be eliminated in this type of studies. The current design and study results reinforce the usefulness of orofacial treatment in patients with temporomandibular related somatosensory tinnitus.

Patients further improved after the TMD treatment was stopped, as was noted in an additional decrease in TQ and TFI scores between the post-treatment and the follow-up measurements, which is in line with previous studies on tinnitus treatment [138, 139]. This might be due to the fact that patients continue their exercises and habit reversal after the last treatment session. The after-effect might also be due to the fact that patients are less focussed on their tinnitus during the follow-up period than during the treatment period, as there is no more therapist contact [139].

The current study used a delayed-treatment design, because the use of a control group that received no treatment was found to be unethical. Moreover, no comparable temporomandibular treatment that could serve as a sham intervention is available. The delayed-treatment design however, has some downsides. The most important one is the fact that we can only compare our groups in week 9 of the study, while the largest effect of the treatment was found after follow-up. This might have caused an

underestimation of the effect of our treatment compared to wait-and-see. A second disadvantage of the delayed-treatment design is the lack of comparison treatment, to rule out placebo effects. Future research should compare the orofacial treatment to other treatments using two-armed randomized controlled trials.

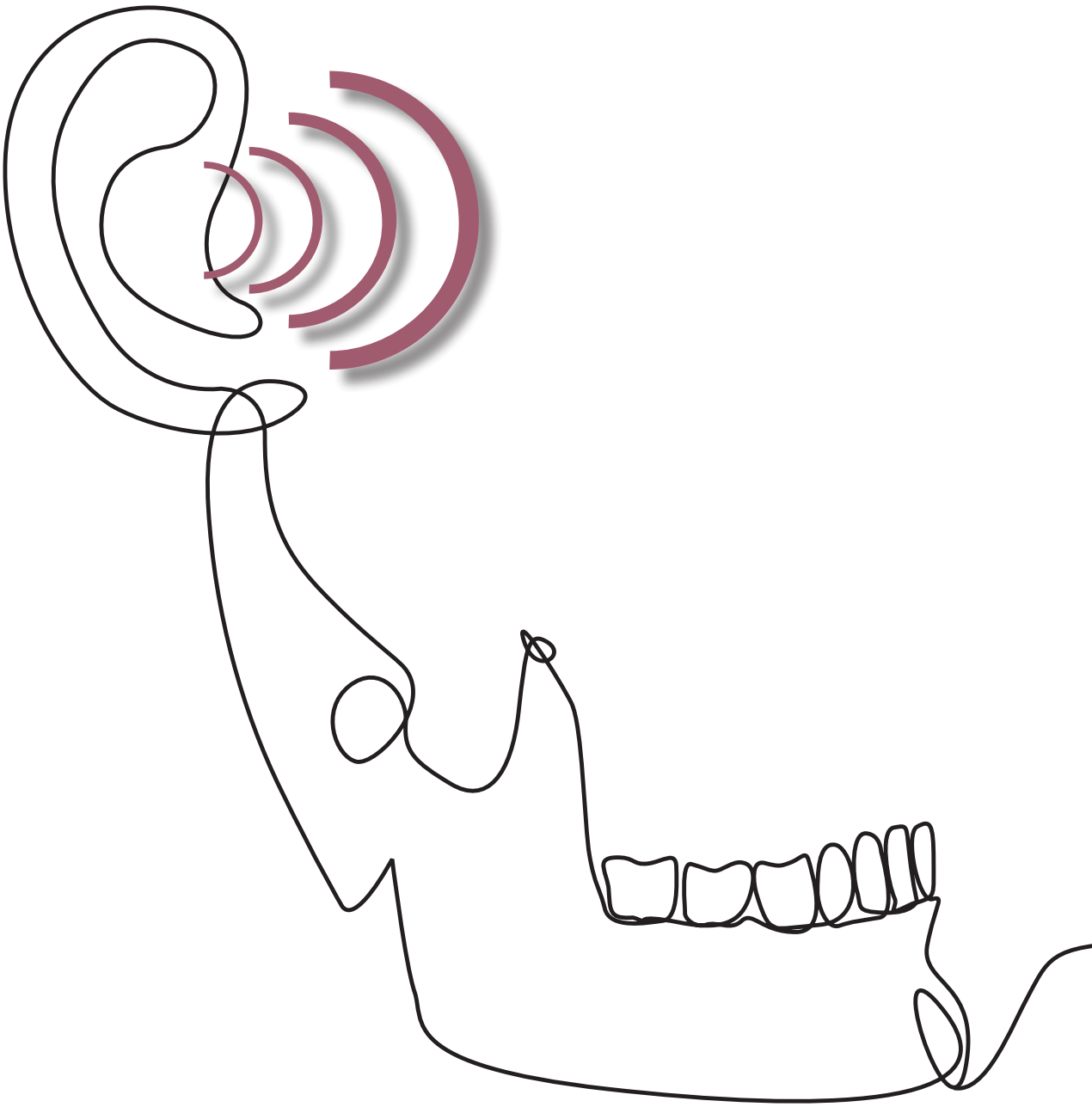
We recruited patients from a tertiary tinnitus clinic. Patients in these settings are known to be more therapy resistant than patients in primary or secondary care. This might lead to an underestimation of the overall treatment effect. It would therefore be interesting to investigate the effect of our treatment in a primary or secondary care population in the future.

Additionally, we compared the effect of a single session of "information and advice" with a maximum of 18 sessions of orofacial treatment. Since the duration of patient-therapist contact can have an influence on the effect of the treatment, the chosen design might also have introduced an overestimation of our treatment effect. To rule out this potential over- or underestimation, future studies should focus on comparing the effect of orofacial treatment to other types treatments.

The randomization procedure using a 1:1 block randomization with variable block lengths was used to reduce bias and achieve balance in the allocation of patients between the early-start and delayed-start group. The lack of stratification on baseline severity of the tinnitus (TFI-scores) might have influenced our results though and is a limitation of our study. In future studies, different randomization procedures should be used, stratifying for baseline TFI-score.

3.6 CONCLUSIONS

A multidisciplinary non-invasive orofacial treatment showed positive effects on tinnitus severity, compared to a single session of information and advice. This effect can be expected in patients with temporomandibular related somatosensory tinnitus.



Chapter 4

Reduction of somatic tinnitus severity is mediated by improvement of temporomandibular disorders

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4.1 ABSTRACT

Background

Successful orofacial treatment can reduce tinnitus severity in patients with somatic tinnitus (ST). However, it is still unclear to what extent the degree of reduction in temporomandibular disorders (TMD) actually contributes to the decrease in tinnitus severity after orofacial treatment. Therefore, the aim of this study was to analyze the mediating effect of reduction in TMD pain on the improvement of tinnitus severity after multidisciplinary orofacial treatment.

Methods

A total of 80 patients with moderate to severe ST attributed to the temporomandibular region, were recruited from a tertiary tinnitus clinic. At baseline, patients were randomly assigned to the orofacial treatment group or to the control group. Both groups received a minimum of information and advice regarding their tinnitus complaints. The orofacial treatment group received orofacial physical therapy complemented with occlusal splints when needed, while the control group received no other treatment. A mediation analysis was performed according to the steps described by Baron and Kenny and the proportion of the mediating effect was calculated for the potential mediator: 'change in TMD pain', measured by a one-point decrease in TMD pain screener score.

Results

Our analysis showed that 35% of the observed decrease in tinnitus severity can be attributed to a reduction in TMD pain. A significant total effect of orofacial treatment compared to control on the change in Tinnitus Functional Index (TFI) score was found (B = 0.253 p = 0.025 CI for B = 1.265 – 18.576). Orofacial treatment was also significantly related to the change in TMD pain (Exp (B) = 2.800 p = 0.034 CI for Exp B 1.081 – 7.251). Additionally, the change in TMD pain screener score was significantly related to the change in TFI score (B = -0.273 p = 0.016 CI for B = -19.875 - -2.119).

Conclusion

Reduction of TMD pain is a mediating factor in the decrease of tinnitus severity after multidisciplinary orofacial treatment.

Practical implications

Orofacial treatment can be used to decrease tinnitus severity in patients with TMD related somatic tinnitus.

Keywords

tinnitus, temporomandibular disorders, mediation, somatic, treatment

4.2 INTRODUCTION

Subjective tinnitus can have many different aetiologies and often has a multifactorial origin with several influencing factors. A specific subtype of subjective tinnitus is somatic or somatosensory tinnitus (ST), where somatosensory afference from the upper cervical spine or temporomandibular area influences the tinnitus percept through existing brainstem connections between the dorsal cochlear nucleus (DCN) and the somatosensory nuclei [55, 99]. Via these connections, alterations in somatosensory afference, can cause an increase of the spontaneous firing rates in the DCN, inferior colliculus and auditory cortex, either causing tinnitus or, more frequently, altering the pitch or loudness of an existing tinnitus [46-48, 99].

This neurophysiological model of ST explains the greater prevalence of tinnitus in patients with temporomandibular disorders (TMD) (30.4% to 64%), compared to the prevalence in the general population (10% to 15%)[58, 95]. In such patients, it is hypothesized that the increased muscle tension in the masticatory muscles or pressure on myofascial triggerpoints, present in TMD, can evoke or modulate the tinnitus [51].

TMD itself is a disorder with a multifactorial origin and includes emotional, physical, social and cognitive triggers. The diagnosis is made based on history taking and physical examination, as described in the diagnostic criteria for TMD [61]. Currently, the evidence-based conservative treatment for TMD is a multidisciplinary approach. Depending on the etiology, treatment may consist of orofacial therapy applied by the physical therapist and/or an occlusal splint applied by the dentist [74, 135].

Based on the neurophysiological model for ST, it can be hypothesized that normalization of the afferent input from the temporomandibular area, through multidisciplinary TMD treatment, will decrease the patient's tinnitus complaints. This hypothesis was confirmed in several clinical trials that found a positive effect of orofacial treatment on tinnitus loudness and severity [80-82, 86, 140].

These effect studies indicate that patients with temporomandibular related ST can be successfully treated with orofacial treatment and hypothesize that normalization of temporomandibular somatosensory input is the explanation for this success. However, they do not investigate to what extent the actual decrease in TMD pain contributes to the patient's tinnitus improvement. Altough orofacial treatment is primarily aimed at decreasing TMD complaints, it can also have other effects, such as a general relaxation effect.

To investigate a mechanism of a health care intervention a statistical method called 'mediation analyses' can be used. In mediation analysis, the effect of an independent variable on a dependent variable is measured and the influence of an indirect variable 'the mediator' can be calculated. This method is frequently used in psychological research to understand the working mechanism of an intervention, but for the field of physical therapy and tinnitus research, this is a relatively new

technique. Since animal studies or basic scientific studies are hard to develop for a subjective complaint as somatic tinnitus, this indirect method via mediation analyses is a realistic approach to gain insight in tinnitus pathophysiology and underlying working mechanisms [17, 18]. Therefore, mediation analyses will aid us to reveal to what extent a decrease in TMD pain contributes to the overall reduction of tinnitus severity in patients with temporomandibular related ST.

4.3 METHODS

In this study, we used the data collected for a RCT investigating the effect of multidisciplinary orofacial treatment on tinnitus severity [136, 140]. More details on the inclusion process and treatment can be found in the published protocol [136] and the original article on the results of the RCT [140]. Below, we provided brief descriptions of the study design, participants, intervention procedures and patients characteristics, relevant for the current analysis.

4.3.1 Methodology of the used randomized controlled trial

4.3.1.1 Patients

Patients were recruited from the tertiary tinnitus clinic of the Antwerp University Hospital in Belgium. To exclude any objective causes of tinnitus and to ascertain a strong contribution of temporomandibular afference on the included patients' tinnitus, patients were thoroughly assessed by a multidisciplinary team with otorhinolaryngologists, audiologists, dentists and physical therapists. Patients were included in the study if they suffered from moderate to severe chronic subjective tinnitus (defined as a Tinnitus Functional Index (TFI) score between 25 and 90) that had been stable for at least three months. Furthermore, the tinnitus should be attributed to a TMD or be combined with excessive parafunctions such as bruxism. To diagnose the type of TMD, patients were classified by the dentist and physical therapist in TMD myalgia or TMD arthralgia according to the DC-TMD. Patients were excluded in case the patient had: (a) a clear otological or neurological cause of the tinnitus, (b) a severe depression or anxiety disorder diagnosed by a psychiatrist, (c) a traumatic cervical spine or temporomandibular injury in the past six months, (d) tumors or previous surgery in the orofacial area or (e) already received TMD treatment in the past three months.

4.3.1.2 Study design

At baseline, patients were randomly assigned to the orofacial treatment group or to the control group. Both groups received a minimum of information and advice about their tinnitus by the ENT-specialist before entering the study. The treatment group then received the multidisciplinary orofacial treatment for 9 weeks, while the control group received no further treatment. Nine weeks after baseline all patients were evaluated again. Figure 4.1 shows the flow chart of participation of the patients through the study.

A total of 80 patients were included in the study: 40 patients were randomly assigned to the control group and 40 to the orofacial treatment group. In the control group, two patients were lost to follow-up. Reasons for drop-out are specified in figure 4.1. Baseline characteristics of the usual care with orofacial treatment group and the usual care group are displayed in table 4.1. In the orofacial treatment group, all 40 patients received the orofacial physiotherapy and 21 (52%) received an occlusal splint.

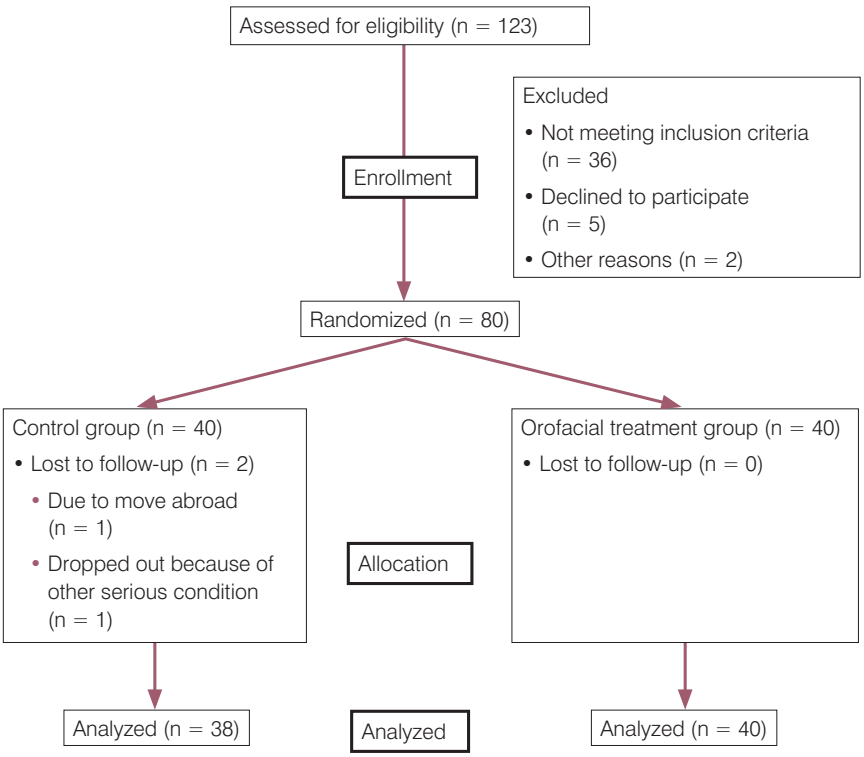


Figure 4.1: flow chart of participation of the patients through the study.

Table 4.1: Baseline characteristics of the usual care with orofacial treatment group and the usual care group.

Characteristic	orofacial treatment group	Control group	p-value
Number of subjects	40	40	
Gender male/female	18/22 (45%/55%)	24/16(60%/40%)	0.168
Age in years (SD)	46 (13)	45 (15)	0.769
Mean duration of the tinnitus in months (SD)	58 (16)	73 (13)	0.209
TFI (SD)	55 (17)	48(15)	0.086
TMD pain screener score			0.340
0	15.0%	7.5%	
1	10.0%	15.0%	
2	10.0%	22.5%	
3	15.0%	17.5%	
4	22.5%	7.5%	
5	17.5%	22.5%	
6	10.0%	7.5%	
% diagnosed with TMD myalgia	80.0%	85.0%	
% diagnosed with both myalgia and arthralgia	20.0%	30.0%	
%only oral parafunctions	20.0%	15%	
HQ (SD)	17 (8)	19 (9)	0.958
% HQ score ≥ 28	12.5%	17.5%	
HADS anxiety (SD)	9 (4)	8 (4)	0.076
HADS depression (SD)	7 (5)	5 (4)	0.257
% with hearing loss	30.0%	43.6%	0.210
Pure tone average left (SD)	13 (17)	11 (11)	0.725
pure tone average right (SD)	11 (10)	13 (14)	0.359

SD : standard deviation. TFI : Tinnitus Functional Index. TMD: Temporomandibular Disorders. HADS: Hospital Anxiety and Depression Scale. HQ: Hyperacusis questionnaire.

4.3.1.3 Intervention

The multidisciplinary orofacial treatment comprised a maximum of 18 sessions of orofacial physiotherapy in a 9-weeks treatment period. In case of nighttime grinding, therapy was complemented with an occlusal splint. The orofacial physiotherapy consisted of counselling (mouth habit reversal, sleep hygiene, lifestyle advice, mindfulness-based exercises and biofeedback), massage of the masticatory muscles, stretching exercises and relaxation therapy. In addition, cervical spine treatment (mobilization and exercises) was allowed if patients also suffered from cervical spine problems. This type of multidisciplinary orofacial treatment is currently the evidence-based treatment for the conservative management of TMD [61, 74]. No other tinnitus treatments were permitted during participation in the study.

4.3.1.4 Patient characteristics

Medical history related items and questionnaires were used to identify patients characteristics. Since chronic tinnitus is often accompanied with anxiety or depression, the presence of anxiety and depression was inventoried using the Hospital Anxiety and Depression Scale (HADS) [113, 141]. Anxiety or depression affects tinnitus severity and annoyance and can negatively influence the outcome after treatment [142, 143]. The HADS is specifically developed for patients in non-psychiatric hospital clinics and has been found to be reliable as a first indication of a depression or anxiety disorder. The questionnaire contains two subscales, an Anxiety subscale (HADS-A) and a Depression subscale (HADS-D). Each subscale has 7 questions that are answered on a four point (0–3) scale and range from 0 to 21 [113, 141, 144]. A score greater than or equal to 11 indicates the potential presence of an anxiety or depression disorder.

Besides, the presence of hyperacusis was assessed using the Hyperacusis Questionnaire (HQ) [115]. The HQ consists of 14 questions answered on a 4-point scale from 0 to 3. The answers on the questions are 'No' (scoring 0 points), 'Yes, a little' (scoring 1 point), 'Yes, quite a lot' (scoring 2 points) and 'Yes, a lot' (scoring 3 points). Total scores on the HQ range from 0 to 42. A score from 28 points or more indicates the presence of hyperacusis.

In addition, TMD characteristics and audiological related items were investigated. The temporomandibular area was examined using the standardised protocol of the Diagnostic Criteria for TMD (DC-TMD) [61]. The DC-TMD offers criteria for articular and muscle diagnoses. Both can be present at the same time. Based on this protocol, the clinician was able to diagnose the specific type of TMD.

To assess hearing impairment, hearing thresholds were measured using pure tone audiometry. Air conduction thresholds were measured at 125 Hz, 250 Hz, 500 Hz, 1 kHz, 2 kHz, 3 kHz 4 kHz, 6 kHz and 8 kHz according to the current clinical standards (ISO 8253-1, 1989). Based on these results, the Pure Tone Average (PTA) was calculated as the mean of the pure tones at 500 Hz, 1 kHz and 2 kHz.

4.3.1.5 Methodology of the mediation analyses

To analyze the mediating effect of reduction in TMD pain on the improvement in tinnitus severity, the methodology described by Baron and Kenny (figure 4.2) [119] was used. The mediation analyses by Baron and Kenny is initially developed for social psychological research, but is nowadays used to understand the mechanism of health interventions in a broader context, for example in rehabilitation research [145]. A mediation comprises three steps of regression: Step 1 regress the dependent variable (Y) on the independent variable (X) to confirm that the independent variable is a significant predicator of the dependent variable. This is called the total effect path c. Step 2 regress the mediator (M) on the independent variable (X) to confirm that the independent variable is significant predictor of the mediator (path a). It is important that the mediator is associated with the independent variable, because the mediator has to mediate the relationship between the independent and dependent

variable. Step 3 Regress the dependent variable (Y) on both the mediator (M) (path b) and independent variable (X) (the direct effect path c'). In this step the mediator should be a significant predicator of the dependent variable. Furthermore, the direct effect path c' should be smaller than the total effect path c. Finally, the mediating effect can be calculated using the standardized coefficients from the abovementioned paths with the formula: ((c – c')/c) x 100%.

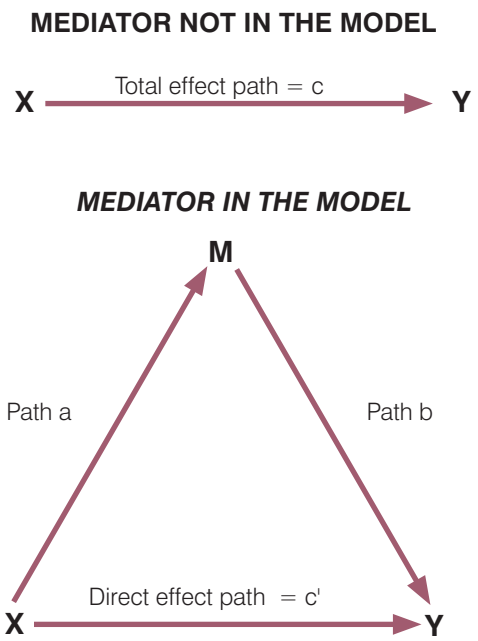


Figure 4.2: model to assess mediation described by Baron and Kenny [119]. M: TMD pain screener, X usual care group versus usual care with adjuvant orofacial treatment group. Y: change in TFI score.

4.3.1.6 Outcome measures

The TFI was used to evaluate the effect of the treatment on tinnitus severity. The TFI consists of 25 questions covering eight domains; intrusiveness, sense of control, cognitive complaints, sleep disturbance, auditory difficulties, relaxation, quality of life and emotional distress. Each question is scored on a Likert scale from zero to ten in which the higher scores indicate higher levels of negative impact of tinnitus. A reduction of 13 points or more has been indicated as a clinically relevant improvement [112]. The internal consistency of the Dutch version of the TFI is high with a Cronbach's alpha value of 0.96 [146] and the test-retest reliability of the TFI is good (r=0.78)[112].

Reduction of TMD pain was chosen as the potential mediator in this study. To objectify this reduction, the TMD pain screener questionnaire is used. This questionnaire is designed to detect symptoms of painful TMD. The TMD pain screener consists of 6 items regarding pain or stiffness in the orofacial

region and during functioning, e.g. opening the mouth or chewing. The score is determined by summing the number of items that are present. Consequently, the total score of this questionnaire ranges from 0 to 7, with higher scores indicating more pain. For the mediation analysis, we considered a decrease of one point as a true decrease in TMD pain, since a decrease of one point reflects one movement that is no longer painful.

4.3.1.7 Statistics

Before the actual mediation analysis, the normality of the data was investigated using a Kolmogorov-Smirnov test. Descriptive statistics were used to describe baseline characteristics of the patients and to assess baseline comparability of both groups ($p > 0.05$). For these analyses, an independent samples-t-test was used for the normally distributed data, the Mann-Whitney U-test for the non-normally distributed data and the Chi-square test to calculate differences between dichotomous variables.

Then, the change in the TFI scores (Δ TFI) from baseline to week 9 was calculated. With this new variable we were able to compare the evolution of the TFI scores between both groups. Next, the change in TMD pain screener scores from baseline to week 9 was calculated. This new variable was then dichotomized into 0 for patients showing no change or an increase in TMD pain screener score and 1 for patients who decreased at least 1 point on the TMD pain screener.

The mediation analysis started with a linear regression analysis that was performed to calculate the effect of orofacial treatment on the outcome, being Δ TFI. In this analysis the independent variable X (indicating the assigned group) has to be significantly related to the dependent variable Y (ΔTFI). In figure 1 this analysis is referred to as path c. Second, a logistic regression analysis was performed to calculate the effect of the independent variable X on the mediator M (the dichotomous change-score on the TMD pain screener (ΔTMD)), which is referred to as path a. Finally, a linear regression analysis was performed to calculate the effect of both mediator M and independent variable X on the dependent variable Y. This analysis calculates both path b and path c'. The mediator had to be significantly related to the Δ TFI (path b). Additionally, in this linear regression the effect of path c' had to be smaller than the total effect path c. The mediation effect was estimated by the product-of-coefficients method (path a times path b).

Finally, the mediating effect was calculated using the standardized coefficients from the abovementioned analyses using the following formula: $((c - c')/c) \times 100\%$ [119, 145]. For the analysis we used SPSS Statistics, version 26.

In a prior study we found that age, gender and duration of the tinnitus are prognostic indicators for a positive effect of orofacial treatment on tinnitus severity (measured on TFI) [146]. To investigate if the TMD change score remains a significant mediating factor when accounting for these predicting factors, we performed three multiple regression analyses with Δ TFI as the dependent variable,

ΔTMD as the fixed independent variable and age, gender or duration of tinnitus as an additional independent variables In this way, standardized beta coefficients and p-values were determined and the influence of the predicting factors was analyzed.

4.4 RESULTS

The results of the regression analysis with the standardized Beta coefficients are shown in figure 4.3 and table 4.2.

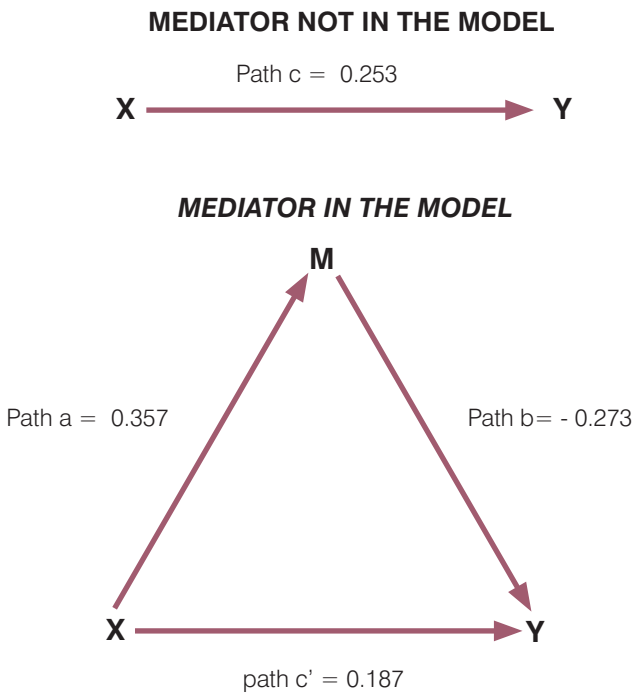


Figure 4.3: The results of the regression analysis with their standardized Beta coefficients.

Table 4.2: Mediation analyses: results of the linear and logistic regression analyses

Path/ regression model	Dependent variable	Independent variable	Regression coefficient (B) *	R-square	p-value	Odds Ratio	95% confidence interval for B or OR	Calculation of the proportion of the mediated effect
Path c, linear	Δ TFI	Control group versus orofacial treatment group	0.253	0.064	0.025		1.265 – 18.576	
Path a, logistic	Δ TMD-pain	Control group versus orofacial treatment group			0.034	2.800	1.1081 – 7.251	
Path b, linear	Δ TFI	Δ TMD-pain	-0.273	0.134	0.016		-19.875 – -2.2119	(c – c') / c x 100% = (0.253 – 0.187)/ 0.253 x 100% = 35%
Path c', linear	Δ TFI	Control group versus orofacial treatment group	0.187	0.134	0.096		- 1.325 – 15.957	

*Based on standardized coefficients

Abbreviations: TFI: tinnitus functional index Δ TFI: change in the TFI scores ΔTMD: dichotomous change-score on the TMD pain screener

The mediation analysis showed a significant total effect (path c) of orofacial treatment compared to control on the Δ TFI (B = 0.253 p = 0.025 CI for B = 1.265 – 18.576), indicating that patients who received the orofacial treatment improved more on TFI than patients who did not receive the treatment. Orofacial treatment was also significantly related to the Δ TMD (path a) (Exp (B) = 2.800 p = 0.034 CI for Exp B 1.081 – 7.251), indicating that the treated patients are more likely to show a decrease in TMD pain. Δ TMD in turn was also significantly related to the ΔTFI (path b) (B = - 0.273 p = 0.016 CI for B = -19.875 - -2.119), indicating that patients who showed a decrease in TMD pain were more likely to also show a decrease in tinnitus severity. The fact that both path a and path b were significantly related means that Δ TMD mediates the relationship between the orofacial treatment compared to control and ΔTFI .To calculate the mediating effect, the direct effect (path c') (B = 0.187 p = 0.096 CI for B = -1.325 – 15.957) was smaller than the total effect, as required for the last step. The proportion of the mediated effect was (c – c') / c x 100% = (0.253 – 0.187)/ 0.253 x 100% = 35%, which means that 35% of the decrease in TFI score after orofacial treatment is explained by the reduction in TMD pain.

Afterwards, we investigated whether the ΔTMD remains a significant mediating factor when adding each one of our prognostic indicators. The three factors: age (B = 0.189 p = 0.079), gender (B

= 0.208 p = 0.069) and duration of the tinnitus (B = 0.144 p = 0.192) did not have a significant influence on the mediator Δ TMD. This indicates that, regardless the patient's age, gender or duration of the tinnitus, a reduction in TMD pain after orofacial treatment still results in a decrease of tinnitus severity.

4.5 DISCUSSION

The aim of our study was to investigate to what extent a decrease in TMD pain contributes to the overall reduction of tinnitus severity in patients with temporomandibular related ST. Mediation analyses revealed that 35% of the decrease in tinnitus severity can be solely attributed to the reduction in TMD pain. This percentage is similar to other mediation analyses on cognitive behavioral therapy in tinnitus patients [147], but higher than what was expected based on a previous physical therapy study in headache [145].

Our results indicate that more than one third of the decrease in tinnitus severity after orofacial treatment is explained by the reduction in TMD pain, but the remaining 65% is yet to explain. A part of this 65% might be contributed to the additional effects of the temporomandibular counseling and exercises, apart from the pain reduction. Currently, TMDs are considered to have a multifactorial aetiology with both local and systemic factors playing a role [148, 149]. One of the systemic factors that seems to be associated with TMD, is the dysregulation of the hypothalamic-pituitary-adrenal axis [149, 150]. Since this dysregulation is often due to prolonged stress, reducing a patient's stress is an important part of orofacial treatment [65]. Therefore, relaxation exercises, mindfulness training or other exercises to decrease stress levels are frequently used in orofacial treatment. It must be noted, that not only TMD patients, but also tinnitus patients have been demonstrated to show signs of impaired stress responsivity via inhibited hypothalamic-pituitary-adrenal axis activation [151-153]. So similar exercises, to reduce stress levels, are also successfully used in tinnitus treatment [31, 154]. Therefore, the orofacial treatment techniques, primarily aiming to decrease TMD pain, probably also directly decrease the tinnitus severity by decreasing the patient's stress levels. Future studies are needed to investigate the proportion of the mediating effect of this stress reduction in tinnitus improvement after orofacial treatment.

In the current study, we only analyzed the mediating effect of one parameter, being the reduction in TMD pain. Adding more potential mediators would have been too time consuming for the participants in our study, due to the design of the RCT and would have largely increased the number of drop-outs. Although the analysis answers our research question, it remains a limitation of our study, because the complex aethiology of both tinnitus and TMD may lead to the assumption of a complex working mechanism. Future studies should focus on investigating the mediating effect of changes in other temporomandibular outcome measures, such as increase in mouth opening. Additionally, other parameters, such as stress reduction can be added to the analysis.

Using the TMD pain screener as a potential mediator showed us one downside. At baseline, 15 % of the patients of the orofacial treatment group and 7.5% of the patients of the control group had a TMD pain screener of 0 points. This means that those patients had no TMD pain, but were only diagnosed with orofacial parafunctions, such as bruxism. Patients already scoring 0 points at baseline can evidently not decrease another point, although their parafunctions might have decreased after treatment. This might have caused an underestimation of the mediating effect of reduction in TMD pain on improvement in tinnitus severity.

For our mediation analysis, we used a decrease of one point on the TMD pain screener questionnaire as a potential mediator. It must be noted however, that this questionnaire is primarily designed as a diagnostic tool for painful TMD. In the absence of an evaluative instrument to measure changes in TMD after treatment, we used the change in TMD pain screener score to get an indication of decrease in TMD pain. The rationale was that a decrease of one point on the questionnaire matches at least one activity that is not painful anymore after treatment and thus reflects an improvement of the TMD complaints. Future studies though, should investigate the responsiveness of the TMD pain screener for evaluating changes in TMD after treatment and a cut-off point for clinically relevant improvement should be calculated.

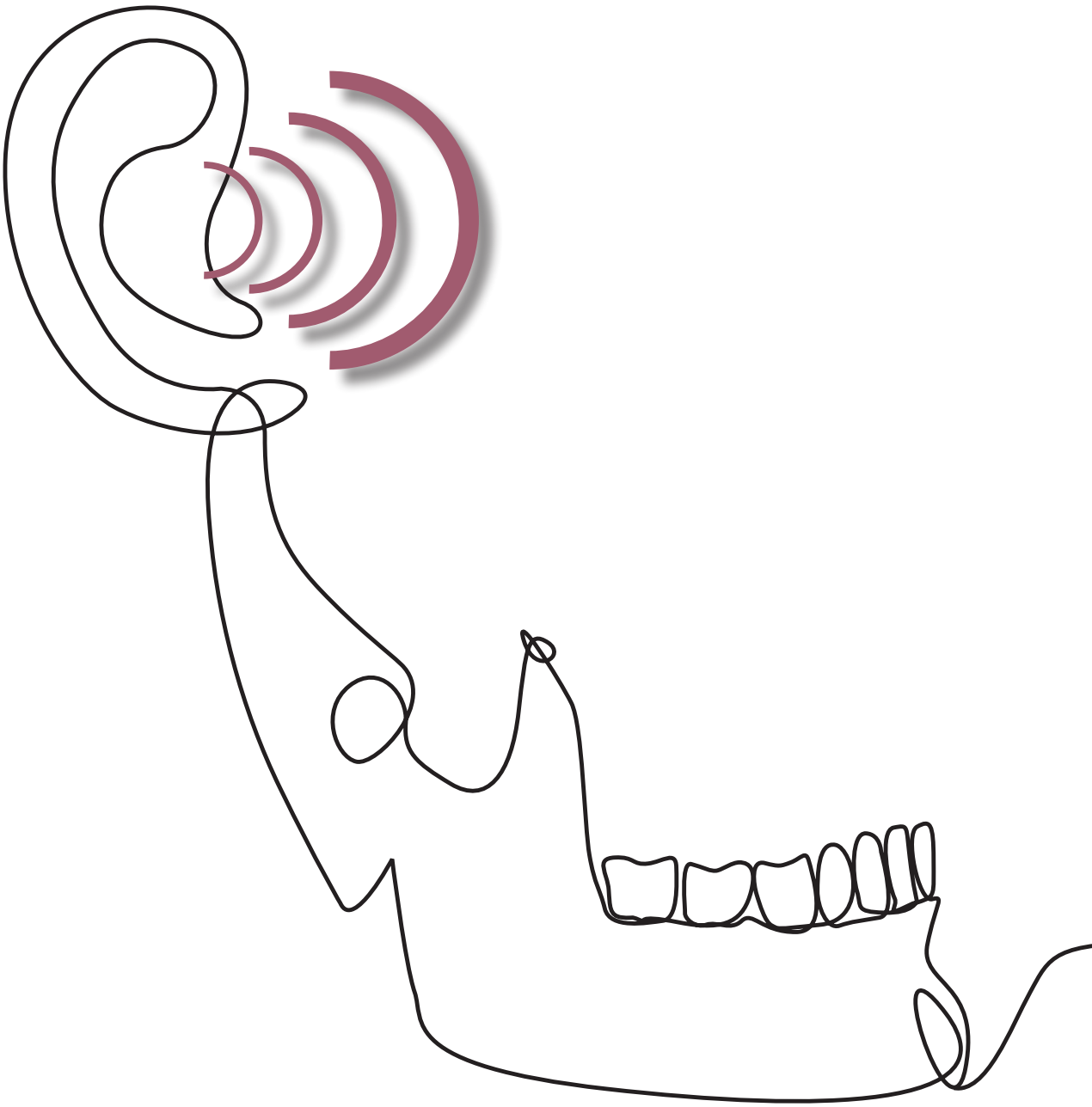
Since we know that reduction in TMD pain actually has a mediating effect on perceived tinnitus improvement after multidisciplinary orofacial treatment, it is important that patients with temporomandibular related somatic tinnitus can receive this type of treatment in routine clinical setting. Currently, the most common treatments for tinnitus are cognitive behavior therapy and tinnitus retraining therapy. These therapies do influence the psychological factors (thoughts and beliefs of the patient regarding their tinnitus), however, do not treat the TMD pain. In addition, a combination of cognitive behavior therapy and tinnitus retraining therapy might even be more effective than multidisciplinary orofacial treatment alone for this specific group of patients.

4.6 CONCLUSIONS

In conclusion, reduction of TMD pain after multidisciplinary orofacial treatment explains 35% of the decrease in tinnitus severity in patients with somatic tinnitus attributed to the temporomandibular area. Future studies are needed to confirm these results and to explain the remaining 65% improvement.

PART 2:

PROGNOSTIC INDICATORS FOR A POSITIVE TREATMENT OUTCOME



Chapter 5

Prognostic indicators for positive treatment outcome after multidisciplinary orofacial treatment in patients with somatosensory tinnitus

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5.1 ABSTRACT

Introduction

Subjective tinnitus that is influenced by the somatosensory system, is called somatosensory tinnitus (ST). When ST is related to the temporomandibular area, multidisciplinary orofacial treatment can reduce tinnitus severity. It is however unknown if we can predict this positive outcome. The aim of this study is to look for prognostic indicators that can predict a positive outcome after multidisciplinary orofacial treatment in patients with ST.

Methods

Patients were included when they were diagnosed with temporomandibular related ST and received a maximum of 18 sessions of orofacial treatment during a 9-week program. Predictors for positive treatment outcome were identified using univariate and multiple logistic regression analyses with the Tinnitus Questionnaire (TQ) and the Tinnitus Functional Index (TFI) as dependent variable.

Results

The results of 101 patients were included in the analysis. Immediately after multidisciplinary orofacial treatment, a clinically relevant decrease in TQ-score was significantly associated with 'shorter duration of the tinnitus' (OR 0.99), 'higher initial score on the TQ somatic subscale' (OR 1.52) and 'painful palpation of the temporomandibular joint (TMJ)' (OR 2.46). After 9 weeks follow-up, the 'higher initial score on the TQ somatic subscale' remained as the sole predictor (OR 1.44). A clinically relevant decrease on TFI after 9-weeks follow-up, was predicted by 'female gender' (OR 2.70), 'younger age' (OR 0.96), 'shorter duration of the tinnitus' (OR 0.99), 'lower pressure pain thresholds (PPT) on TMJ' (OR 0.99), 'lower PPT on sternocleidomastoid origin' (OR 0.99) and 'better speech in noise perception' (OR 0.88).

A multivariate model comprising 'shorter duration of the tinnitus' and 'higher initial score on the somatic subscale of the TQ' correctly predicts the clinically relevant decrease in TQ-score after treatment in 68.5%. A second multivariate model comprising 'female gender', 'younger age' and 'shorter duration of the tinnitus' correctly predicts a clinically significant decrease on TFI after follow-up in 68.1%.

Conclusion

We were able to identify various prognostic indicators. 'Younger female patients' with a 'shorter duration of the tinnitus' and a 'higher initial score on the TQ somatic subscale', appear to have the best prognosis after multimodal orofacial therapy.

Keywords

innitus; temporomandibular disorders; prognosis; somatic; treatment

5.2 INTRODUCTION

Tinnitus or ringing in the ears is a common symptom that can have many different aetiologies. It occurs in 10 to 15% [8] of the adult population and is often related to hearing loss or a noise trauma. Cochlear abnormalities are considered to be the initial cause, followed by neural changes in the central auditory system that maintain the tinnitus [8]. In many patients, the perception of tinnitus is not constant and can vary [155]. This fluctuation of tinnitus can depend on various factors, such as stress [156], emotional state [157], anxiety [158], depression [158], cervical spine dysfunction [92] and temporomandibular disorders (TMD) [96]. In these last two cases, tinnitus is called somatosensory (or somatic) tinnitus (ST) which is present in 12 to 43% of the patients with subjective tinnitus [54, 92]. A physiological explanation for ST can be found in animal studies where connecting fibers between the dorsal cochlear nucleus (DCN) and the somatosensory nuclei are found [99]. Through these fibers, altered cervical and temporomandibular somatosensory afference can increase the spontaneous firing rates of the DCN, causing tinnitus or altering an existing tinnitus [45-48]. Thus, tinnitus can be evoked or modulated by inputs from the somatosensory system through increased muscle tension in the masticatory muscles or the muscles of the cervical spine or pressure on myofascial trigger points [51, 128]. This mechanism explains the larger prevalence of tinnitus in patients with temporomandibular disorders (TMD) (30.4% to 64% [58, 95]) compared to the general population.

As suggested by these pathophysiological models, studies investigating the effect of orofacial treatment show positive results on tinnitus severity, loudness and annoyance [80-82, 85, 140]. Our recently published RCT showed a clinically relevant improvement, after multidisciplinary orofacial treatment, of the tinnitus severity in 61% and of tinnitus annoyance in 46% of the temporomandibular related ST patients [140]. This is in accordance with previous studies [80, 81], but does not provide information on predicting factors for an individual outcome in a clinical environment. If prognostic indicators, i.e. factors that can predict treatment outcome, could be identified, the clinical success rates would dramatically improve and unnecessary treatments could be avoided.

This study therefore, aims to identify prognostic indicators that predict a positive outcome after multidisciplinary orofacial treatment in patients with temporomandibular related somatic tinnitus.

5.3 METHODS

5.3.1 Patients

Patients were recruited from the tinnitus clinic of the Antwerp University Hospital (UZA, Edegem) in Belgium. For this study, we used data collected for a RCT (80 patients) investigating the effect of multidisciplinary orofacial treatment. These data were complemented with an additional cohort of 21 patients to increase the power of our analysis [136, 140]. The patients in the cohort met the same

inclusion criteria and received the same treatment as the patients from the RCT. The only difference was that there was no randomization.

Before inclusion in the study, patients got a thorough assessment by a multidisciplinary team of otolaryngologists, dentists, physical therapists and audiologists to identify influencing factors of their tinnitus and to exclude any objective causes[28]. Only adult patients (≥ 18 years) were included in the study. All patients were suffering from moderate to severe chronic subjective tinnitus, attributed to the temporomandibular area, that had been stable for at least three months. Moderate to severe tinnitus was defined as a Tinnitus Functional Index (TFI) score between 25 and 90 (2). Apart from the tinnitus, patients had to have a painful TMD, diagnosed according to the Diagnostic Criteria for TMD (DC-TMD), [61] and/or oral parafunctions.

Patients suffering from clear otological or neurological causes of the tinnitus such as Meniere's disease, progressive middle ear pathology or intracranial pathology, were excluded from the study. Likewise, patients with severe depression or anxiety disorders, diagnosed by a psychiatrist, traumatic cervical spine or temporomandibular injury in the past 6 months, tumours or previous surgery in the orofacial area, were excluded. Patients who received orofacial treatment in the past three months were excluded as well.

5.3.2 Intervention

Patients received a maximum of 18 sessions of orofacial physical therapy during a 9-week program. This treatment consisted of counselling regarding mouth habit reversal, bruxism, sleep hygiene, lifestyle advice and biofeedback; massage of the masticatory muscles; stretching exercises and relaxation therapy. In case of grinding, the orofacial physical therapy was complemented with an occlusal splint. In case the patient also suffered from cervical spine dysfunctions (as detected during clinical examination at baseline), additional cervical spine treatment (mobilisations and exercises) were added by the physiotherapist. This type of multidisciplinary orofacial treatment is currently the evidence-based treatment for the conservative management of TMD [61, 74].

5.3.3 Outcome measures

5.3.3. 1 Tinnitus assessment

The effectiveness of the treatment was measured using the Tinnitus Questionnaire (TQ) and the Tinnitus Functional Index (TFI).

The 52 questions of the Tinnitus Questionnaire (TQ) [109] assess tinnitus annoyance, covering five tinnitus domains (emotional and cognitive distress, intrusiveness, auditory difficulties, sleep, and somatic complaints). The somatic subscale consists of the following three questions: (1) The noises sometimes give me a pain in the ear or head, (2) Because of the noises I have tension in the muscles of my head and neck and (3) The noises sometimes produce a bad headache. For each question, the level of agreement should be given on a three-point scale ranging from "true" (scoring 0), over

"partly true" (scoring 1), to "not true" (scoring 2). Since two items must be counted double and 12 out of 52 items are excluded from the scoring, the total score ranges from 0 to 84, with higher scores indicating higher levels of annoyance. A decrease of 8.72 points on the TQ is considered clinically relevant [110]. The TQ showed a good correlation with the Tinnitus Handicap Inventory, Tinnitus Impairment Questionnaire and Tinnitus Functional Index (0.79 – 0.90) [110, 137].

Apart from the use as dependent variable, the 'somatic subscale' of the TQ was used as a potential prognostic indicator.

Tinnitus Functional Index (TFI) was used to measure change in tinnitus severity (Meikle et al., 2012; Rabau et al., 2014) and consists of 25 questions covering eight tinnitus domains (intrusiveness, sense of control, cognitive interference, sleep, auditory difficulties, relaxation, quality of life and emotional distress). Questions are answered on an 11-point Likert scale (i.e. from 'no disturbance' to 'maximal disturbance'), with higher scores indicating higher severity levels. A reduction of 13 points is considered clinically relevant [112]. The test-retest reliability of the TFI is good ($r = 0.86$) and the convergent validity with the Tinnitus Handicap Inventory ($r = 0.86$) and Visual Analogue Scale (VAS) ($r = 0.75$) is good [112, 159].

5.3.4 Potential prognostic indicators

Below, the potential prognostic indicators we used in our analyses are clustered into medical history related items, TMJ related items and audiological items. All included potential prognostic indicators were selected based on existing knowledge about potential influence on the outcome after treatment. More information can be found in the RCT paper and the study protocol [136, 140].

5.3.4.1 Medical history

At baseline, age, gender and duration of the tinnitus were inventoried, apart from a specific set of ST-related questions (Table 5.1). These specific questions are related to the diagnostic criteria for ST [131] and it is generally accepted that the more criteria present, the stronger the somatic influence on the tinnitus will be. Because we expect patients with a stronger somatic influence on their tinnitus to have a larger treatment effect, we included these questions as potential prognostic indicators

Next, the scores of three questionnaires were added as potential prognostic indicators.

The Hospital Anxiety and Depression Scale (HADS) was added to identify the presence of anxiety and depression [113, 141]. The presence of anxiety or depression was selected, because these conditions strongly affect the tinnitus severity and annoyance and can negatively influence the outcome after treatment.

The HADS is specifically developed for patients in non-psychiatric hospital clinics and contains two subscales, an Anxiety subscale (HADS-A) and a Depression subscale (HADS-D). Each subscale

contains 7 questions that are answered on a four point (0–3) scale. The scores range from 0 to 21 [113, 141, 144]. A score greater than or equal to 11 indicates the potential presence of an anxiety or depression disorder. The HADS has been found to be reliable as a first indication of a depression or anxiety disorder in somatic, psychiatric and primary care [114].

Table 5.1: Potential prognostic indicators from medical history.

Medical history
Age in years
Gender: male/female
Duration of the tinnitus in months
HADS score
NBQ score
Specific anamnestic questions:
• Modulation of the tinnitus with movements of or pressure on the neck or jaw
• Modulation of the tinnitus by clenching the teeth
• Modulation of the tinnitus during specific postures or movements
• Tinnitus modulation with stress
• Tinnitus modulation with noise exposure
• Simultaneous increase of pain in neck or jaw and tinnitus
• Temporal coincidence of the onset of pain complaints in the jaw and tinnitus
• Grinding of the teeth during the day or night
• Clenching of the teeth during the day or night
• Temporal headache related to TMD

HADS: Hospital Anxiety and Depression Scale. NBQ: Neck Bournemouth Questionnaire.

Additionally, the presence of hyperacusis, objectified using the Hyperacusis Questionnaire (HQ) [115], was included. As the presence of hyperacusis, in addition to the tinnitus, might negatively influence the outcome after treatment. Hyperacusis and tinnitus complaints are highly intertwined and patients whose tinnitus complaints improve, might not always notice this improvement when their hyperacusis remains unchanged [160].

Q consists of 14 questions answered on a 4-point scale from: ‘No’ (scoring 0 points), ‘Yes, a little’ (scoring 1 point) and ‘Yes, quite a lot’ (scoring 2 points) to ‘Yes, a lot’ (scoring 3 points). Total scores on the HQ range from 0 to 42 and a score from 28 points upwards indicates the presence of hyperacusis.

The presence of neck complaints, identified as a score of 13 points or more on the Neck Bournemouth Questionnaire (NBQ), was added because these neck complaints can influence the temporomandibular complaints or the tinnitus directly.

The NBQ is used to assess self-reported pain intensity, limitations in activities of daily living, depression and self-control. The test-retest reliability of the NBQ is moderate (ICC 0.65) an the construct validity with the Neck Disability Index is acceptable (r 0.50) [161].

5.3.4.2Temporomandibular assessment

Apart from the potential prognostic indicators retrieved from medical history, a set of baseline TMD tests were added to investigate the importance of the degree or nature of the TMD in the prediction of positive treatment outcome. An overview of the assessment is presented in table 5.2.

Firstly, the TMD pain screener was completed as an indication for the presence of painful TMD. The TMD pain screener consists of 6 questions and total scores range between 0 and 7. Scores of 3 points or more, are suspected to have a painful TMD based on the Diagnostic Criteria/TMD (DC/TMD)[61]. The TMD pain screener has excellent sensitivity and specificity (0.99 and 0.95-0.98) to detect painful TMD and the reliability is good (intraclass correlation coefficient 0.79).

Secondly, an orofacial assessment was performed according to the standardised protocol of the DC/TMD [61]. This assessment comprises the measurement of active mouth opening (including questioning of any pain sensation), tenderness on palpation of the jaw muscles and temporomandibular joint and pain provocation during static and dynamic movements. Based on the DC/TMD protocol, the assessor was able to diagnose the presence of TMD and give an indication if this TMD was mostly articular, mainly muscular or combined articular and muscular in origin.

Lastly, pressure pain thresholds (PPT's) were measured using a hand held algometer (Somedic AB, farsta, Sweden). These measurements were added because they give us an indication on the presence of central sensitization of the patient's TMD pain complaints [162, 163]. Patients showing clear central sensitization are known to react less to the orofacial treatment we used is this study, what might negatively influence the prognosis.

PPT's were measured on the following locations: the anterior portion of the temporalis muscle, the muscle belly of the masseter, the insertion of the sternocleidomastoid muscle (on the mastoid process), the lateral pole of the temporomandibular condyl and on the muscle belly of the tibialis anterior muscle. The patients were instructed to indicate the exact moment the sensation changed from pressure to pain. The test was repeated three times with a 1-minute rest between the tests and average values were calculated for each area [164].

Table 5.2: Potential prognostic indicators from the temporomandibular assessment.

Temporomandibular assessment
TMD pain screener questionnaire [106]
Orofacial assessment: • Measurement of active mouth opening (including questioning of any pain sensation) according to the DC/TMD [61] • Tenderness on palpation of the jaw muscles and temporomandibular joint according to the DC/TMD [61] • Pain provocation testing during static and dynamic movements described by Visscher[165] • Diagnosis of arthralgia or myalgia according to the DC/TMD [61]
Mean pressure pain threshold described by Visscher [164]: • on the anterior portion of the temporalis muscle • on the muscle belly of the masseter • on the insertion of the sternocleidomastoid muscle (just below the mastoid process) • on the lateral pole of the temporomandibular condyl • on the muscle belly of the tibialis anterior muscle (7 cm below the tibial tuberosity)

TMD: Temporomandibular Disorders. DC/TMD: Diagnostic Criteria for Temporomandibular Disorders.

5.3.4.3 Audiological assessment

Potential prognostic indicators from the audiological assessment are presented in table 5.3.

As a first item, hearing loss was added because hearing loss is in many patients the major cause for their tinnitus. The presence of (severe) hearing loss might therefore negatively influence the outcome after treatment. Hearing loss was objectified using pure tone audiometry. Air conduction thresholds were measured at 125 Hz, 250Hz, 500Hz, 1kHz, 2 kHz, 3kHz 4 kHz, 6 kHz and 8 kHz according to the current clinical standards (ISO 8253-1, 1989). Based on these results, the Fletcher Index low was calculated as the mean of the pure tones at 500 Hz, 1kHz and 2 kHz.

Secondly, speech in noise tests were added because, even in patients without hearing loss, speech perception in noise is often decreased in patients with tinnitus. The presence of these speech perception problems might negatively influence the outcome after treatment, especially if this treatment is not directed to influence the patients' hearing.

The Leuven Intelligibility Sentence Test (LIST)[117], a Dutch sentence test, was used. The LIST consists of 35 lists of 10 sentences that are a reflection of daily communication and are of equivalent difficulty. An adaptive procedure is used with the noise at a fixed level of 65 dB SPL. The procedure starts at a signal-to-noise ratio (SNR) of 0 dB meaning that speech and noise are presented equally loud (65 dB SPL). Subsequently, the intensity level within a list of sentences is varied in steps of 2 dB adaptively in a 1-down (when the keywords in the sentence are correctly repeated), 1-up (when the keywords in the sentence are incorrectly repeated) procedure to determine the 50% correct

identification point which is called the speech reception threshold (SRT), expressed in dB SNR. Before starting the actual procedure, one list will be performed as a training list.

Finally, we added psychoacoustic tinnitus properties because previous research showed that patients with a low pitched somatic tinnitus were more likely to benefit from cervical spine treatment [126]. The audiologist measured the type of tinnitus, tinnitus pitch and tinnitus loudness. For identifying the type of tinnitus, the patient was asked whether he/she perceived a pulsatile or non-pulsatile tinnitus, whether the tinnitus was present constantly or intermittent and whether the tinnitus sound is a pure tone, a noise or polyphonic (a mixture of different sounds). The tinnitus pitch measurement is a technique where the audiologist identifies the pitch of the tinnitus by presenting a set of pure tones or noises (depending on the type of tinnitus) to the patient. This procedure is repeated until the exact match is obtained. Finally, tinnitus loudness matching is performed.

Table 5.3: Potential prognostic indicators from the audiological assessment

Audiological assessment
Pure tone audiometry: Fletcher index low according to the current clinical standards (ISO 8253-1, 1989)
Speech reception threshold (SRT) in noise, using the Leuven Intelligibility Sentence Test (LIST) [117]
Psychoacoustic tinnitus analyses described in our study protocol [136]: • Type of tinnitus (e.g. pure tone, noise) • Tinnitus pitch • Tinnitus loudness (expressed in dB SL)

5.3.4 Statistics

The relationship between the presence of a clinically relevant reduction on TQ and TFI after orofacial treatment and potential prognostic indicators was evaluated using binary logistic regression analyses.

Before the actual analysis, the normality of the data was assessed using the Kolmogorov-Smirnov test. Second, correlations between potential prognostic indicators and the clinical outcome on TQ and TFI were calculated using Pearson or Spearman correlation coefficients, depending on the normality of the data. Potential prognostic indicators that correlated significantly ($p < 0.10$) with the clinical outcome, where included in the logistic regression analysis. Significance levels were chosen to allow a broad screening for potential prognostic indicators, as suggested by Hicks et al. [166]. Correlation coefficients were additionally used to avoid multicollinearity and shared variance ($r > 0.80$) between the different potential prognostic indicators.

Then, a univariate logistic regression analysis was performed. As dependent variable, the dichotomous variables of clinically relevant reduction on TQ and TFI were used (obtained yes/no). These variables were computed based on a decrease of 8.72 points for the TQ and 13 points for the TFI [110, 112]. In total, four different variables were used as a dependent variable: clinically relevant

reduction described as a decrease of 8.72 on the TQ scale immediately after treatment and after 9 weeks follow-up and a clinically relevant reduction described as a decrease of 13 points on the TFI immediately after treatment and after 9 weeks follow-up. As potential prognostic indicators, the characteristics described in tables 1 to 3 that correlated significantly with the dependent variable ($p < 0.10$), were used. Odds ratio's, 95% confidence intervals and p-values were calculated for every potential prognostic indicator.

Afterwards, a multivariate model for the prediction of a clinically relevant improvement on TQ and TFI was created using multivariate logistic regression analyses. For these analyses, only the strongest prognostic indicators ($p < 0.10$) from the univariate analyses were retained. In case of multicollinearity or shared variance between two or more indicators, only the strongest indicator was entered in the multivariate logistic regression analysis.

5.4 RESULTS

In total, data from 101 patients were included in the analysis. All patients suffered from a moderate to severe tinnitus with an average TQ-score of 38 points (SD 16) and an average TFI-score of 53 points (SD 17). Most patients (81.2%) were diagnosed with myalgia and 24.8% of the patients had both myalgia and arthralgia according to the DC-TMD [61]. In total, 35.6% of the patients had hearing loss, using the pure tone audiometry as main hearing test to determine if the patient's hearing levels fall within normal limits according to age. In addition to the physical therapy treatment, 54% of the patients received an occlusal splint (48% female/ 52% male). An overview of the patient characteristics is summarized in table 5.4.

5.4.1 Prognostic indicators

Table 5.5 shows the statistically significant prognostic indicators for a clinically relevant reduction in TQ-score after treatment and after 9 weeks follow-up.

Table 5.6 shows the statistically significant prognostic indicators for a clinically relevant reduction in TFI-score after 9-weeks follow up. No statistically significant associations were found for clinically relevant improvement immediately after treatment.

The multivariate logistic regression analysis, based on the clinically relevant change in TQ-score after treatment, created a model comprizing two characteristics: 'duration of the tinnitus' and 'a higher initial score on the TQ somatic subscale'. This model correctly predics the outcome on TQ in 68.5% (table 5.7).

Table 5.4: Patients characteristics at baseline (n = 101)

Characteristic	Mean and Standard Deviation
Age (SD)	47 years (14)
Gender: % female/male	49%/51%
Mean duration of the tinnitus	64 months (89)
% subacute tinnitus (3-6 months)	25.7%
% chronic tinnitus (> 6 months)	74.3%
TFI-score (SD)	53 (17)
TQ-score (SD)	38 (16)
VAS mean loudness left ear (SD)	48 (29)
VAS mean loudness right ear (SD)	51 (29)
Hyperacusis Questionnaire	18 (8)
% HQ score ≥ 28	12.9%
% HQ score < 28	87.1%
HADS (anxiety) (SD)	9 (4)
HADS (depression) (SD)	6 (5)
% diagnosed with TMD myalgia	81.2%
% diagnosed with TMD arthralgia	23.8%
% diagnosed with both myalgia and arthralgia	24.8%
% with bruxism	91%
TMD pain screener (% < 3 / % ≥ 3)	41%/59%
NBQ (SD)	23 (14)
% with hearing loss	35.6%
Fletcher index low left	12 (15)
Fletcher index low right	11 (12)
Tinnitus Loudness dBHL left	32 dB (21)
Tinnitus Loudness dBHL right	29 dB (20)
Tinnitus Loudenss dBSL left	8 dB (9)
Tinnitus Loudness dBSL right	9 dB (13)
Mean SPIN (signal to noice ratio)	-3 (5)

SD: Standard Deviation.TFI: Tinnitus Functional Index. TQ: Tinnitus Questionnaire. VAS mean loudness: Visual Analogue Scale. HADS: Hospital Anxiety and Depression Scale. TMD: Temporomandibular Disorders. NBQ: Neck Bournemouth Questionnaire. dBHL: decibels hearing level dBSL: decibels sensation level. SPIN: Speech in noise.

Table 5.5: The statistically significant prognostic indicators of clinically relevant improvement on the Tinnitus Questionnaire.

Variable	Tinnitus Questionnaire					
	Univariate Regression analysis					
	After treatment			After 9-weeks follow-up		
	OR	95%	P	OR	95%	p
Duration of the tinnitus	0.99	0.98 – 0.99	0.03			
Somatic subscale Tinnitus Questionnaire	1.52	1.16 – 1.99	0.002	1.44	1.12 – 1.84	0.004
Palpation TMJ	2.46	1.00 – 6.04	0.05			

Table 5.6: Prognostic indicators of clinically relevant improvement on the Tinnitus Functional Index

Variable	Tinnitus Functional Index		
	Univariate Logistic Regression analysis		
	After 9 weeks follow-up		
	OR	95%	p
Female gender	2.70	1.12 – 6.21	0.02
Age	0.96	0.94 – 0.99	0.02
Duration of the tinnitus	0.99	0.98 – 0.99	0.008
Mean PPT TMJ	0.99	0.99 – 1.00	0.03
Mean PPT SCM	0.99	0.99 – 1.00	0.04
Mean SPIN	0.88	0.77 – 0.99	0.04

TMJ: Temporomandibular Joint PPT: Pain Pressure Threshold SCM: M. Sternocleidomastoideus SPIN: speech in noise.

Table 5.7: Multiple regression analyses based on the clinically relevant change in TQ-score after multidisciplinary orofacial treatment.

	Multiple regression analyses on TQ-score after treatment		
	OR	95% CI	P
Duration of the tinnitus	0.99	0.98 – 0.99	0.03
Somatic subscale Tinnitus Questionnaire	1.57	1.19 – 2.08	0.002

Additionally, the multivariate binary logistic regression analysis, based on the clinically relevant change in TFI-score after follow-up, created a model consisting of three items: 'age', 'female gender' and 'duration of the tinnitus'. This model correctly predics the outcome on TFI in 68.1% (table 5.8).

Table 5.8: Multiple regression analyses for the TFI-score at 18 weeks.

	Multiple regression analyses on TFI-score after follow- up		
	OR	95% CI	P
Age	0.96	0.93 – 0.99	0.01
Female gender	3.24	1.27 – 8.26	0.04
Duration of the tinnitus	0.99	0.98 – 0.99	0.03

5.5 DISCUSSION

The aim of this study was to identify prognostic indicators that can predict a positive outcome after multidisciplinairy orofacial treatment in patients with temporomandibular related somatic tinnitus.

We were able to identify three prognostic indicators for a positive treatment effect immediately after treatment and seven for a positive treatment effect after 9 weeks follow-up. A prognostic model with two variables was made that allowed to correctly predict a positive outcome on TQ in 68.5%. Additionally, a second prognostic model with three variables was created that correctly predicts a positive outcome on TFI in 68.1%.

The most important predictors from medical history were 'female gender' (OR 2.70) and 'a higher score on the somatic subscale of the TQ' (OR 1.52). From the temporomandibular assessment, 'painful palpation of the TMJ' (OR 2.46) was retrieved as prognostic indicator. Furthermore, a 'better score on the speech in noise test' (OR 0.88) was found to be an important prognostic indicator from audiological assessment. The clinical relevance of other significantly associated prognostic indicators is limited, because their OR's are very close to one.
The fact that patients with a higher initial score on the somatic subscale of the TQ perform better after orofacial treatment seems logical for two reasons. First, a higher somatic subscore on TQ, might be an indication that patients have more TMD complaints at baseline and greater alterations in somatosensory afference that can influence the tinnitus. Since our orofacial treatment aims to decrease TMD complaints and normalize somatosensory afference, a larger improvement can be expected in patients with more complaints at baseline. Second, a higher initial score on one subscale of the TQ gives more room for decrease in the total score after treatment, especially since our treatment aims to decrease the somatic burden. This explanation is in accordance with the most important prognostic indicator from the temporomandibular assessment. A painful palpation of the TMJ might suggest a higher somatic burden that can explain a better outcome after multidisciplinary orofacial treatment.

Shorter duration of tinnitus is a positive prognostic indicator for clinically relevant improvement on both TQ and TFI. This is in line with Ariizumi et al. 2010, who also found that subjective tinnitus patients with a shorter duration of tinnitus performed better after tinnitus retraining therapy with a

sound generator [167]. It must be noted though, that 'shorter duration of the tinnitus' only predicts a better short term outcome on TQ.

When looking at improvement on TFI, young females are more likely to benefit from orofacial treatment. This observation might be explained by the fact that TMD is more prevalent in females, also in female tinnitus patients, [53, 168-172] and our treatment might be more effective in patients with painful TMD, than in patients with oral parafunctions without pain complaints.

Additionally, patients with better SPIN scores were more likely to benefit from orofacial treatment. A good performance on the SPIN test indicates that there is no significant hearing loss. In these patients, other factors, such as TMJ dysfunctions, may have a larger influence on the tinnitus. This can explain their better performance in our study.

On the other hand, several potential prognostic indicators that were assumed to have a large influence based on previous studies, were not able predict the outcome after orofacial treatment in our study. Surprisingly, the patients ability to modulate tinnitus was not identified as a prognostic indicator. Although the ability to modulate the tinnitus is an important diagnostic criterion when combined with other criteria, the Delphi panel in 2018 [55] already warned that tinnitus modulation is not specific for somatic tinnitus. The results of our study confirm this statement, since the ability to modulate the tinnitus did not predict a positive treatment outcome.

A second item that was thought to be an important prognostic indicator is the presence of anxiety or depression symptoms. Unexpectedly, lower scores on the HADS did not predict a better outcome after treatment. This might be caused by consistent relatively high HADS scores in all our patients. These relatively high scores can be expected in our population, because anxiety and depression are not only associated with tinnitus, but also with the occurrence of temporomandibular disorders [65, 173, 174].

Additionally, our results indicate that patients, showing more severe local pain complaints in the temporomandibular area at baseline, are more likely to benefit from orofacial treatment. This predictive value of local orofacial pain perception was not associated with a difference in central pain sensitization, because PPTs on the anterior tibialis muscle did not significantly differ between the clinically improved and not clinically improved patients. This is in contrast with the current literature, which indicates that patients with central sensitization are less likely to benefit from the applied orofacial treatment [175-178].

Finally, it could be expected that the absence of hyperacusis would be a prognostic indicator for positive treatment outcome. Patients with higher scores on the hyperacusis questionnaire represent a stronger auditory hypersensitivity and might be more difficult to treat [179]. It should be specified that we only calculated with the continuous data of the hyperacusis questionnaire, because there is

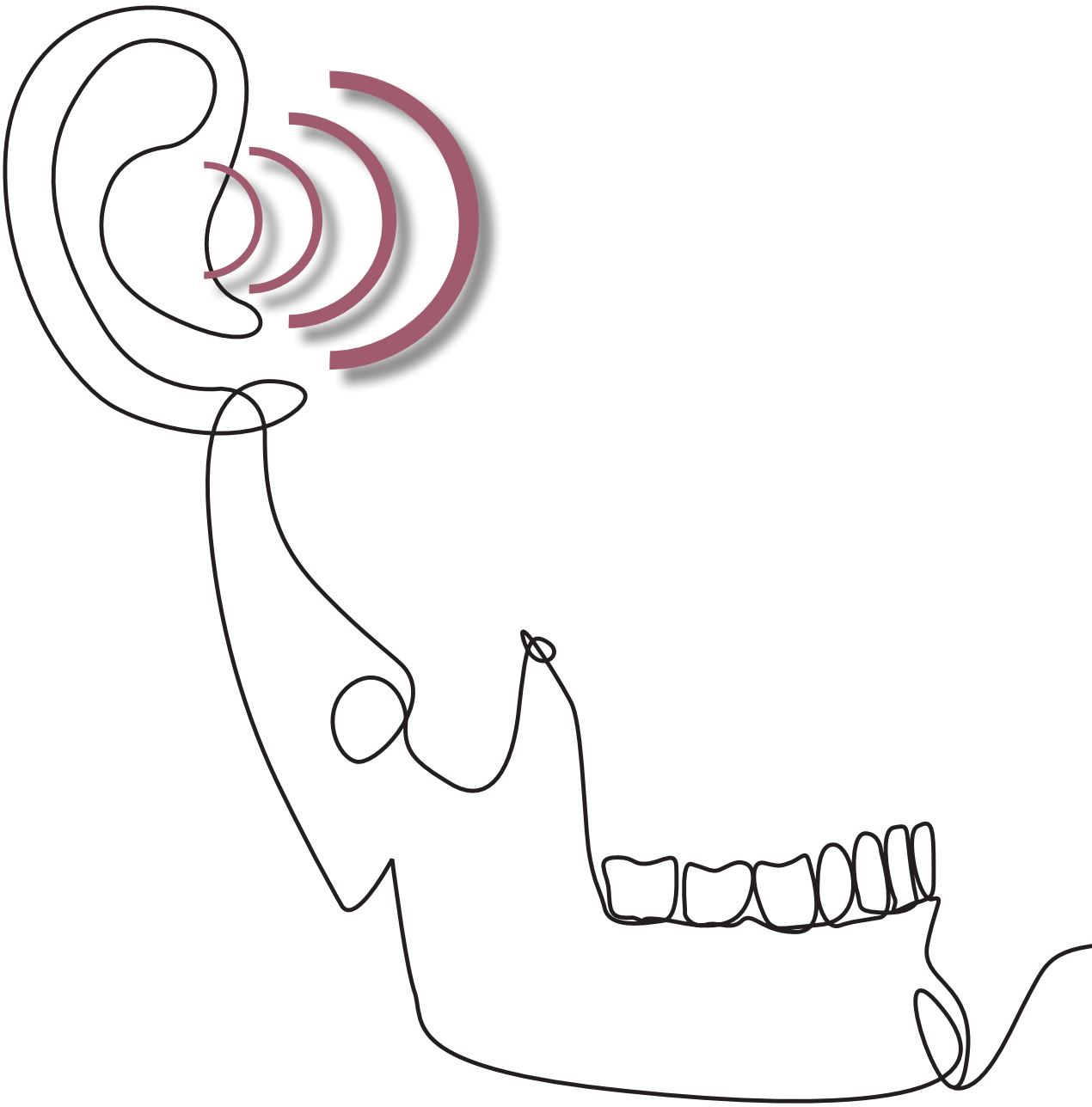
no consensus among authors what should be an appropriate cut-off for classifying hyperacusis at the moment [180, 181].

It must be noted that some of the identified prognostic indicators might secondarily be influenced by the fact that the treatment in our study was tailored to each patient's individual needs. Some patients received additional cervical spine treatment and 54% of the patients received an occlusal splint. Consistent differences in the use of splints between females and males, for instance, would be a potential explanation of the better outcome in females. After thorough post-hoc investigation though, no such consistent differences could be identified.

Based on the current analysis, we cannot be sure to what extend the changes in TMD are directly responsible for the decrease in tinnitus severity and annoyance. Other factors that are part of the orofacial treatment (for example counseling for stress reduction) may also have a direct influence on the tinnitus complaints. Future research is to investigate if there is a mediating effect of reduction in TMD pain on the improvement of tinnitus severity and annoyance.

5.6 CONCLUSIONS

We were able to identify various prognostic indicators. 'Younger female patients' with a 'shorter duration of the tinnitus' and a 'higher initial score on the TQ somatic subscale' are the most consistent indicators with the highest predictive value. The presented prognostic indicators can be used to increase the clinical success rates of orofacial treatment on tinnitus severity and annoyance, by better targeted referral. However, these results need to be confirmed in RCTs using these prognostic indicators as inclusion criteria.



Chapter 6

Sex differences in the response to different tinnitus treatment

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6.1 ABSTRACT

Introduction

Tinnitus is a complex symptom requiring a thorough multidisciplinary assessment to construct an individual's tinnitus profile. The Antwerp University Hospital hosts a tertiary tinnitus clinic providing intensive, multidisciplinary tinnitus care in the form of combinational psychological treatment with either Tinnitus Retraining Therapy (TRT)/ Cognitive Behaviour Therapy (CBT) or TRT/Eye Movement Desensitisation and Reprocessing therapy (EMDR), high-definition transcranial direct current stimulation (HDtDCS), and physical therapy treatment (in cases of somatic influence of the neck or the temporomandibular area). Several factors may contribute to therapy effect of which the role of gender has recently gained more interest. As such, the current manuscript explores gender differences in the outcome of different tinnitus treatments.

Methods

Data on treatment outcome of four distinct tinnitus treatments (1. HDtDCS; 2. Orofacial physical therapy; 3. Combination TRT + CBT and 4. Combination TRT + EMDR) were pooled and compared. Treatment outcome was assessed via the Tinnitus Functional Index (TFI). Participants completed the TFI at baseline, immediately after treatment and after 9 weeks (± 3 weeks) follow-up. To explore the effect of gender on different treatment outcomes, a linear mixed model was designed including *Time point*, *Gender* and *Therapy Group* as fixed factors as well as all interactions between these factors.

Results

TFI scores improved significantly over time regardless of therapy group ($p < 0.0001$). A mean TFI decrease of at least 13 points was obtained by all participants except by those in the HD-tDCS. Significant interactions between Gender and Time point were identified in all groups except for the TRT +EMDR group. Female subjects improved more extensively than males in the HD-tDCS ($p = 0.0009$) and orofacial therapy group ($p = 0.0299$). Contrarily, in the TRT +CBT group, male participants showed a significant improvement whereas the mean TFI scores of female subjects remained on baseline levels ($p = 0.0138$).

Conclusion

Our data suggest that male and female tinnitus patients seem to react differently to different therapy options**.** We strongly encourage further prospective studies to discern the relevance of gender in therapy outcome.

6.2 INTRODUCTION

Tinnitus, the perception of sound in the absence of an external sound source, is a frequently experienced symptom in modern society. The prevalence of tinnitus in an adult population is around 15% [182, 183]. In 2-3% of patients the tinnitus is sufficiently bothersome to affect the quality of life due to the association with anxiety, depression, sleep disorders, concentration difficulties and elevated stress levels [184]. As a consequence, many patients find their way to the clinic seeking for alleviating treatment. In the management of tinnitus, a multi-disciplinary approach is essential in order to tailor therapy towards the patient's requirements and needs. Thorough evaluation of the patient comprises a systematic history including tinnitus characteristics, potential tinnitus triggers and the evaluation of coexisting symptoms such as subjective hearing loss, otalgia, decreased speech understanding [116], vertigo and hyperacusis [28]. The presence of cervical spine dysfunction as well as bruxism or known history of temporomandibular dysfunctions should be inquired and assessed accordingly as somatosensory influences may cause tinnitus and/or increase pre-existing tinnitus loudness or alter pitch [92, 136]. In addition, the comorbidity with depression or anxiety disorders should be assessed, as emotional factors typical in these disorders are strong predictors of poor adjustment to the symptom of tinnitus [185] [186]. Following extensive anamnesis, further multidisciplinary investigations as well as imaging may be required leading towards an individual tinnitus profile guiding the patient towards the most appropriate patient-specific therapy [28].

Yearly, approximately 1500 patients consult the tertiary expertise tinnitus clinic (Tinnitus Treatment and Research centre Antwerp – TINTRA) at the Antwerp University Hospital, with tinnitus being their primary complaint. Through a multidisciplinary approach, patients receive treatment according to their tinnitus profile, underlying causes/mediators and psychological burden. For all patients, pre-therapeutic tinnitus burden is measured at baseline, post-therapy and at 9 weeks (± 3 weeks) follow-up moment using tinnitus questionnaires.

Several treatments provided at TINTRA are psychology-based focusing on altering the coping strategies in order to change emotional responses towards the tinnitus. Cognitive behavioural therapy (CBT) in particular aims to change non-constructive cognitive distortions/behaviours and develop personal coping strategies targeting the tinnitus issues. Tinnitus Retraining Therapy (TRT) on the other hand, is a habituation therapy in which directive counselling aims to reclassify the tinnitus percept to a neutral signal in combination with the use of sound therapy. Both CBT and TRT have proven to be effective in the treatment of tinnitus [29, 187-189]. Eye movement desensitization and reprocessing (EMDR) therapy is a form of psychotherapy in which the patient is enquired to recall distressing thoughts/images (i.e. associated with the tinnitus) after which the therapist directs the patient with bilateral sensory input (i.e. hand tapping, auditory stimuli or side-to-side eye movements). EMDR is a widely used technique in the treatment of post-traumatic stress disorder [190]. In the field of tinnitus a first preliminary study on EMDR was recently published showing promising results as significant improvement on tinnitus burden (measured by the Tinnitus Handicap Inventory) and

depressive symptoms (measured by the Beck Depression Inventory) was shown up until 6 months after EMDR treatment [191].

Also, transcranial direct current stimulation (tDCS) has been a topic of research at TINTRA. TDCS is a form of neuromodulation delivering a constant, low direct current to the brain through electrodes positioned on the head. Up until now, a total of 31 studies evaluated the effects of tDCS on tinnitus reporting various degrees of effect, ranging from no effect to significant tinnitus reduction. A large heterogeneity in used tDCS protocols and outcomes is apparent which constrains the comparability of these studies [192, 193]. At our department tDCS trials have shown clinically significant improvement in 32% of patients with large inter-individual variability [38].

For patients who experience a somatosensory influence on tinnitus originating in a dysfunction of the cervical spine or temporomandibular area [55, 86, 194], physiotherapy treatment is provided. Depending on the area of the dysfunction that is primarily influencing the tinnitus, the physical therapy treatment is adjusted. In case of a primary influence from the cervical spine, a multimodal manual physical therapy can be provided [126, 195]. This type of treatment showed a significant improvement on the global perceived effect in 53% of the patients in our clinic [196]. In case temporomandibular dysfunctions are primarily influencing the tinnitus, orofacial physiotherapy is provided, when needed combined with occlusal splints provided by the dentist. A recent systematic review on the topic showed promising results, although differences in treatment modalities and outcome measures make it hard to draw any definitive conclusions [197].

As the tinnitus population is highly heterogeneous, a one-therapy-fits-all approach is non-existent and many treatments may add to tinnitus alleviation depending on the patients' tinnitus profile. Due to the heterogeneity, treatment outcomes also tend to vary tremendously. Recently the role of gender on the perception of tinnitus has gathered more attention. In a study by Seydel et al. women showed more tinnitus-related distress compared to men with this effect depending on age and duration of the tinnitus [198]. These results were partially confirmed by a recent study by Han et al. [199] and some authors have mentioned gender difference in the amount of tinnitus-related distress as well [179], whereas others did not find any gender differences [200, 201]. As a result, the role of gender remains elusive. Recently, severe tinnitus was shown to be associated with an increased risk of suicide attempts in female patients only [202]. Interestingly, those patients who had been diagnosed with tinnitus in a clinical setting were no longer at risk, highlighting the need for specialty care in the tinnitus population. If males and females perceive tinnitus differently and, as a consequence, possibly show distinct reactions towards therapeutic intervention, caregivers should take these gender differences into account. The current manuscript reports on the effects of gender on the outcomes of the distinct tinnitus therapies provided at TINTRA.

6.3 METHODS

6.3.1 Study protocol

The current manuscript describes the effects of gender on tinnitus treatment outcome. Therefore, all data collected prior to treatment, post-treatment and at a follow-up visit (9 weeks ± 3 weeks) of patients who received tinnitus treatment, were analysed retrospectively. All patients had chronic, non-pulsatile, subjective tinnitus for longer than 3 months. Patients with active middle ear pathology were excluded from analysis. Pure tone audiometry was performed at baseline using a 2-channel Interacoustics AC-40 audiometer and headphones in a soundproof booth. Air conduction thresholds were measured at 125, 250, 500, 1000, 2000, 3000, 4000, 6000 and 8000 Hz. Bone conduction thresholds were tested at 250, 500, 1000, 2000, 3000 and 4000 Hz. Tinnitus evaluation was performed using self-administering questionnaires.

6.3.2 Treatment

6.3.2.1 Psychological treatment

Two combination psychological therapies were provided with either TRT +CBT combination (5 sessions TRT/5 sessions CBT) or TRT+EMDR combination (5 sessions TRT/5 sessions EDMR). All therapies were provided by licensed TRT audiologists and CBT/EMDR psychologists. The full approach of this bimodal psychotherapy is described in Luyten et al. [33].

6.3.2.2 High-definition Transcranial Direct Current Stimulation

Patients received six sessions of high-definition transcranial direct current stimulation (HD-tDCS) over three weeks' time (2x/week) with silver/silverchloride electrodes placed on the right dorsolateral prefrontal cortex (dLPFC). A direct current of 2mA was applied with a 20 seconds fade-in/fade-out time delivered by a battery-driven 1x1 tDCS low-intensity stimulator and 4x1 multichannel stimulation adaptor (Soterix Medical Inc, New York, NY) as described in the HD-tDCS stimulation guidelines [203]. During each session the patient received 20 minutes of stimulation.

6.3.2.3 Conservative temporomandibular treatment

Patients received a maximum of 18 sessions of orofacial therapy during a fixed time window of nine weeks. This therapy was primarily directed to the temporomandibular joint and masticatory muscles.If present, cervical spine dysfunctions were treated as well, using a combination of manual mobilizations and exercise therapy. In case of severe bruxism an occlusal splint was provided in addition to the physiotherapy. Therapists, providing the orofacial physiotherapy, were trained to the study protocol prior to the start of the study. More details can be found in the published study protocol [136].

6.3.2.4 Treatment allocation

Treatment allocation to one of the four interventions described below was based on patients' complaints and needs as discussed during an intake visit at the TINTRA tinnitus consultation. For

instance, only patients with self-reported temporomandibular complaints were considered for the orofacial therapy. Different therapy options were discussed based on individual patients' tinnitus profiles, and final treatment decisions were made by the patients. Thus, a certain level of selection bias was present in the treatment allocation, but this was solely based on individual patients' needs. Demographic variables, such as gender, were never taken into account as a deciding factor for treatment choice.

6.3.4 Ethics

All patients filled out an informed consent in which permission was granted to use their data gathered during and prior to tinnitus treatment. Ethics Committee approval numbers involved in the current analysis are 16/41/415, 16/35/360, and 16/48/513.

6.3.5 Questionnaires

6.3.5.1 Tinnitus Functional Index

The Tinnitus Functional Index (TFI) [204] consists of 25 items assessing the tinnitus severity as well as the impact of tinnitus in daily life. In addition to a total score reflecting the total tinnitus burden, eight subscales define the level of inconvenience for the following aspects: intrusiveness, reduced sense of control, cognitive interference, sleep disturbance, auditory difficulties, interference with relaxation, reduced quality of life and emotional distress. The TFI has proven to be useful in the assessment of treatment-related changes in tinnitus. As such, a reduction of 13 points on the total TFI score after tinnitus treatment is considered as a clinically relevant and subjectively perceived reduction for the patient [204].

6.3.5.2 Visual Analogue Scale

The mean tinnitus loudness throughout the day was assessed by use of a Visual Analogue Scale (VAS). In this case the patient had to indicate the mean tinnitus loudness over the last week on a scale from 0 (no tinnitus at all) to 100 (the most extreme loudness one can imagine) by use of a ruler.

6.3.5.3 Hyperacusis Questionnaire

The Hyperacusis Questionnaire (HQ) [205, 206] determines the presence/absence of hyperacusis. According to Khalfa's original HQ, one can speak of hyperacusis when the score on the HQ is 28 or higher [205].

6.3.5.4 Hospital Anxiety and Depression Scale

The Hospital Anxiety and Depression Scale (HADS) is a screening tool to detect symptoms of anxiety and/or depression [207]. The HADS consists of 14 items in total assessing increased signs of anxiety (7 items) or depression (7 items). For each of the subscales, a score between 8 and 10 is considered as 'borderline' while a score of 11 and higher is considered as 'case'.

6.4.6 Statistics

A linear mixed model was designed using JMP® Pro software (JMP® Pro, Version 14.0.0, 2018 SAS Institute Inc., Cary, NC, 1989-2019) to explore the effects of gender on outcomes of different tinnitus treatments. Total TFI score was chosen as the outcome variable. The model applied the following fixed factors: Time point (baseline, post-treatment, follow-up), Gender (male, female) and Therapy group (HD-tDCS, orofacial therapy, TRT combined with CBT, TRT combined with EMDR). All possible two-way interactions between these factors were added to the model, as well as the three-way interaction Time point*Gender*Therapy group. Possible confounding factors were added to the model in a stepwise additive manner. These factors were age, hearing level (pure tone averages for 1, 2 and 4 kHz), tinnitus characteristics (type, duration and laterality of the tinnitus), scores on the HADS depression and anxiety subscales and scores on the HQ. Considerably more men than women were in all therapy groups except for the orofacial therapy group, in which the gender distribution was more balanced. Participant was added as a random intercept. Post hoc analyses were performed using linear mixed models for each of the four therapy groups separately. Here, Time point and Gender were added as fixed factors with an additional two-way interaction of Time point*Gender. P values of <0.05 were considered significant.

6.4 RESULTS

Data from 316 patients were included in the analysis. An overview of patients' characteristics at baseline can be found in table 6.1. Considerably more men than women were included in all therapy groups except for the orofacial therapy group, in which the gender distribution was more balanced.Age varied slightly between therapy groups, with mean age in the HD-tDCS group being the highest and participants in the orofacial therapy group being the youngest. Hearing levels did not differ significantly between groups, nor did tinnitus characteristics (duration, type and laterality of the tinnitus) or TFI scores at baseline. Some group level differences were found for the additional questionnaire scores, with participants in the HD-tDCS and orofacial therapy groups scoring lower on the anxiety subscale of the HADS and on the HQ than patients in both psychotherapeutic groups.

Table 6.1: Demographic details and tinnitus characteristics at baseline.

	HD-tDCS (n = 117)			Orofacial therapy (n = 109)			TRT + CBT (n = 44)			TRT + EDMR (n = 46)		
	M	F	*p*	M	F	*p*	M	F	*p*	M	F	*p*
Gender (n)	97	20		56	53		34	10		30	16	
Age (years: mean [SD])	50.02 [12.60]	53.65 [10.81]	0.2329	42.68 [15.44]	47.68 [14.22]	0.0819	49.32 [13.46]	44.5 [12.34]	0.3165	48.33 [12.44]	46 [12.13]	0.5443
Hearing level: PTA (db HL: mean [SD])	19.29 [13.48]	15.38 [11.84]	0.2309	13.85 [13.02]	16.30 [13.92]	0.3491	19.75 [15.60]	8.92 [5.93]	0.0385	17.22 [14.41]	16.09 [17.39]	0.8151
Tinnitus characteristics												
Tinnitus duration (years: mean[SD])	6.59 [7.49]	4.06 [5.63]	0.1546	5.27 [7.30]	4.98 [7.14]	0.8351	9.08 [10.56]	3.35 [1.81]	0.0978	8.23 [8.98]	3.97 [2.89]	0.0728
Tinnitus laterality (*n:* right / left / bilateral / central)	13 / 12 / 57 / 15	1 / 3 / 13 / 3	0.7066	6 / 9 / 27 / 13	6 / 5 / 33 / 7	0.2132	2 / 8 / 15 / 9	0 / 3 / 6 / 1	0.4497	3 / 6 / 12 / 9	2 / 4 / 6 / 4	0.9624
Tinnitus type *n:* pure tone / noise / polyphonic)	67 / 22 / 8	12 / 4 / 4	0.3468	32 / 16 / 7	22 / 25 / 4	0.0862	25 / 7 / 2	3 / 4 / 3	0.0310	18 / 8 / 4	11 / 3 / 2	0.8126
TFI scores (mean [SD])	45.5 [18.62]	55.5 [23.44]	0.0390	50.64 [18.67]	54.02 [15.35]	0.3050	48.92 [22.10]	54.24 [22.11]	0.5068	51.37 [18.31]	58.58 [18.22]	0.2098
Questionnaire scores												
HADS anxiety (mean [SD])	7.29 [3.60]	9.2 [4.82]	0.0443	8.91 [4.06]	8.43 [4.22]	0.5524	8.79 [4.42]	12.6 [4.43]	0.0212	8.53 [4.01]	11 [3.92]	0.0512
HADS depression (mean [SD])	6.77 [4.05]	7.65 [5.49]	0.4106	7.09 [4.49]	5.36 [4.54]	0.0488	6.91 [4.25]	9.7 [4.52]	0.0794	7.53 [4.61]	7.56 [4.07]	0.9831
HQ scores (mean [SD])	18.34 [7.74]	21.25 [9.59]	0.1448	17.22 [7.19]	17.61 [8.89]	0.8039	20.74 [9.15]	26.9 [7.72]	0.0600	20.93 [7.90]	26.81 [3.87]	0.0077

HD-tDCS: High-Definition transcranial Direct Current Stimulation; TRT: Tinnitus Retraining Therapy; CBT: Cognitive Behavioural Therapy; EMDR: Eye Movement Desensitisation and Reprocessing therapy; PTA: Pure Tone Average for 1, 2 and 4 kHz; TFI: Tinnitus Functional Index; HADS: Hospital Anxiety and Depression Scale; HQ: Hyperacusis Questionnaire. Standard least squares (for continuous variables) or nominal logistic models (for dichotomous variables) were designed to test whether male and female participants in each of the four therapy groups differed significantly; resulting p values are shown in the last column.

Results of the linear mixed model analysis are summarized in table 6.2. Of all putative confounding factors, only the HADS depression subscale score and the HQ score were found to contribute significantly to the model. All other possible confounding factors (age, hearing level, tinnitus characteristics and HADS anxiety subscale scores) did not have any demonstrable effect on the model and were excluded from the analysis. Thus, the final model included two additional factors (HADS depression scores and HQ scores) next to the fixed factors Time point, Gender and Therapy group. Overall, a significant fixed effect of time point was found, with TFI scores decreasing over time for all therapy groups and for both genders ($p < 0.0001$) (Fig. 6.1A). Additionally, the main effect of gender was found to be significant, with women generally having a higher TFI score than men ($p = 0.0496$) (Fig. 6.1B). A significant interaction between Time point and Therapy group was identified ($p = 0.0023$), indicating that TFI scores of participants in different therapy groups evolved differently over time. Crucially, a significant three-way interaction between Time point, Gender, and Therapy group was found ($p = 0.0002$). This interaction implies that treatment response in the different therapy groups was modulated by gender (Fig. 6.2).

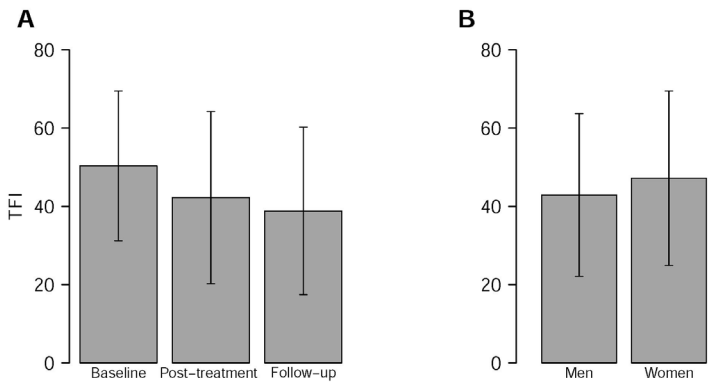


Figure 6.1: Main effects of time point (A) and gender (B).
A: TFI scores change significantly over time, independently of therapy group or gender ($p < 0.0001$). TFI scores at baseline: 50.34 ± 19.13; TFI scores at the post-treatment time point: 42.24 ± 21.99; TFI scores at follow-up: 38.84 ± 21.39; mean ± SD. B: TFI scores are higher in women than in men, independently of therapy group or time point ($p = 0.0496$). TFI scores for women: 47.19 ± 22.28; TFI scores for men: 42.93 ± 20.79; mean ± SD. Error bars represent SD. TFI: Tinnitus Functional Index.

Table 6.2: Results of the linear mixed model analysis.

	***p* value**
Fixed factors	
Time point	<0.0001
Gender	0.0496
Therapy group	0.1072
HADS depression subscale scores	<0.0001
HQ scores	0.0007
Interactions	
Time point * Gender	0.7613
Time point * Therapy group	0.0023
Gender * Therapy group	0.5761
Time point * Gender * Therapy group	0.0002

HADS: Hospital Anxiety and Depression Scale; HQ: Hyperacusis Questionnaire.

To further explore this highly significant three-way interaction, post hoc analyses were performed for each therapy group. Similar to the primary analysis, HADS depression subscale scores and HQ scores were added to the model as confounding factors. In three out of four therapy groups, significant interactions between *Time point* and *Gender* were found. These interactions indicate that the evolution of TFI scores depended on gender in these specific therapy groups. In the HD-tDCS (*Time point*Gender*: $p = 0.0009$) and orofacial therapy group (*Time point*Gender*: $p = 0.0299$), female participants generally had higher TFI scores at baseline, but improved more extensively than male subjects (Fig. 6.2A, B). On average, TFI scores of female participants in the HD-tDCS group decreased by 15.83 ± 24.27 points from baseline to follow-up, whereas male participants' TFI scores dropped by only 2.53 ± 13.79 points. In the orofacial therapy group, female participants' TFI scores decreased by 19.02 ± 16.85 points while scores of male participants decreased by 10.53 ± 19.65 points.

Contrarily, in the TRT + CBT group, male subjects improved significantly over time whereas female participants' mean TFI scores only decreased slightly after treatment ($p = 0.327$) but did not remain stable at follow-up (Fig.6.2C) (*Time point*Gender*: $p = 0.0138$). From baseline to follow-up, male participants' TFI scores decreased by 22.42 ± 23.02 points whereas TFI scores of female subjects in this group actually increased marginally with 0.44 ± 21.26 points. Finally, in the TRT + EMDR group, the two-way interaction *Time point*Gender* was not significant ($p = 0.5240$), with men and women improving over time in a highly similar way (Fig. 6.2D). The decrease in TFI scores from baseline to follow-up was 19.1 ± 18.52 and 16.46 ± 14.3 points in female and male participants, respectively.

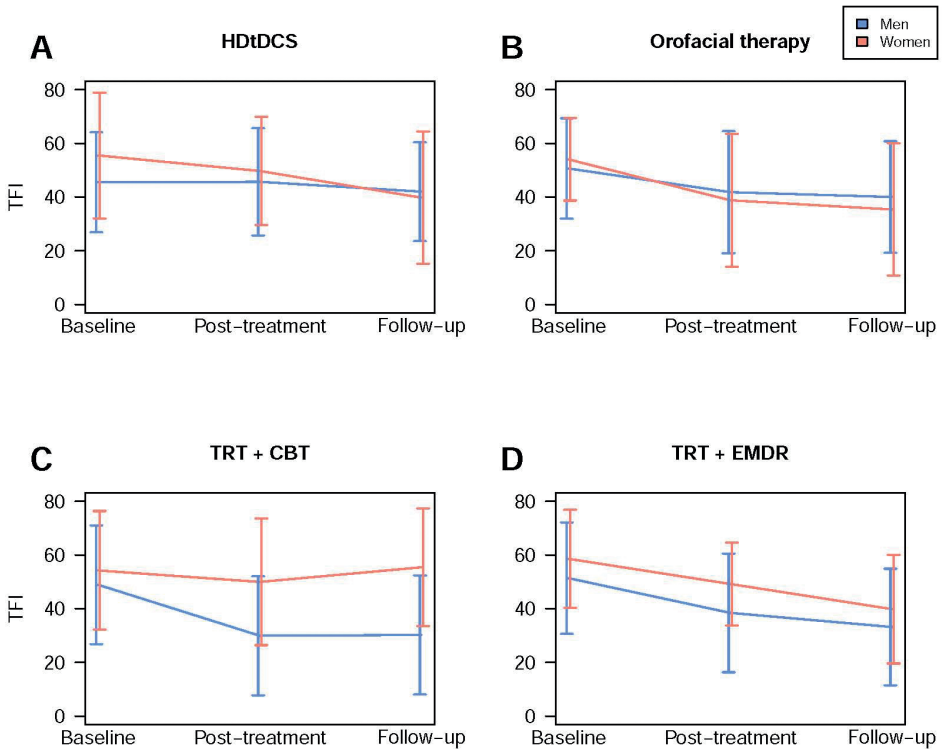


Figure 6.2: Treatment outcome in different therapy groups differs according to gender.
Blue lines represent male subjects and red lines represent female subjects. Data are presented as mean TFI scores for each time point ± SD. A: female participants benefit more from HDtDCS treatment than men. TFI scores decreased more in female participants (-15.83 ± 24.27) than male (-2.53 ± 13.79) from baseline to follow-up. B: female participants benefit more from orofacial therapy than men. TFI scores decreased more in female participants (-19.02 ± 16.85) than male (-10.53 ± 19.65) from baseline to follow-up. C: male participants benefit more from TRT combined with CBT than women. TFI scores decreased more in male participants (-22.42 ± 23.02) than female (0.44 ± 21.26) from baseline to follow-up. D. Male and female participants benefit equally from TRT combined with EMDR. TFI scores decreased similarly in male (-19.1 ± 15.82) and female participants (-16.46 ± 14.3) from baseline to follow-up. TFI: Tinnitus Functional Index; HDtDCS: High-Definition transcranial Direct Current Stimulation; TRT: Tinnitus Retraining Therapy; CBT: Cognitive Behavioural Therapy; EMDR: Eye Movement and Desensitiziation.

HADS depression subscale scores and HQ scores were found to contribute significantly to the model. Post hoc analyses revealed that both questionnaire scores had a significant effect on tinnitus severity, with higher scores on both questionnaires equalling higher total TFI scores. These effects were not dependent on either Time point or Gender, as evidenced by the non-significance of the interactions between these questionnaire scores and Time point ($p = 0.5914$ for HADS depression scores, $p = 0.1814$ for HQ scores) or Gender ($p = 0.6806$ for HADS depression scores, $p = 0.1868$ for HQ scores).

6.5 DISCUSSION

The large variability in tinnitus treatment outcomes may be driven by differences in individual patient characteristics. The current manuscript retrospectively explored whether gender may account for any of this heterogeneity. We report remarkable gender effects on treatment outcomes of several tinnitus therapy options. Overall, our results indicate that gender might be an influential mediator of treatment outcome.

In a large group of tinnitus patients, we found that women benefited from orofacial physiotherapy to a greater extent than men. In the general population, a recent meta-analysis showed that the risk for developing temporomandibular disorders (TMD) is twice as high in women then in men [208]. Likewise, a study of Vielsmeier et al. [209] showed that significantly more women than men had TMD in a population of patients with tinnitus, something which was also found in the general population [210]. Therefore, we hypothesize that the proportion of true TMD sufferers was higher in female than in male patients. This gender difference in baseline TMD burden may then explain the higher success ratio of conservative orofacial treatment in female tinnitus patients. Currently, no other studies reported on gender differences in orofacial treatment effect on tinnitus complaints. It must also be noted that although statistically significant, the difference in decrease in TFI score between males and females in this treatment group is small. Our results should therefore be confirmed in future research, specifically designed to investigate gender differences.

In our study population, women also demonstrated a better treatment response after receiving consecutive sessions of HD-tDCS. These results are in agreement with Frank et al. (2012), who reported larger beneficial effects of frontal tDCS in women [211]. Both protocols comprised anodal stimulation of the right dorsolateral prefrontal cortex, suggesting that this gender difference might be driven by true underlying physiological differences. Indeed, dorsolateral prefrontal cortex volume has been shown to be greater in women than men [212, 213], and anodal tDCS of the prefrontal cortex might have greater effects in females [214]. These findings cannot be explained by the amount of current intensity going through the brain as it was previously shown that females receive significantly less current compared to males when targeting parietal and frontal areas due to more dense parietal bone in females [215]. A significant difference in TFI at baseline between males and females

was observed with females showing higher TFI scores which may imply a greater opportunity for improvement in this population. However, even after correcting for this difference in baseline TFI score, the effect of gender over time remained significant. In addition, no equal proportion of male and female subjects was obtained in this therapy group so these results need to be interpreted with caution.

Conversely, in our study population, male patients benefited more than females from TRT combined with cognitive behavioural therapy (CBT), while both males and females experienced significant improvement through eye movement desensitization and reprocessing (EMDR) therapy. Although some evidence exists for gender differences in tinnitus perception and distress, literature on gender effects on the efficacy of psychological tinnitus treatments is scarce. To date, meta-analyses on psychotherapy outcomes report minimal to no gender differences [216-220].

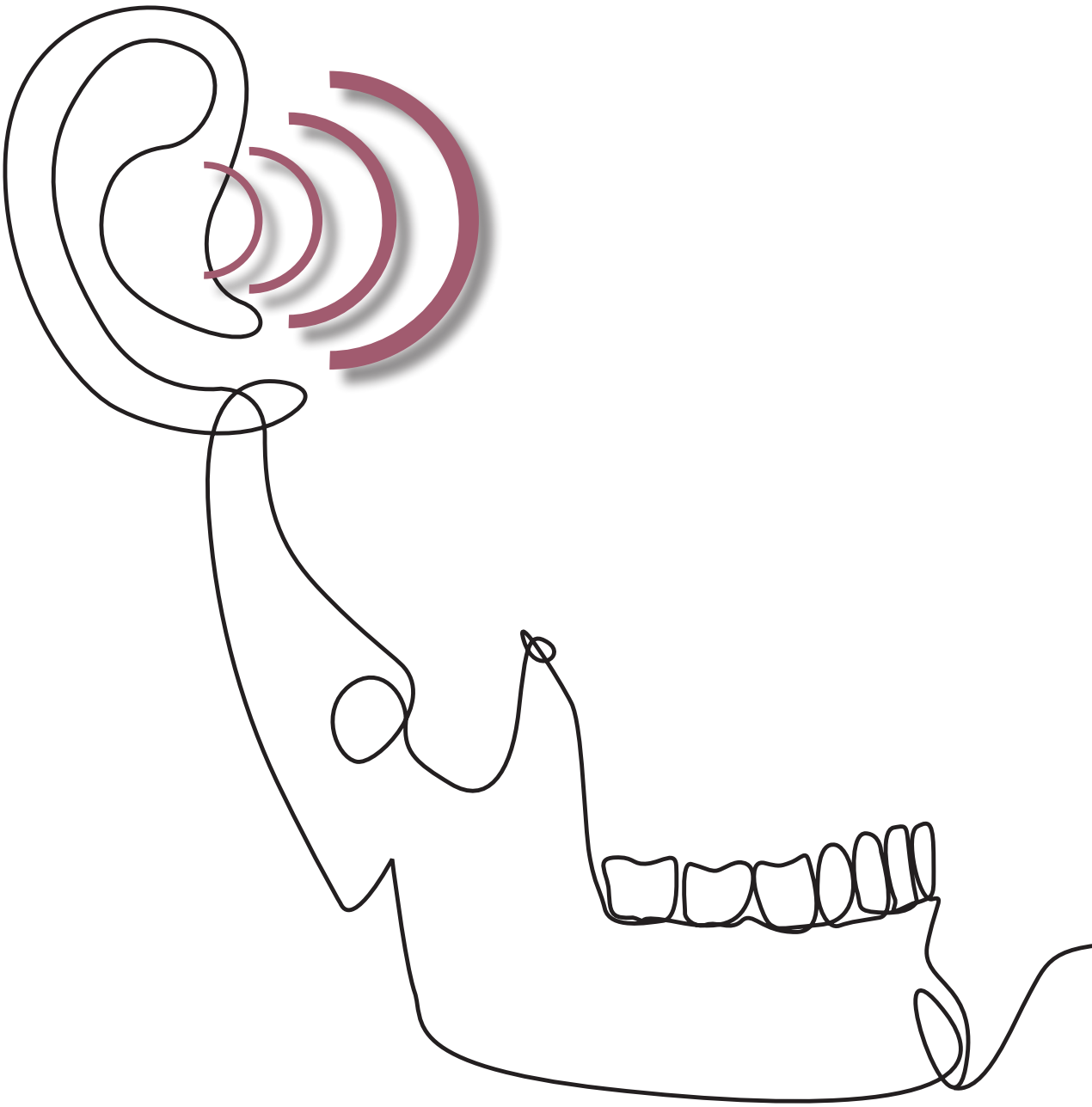
In a study reporting on the long-term effects of TRT combined with cognitive-behavioural elements, Seydel et al. (2010) reported subtle gender differences on treatment outcome [221]. Male and female patients showed similar outcomes of this treatment overall, but women experiencing longer (> 2y and especially > 10y) tinnitus duration were less likely to maintain positive treatment effect at a 1-year follow-up time point. In our dataset we did not identify any effects of tinnitus duration. However, the relatively long average tinnitus duration (7.78y) might account for this gender difference on the outcome of a treatment combining TRT and CBT. About 70% of the female participants included in the TRT + CBT group reported a psychiatric diagnosis in the present or the past. These findings suggest that 10 sessions might not be sufficient to alleviate the complex tangle of aggravating complaints. The proportion of patients with psychiatric comorbidity was lower in the TRT + EMDR group. Given the fact that 40% of female participants did report a significant decrease of 13 points or more in the TRT + CBT group, we emphasise the identifiable influence of psychiatric comorbidity on treatment outcome. However, the cognitive behavioural approach could have influenced therapy outcome on the basis of the cognitive therapeutic techniques that were used. Some evidence can be found on women to experience more therapeutic gain through an emotion-focused treatment [222-225] whereas men tend to react better to a problem-focused therapy which is more integrated in the CBT approach [226]. More empirical evidence is required to investigate whether these findings can be replicated. We interpret these results with caution, taking into account the importance of the individual characteristics of the female participants in this considerably small sample size compared to the proportion of male participants.

The results presented here are highly explorative, and large prospective trials are needed to confirm or disprove the gender effects we demonstrate. It would be especially prudent for future studies to ensure an even inclusion of men and women, as the gender balance is disturbed in many studies, as well as in several of the therapy groups discussed in this paper. Furthermore, as we identified additional effects of symptoms of depression and hyperacusis, controlling for these factors is undeniably crucial.

We have demonstrated considerable effects of gender on tinnitus treatment outcome for different therapy options. Our results suggest that women might experience greater effects of orofacial physiotherapy and transcranial direct current stimulation compared to men. Within the psychotherapeutic treatments, we identified subtle gender differences between the outcome of cognitive behavioral therapy compared to eye movement desensitization and retraining, but mainly note that individual differences and psychiatric comorbidity affect the therapeutic pathway and treatment outcome. We report remarkable gender effects on treatment outcomes of several tinnitus therapy options. Overall, our results indicate that gender might be of influence for treatment outcome. Consequently, it might be important to consider gender when estimating the chance for treatment success.

PART 3

HEALTH STATUS AND PERCEIVED DISABILITY OF PATIENTS WITH SOMATIC TINNITUS.



Chapter 7

ICF domains covered by the Tinnitus Questionnaire and Tinnitus Functional Index

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7.1 ABSTRACT

Purpose

Tinnitus frequently causes disability as it affects daily living, which is objectified using several tinnitus questionnaires. To what extent they cover domains of the International Classification of Functioning, Disability and Health (ICF) is currently unknown. Therefore, this study aims to investigate which ICF domains are measured by two questionnaires and to describe the health status of somatic tinnitus patients in ICF terms.

Materials and methods

All questions of the Tinnitus Questionnaire (TQ) and Tinnitus Functional Index (TFI) were linked to the ICF using linking rules. A count-based method was used to link all individual answers of 80 tinnitus patients, to the ICF categories.

Results

Most of the linked questions concerned 'body functions'. TFI covered more categories of 'activity and participation' than TQ.

Patients reported severe impairments in 'mental functions', 'sensory functions and pain' and 'sleep functions'. Additionally, severe limitations were scored in 'focusing attention'.

Conclusions

The TFI and TQ measure distinct domains but can be used complementary or solely, depending on the research question. The TFI identifies a broad spectrum of problems, where the TQ focusses on the psychological impact of tinnitus. Somatic patients in our study reported impairments and disabilities in all covered domains, especially in 'onset of sleep' and 'sound detection'.

Keywords

ICF classification, disability, tinnitus, health status, participation

7.2 INTRODUCTION

Tinnitus, defined as a perception of sound in the absence of an external acoustic stimulus, is a common symptom with a prevalence ranging from 5.1% to 42.7% of the adult population [8, 227]. Tinnitus can be quite debilitating and often causes disability due to its large influence on daily living [8]. According to a review of Hall et al. [228] the most common problems are aspects of quality of life such as psychological or emotional effects, impact on lifestyle, sleep disturbance, auditory and health effects. As such, tinnitus can also interfere in social relationships.

In general, tinnitus can be divided into objective and subjective tinnitus [9]. When the tinnitus sound originates from an internal source within the patient's body, the tinnitus is called "objective". This form of tinnitus is rare (less than 5%) and can be caused by middle ear tumors, turbulent blood flow or myoclonus of middle-ear palatal muscles [8]. In case of subjective tinnitus, no source can be found for the perceived sound, neither externally nor internally. The pathophysiological mechanism of subjective tinnitus is often multifactorial. The main risk factor for developing tinnitus is hearing loss, but other factors, diseases and malfunctions leading to tinnitus may be otologic (i.e. hearing loss, noise trauma, Meniere's disease, acoustic neurinoma, and ototoxic medications or substances), neurologic (i.e. multiple sclerosis and head injury), metabolic (i.e. thyroid disorder, hyperlipidemia, and vitamin B12 deficiency), psychogenic (i.e. depression and anxiety), or somatogenic [8, 9, 11]. In case a patient's tinnitus is influenced by altered somatosensory afference from the cervical spine or temporomandibular area it is called somatic or somatosensory tinnitus [55]. In this type of tinnitus, dysfunctions in the cervical spine or temporomandibular area, such as restricted mobility or muscle tension, can change the tinnitus loudness and/or pitch or can even cause the tinnitus in some cases [51, 55].

Due to the different etiologies and influencing factors, tinnitus complaints can differ enormously between individuals [228]. For this reason, there are various questionnaires developed to assess the impact of tinnitus on daily living, each covering possible complaints that can influence a patient's quality of life. However, it is still unclear which outcome domains are critical and important to measure for therapy outcome [228]. Therefore, a group of tinnitus experts developed "Core Outcome Domain Sets" representing a consensus which tinnitus-related outcome domains should constitute the common standard in specific tinnitus treatments as sound-based interventions, psychology-based interventions and pharmacology-based interventions [4]. However, it is still unknown which outcome domains should be covered by patients with somatic tinnitus.

In 2001, the World Health Organization (WHO) developed the International Classification of Functioning, Disability and Health (ICF) to compare and describe the health of populations in an international context. It also helps to understand a person's health and perceived disability [87]. The ICF is an international framework providing a standard language and hierarchical concept for documenting information on functioning and disability in relation to a health condition. The ICF model

(figure 7.1) is divided into two main parts: (1) 'functioning and disability' described as impairments of body functions and structure, activity limitations and participation restrictions and (2) 'contextual factors' described as personal and environmental barriers. These two parts are further divided into four components: (b) body functions and (s) body structures (b and s are together one component), (d) activities and participation and (e) environmental factors. The fourth component, personal factors, is not classified in ICF because of the large social and cultural variance associated with them [229].

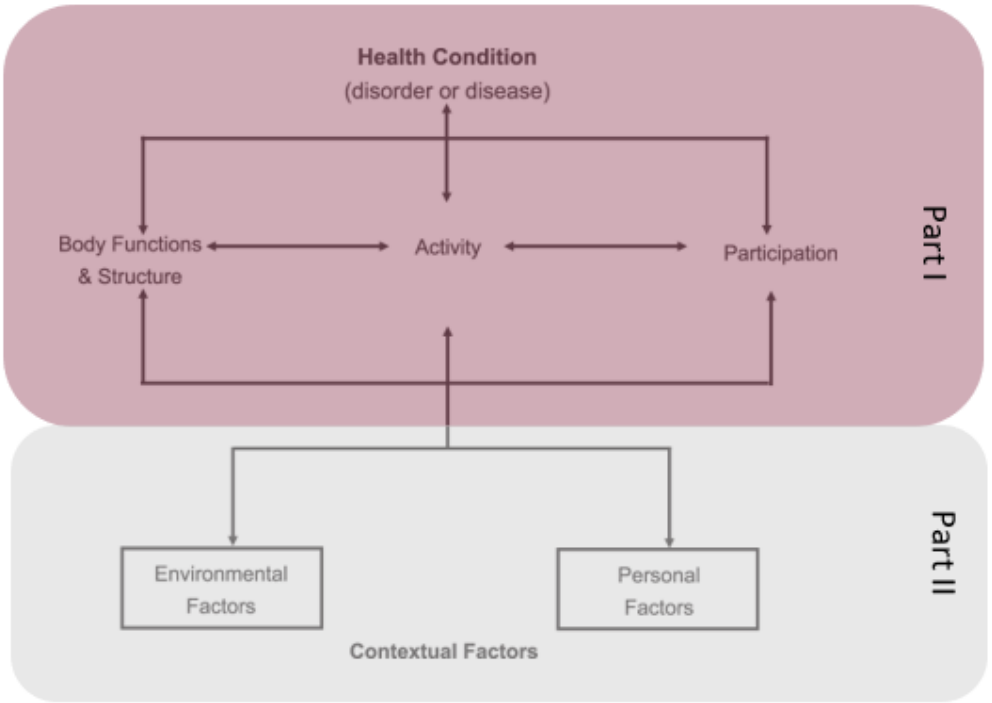

Figure 7.1: Illustration of the International Classification of Functioning, disability and Health model, created by the World Health Organization.

Health outcome measures can be connected to the ICF classification in a standardized way by using a method called "linking rules" [88, 230, 231]. Since 2002, this method has been applied in several health conditions such as sleep disorders, neurological disorders and musculoskeletal disorders, to identify the patient's dysfunctions from existing outcome measures and to classify these dysfunctions in the four different domains of the ICF.

There are many different assessment tools for measuring the impact tinnitus has on a patient's daily living. Two frequently used questionnaires to evaluate the severity of a patient's tinnitus or the annoyance the tinnitus causes, are the Tinnitus Questionnaire (TQ) and the Tinnitus Functional Index

(TFI) [108 - 109 - 112 -228]. Although both TQ and TFI are used to investigate the impact tinnitus has on patients' daily living, it is currently unclear which domains they cover of the patients' disability. In addition, it is also not clear which domain has the greatest impact on a patient's life.

Therefore, the aim of our study is twofold. First, to investigate which domains of disability of the ICF are measured by the TQ and TFI. Second, to describe the health status and perceived disability of patients with tinnitus in terms of the ICF.

7.3 METHOD

The current study is a cross-sectional study conducted at the Antwerp University Hospital. Questionnaires were filled out as part of baseline data in a randomized controlled trial (RCT) [140]. In the RCT we investigated the effect of orofacial treatment in patients with somatic tinnitus on their subjective tinnitus complaints [140]. In our study a patient's tinnitus was called somatic, when the somatosensory system was one of the major influencing factors.

7.3.1 Patients

Adult patients were recruited from the tertiary tinnitus clinic at the University Hospital Antwerp, Belgium. Before entering the study, patients were thoroughly tested by otolaryngologists, audiologists, dentists and physical therapists to objectify all the possible influencing factors, diseases and malfunctions for the tinnitus. Patients were included in the study when suffering from moderate to severe (defined as a TFI score between 25 and 90) subjective tinnitus which had been stable for three months. Furthermore, the somatosensory influence from the cervical spine and temporomandibular area should be one of the major influencing factors [55]. Apart from tinnitus, patients had TMD pain (i.e. arthralgia or myalgia) according to the diagnostic criteria for TMD [61] and/or oral parafunctions. More information about the in- and exclusion criteria can be found in our study protocol and RCT [136, 140].

7.3.2 Study design

The individual answers of 80 patients on two disease-specific questionnaires, the TQ and TFI, were collected [140]. Then, the questions of the TQ and TFI were linked to the ICF model. To use a systematic and standardized approach when linking these health-status measures, the linking rules described by Cieza et al. were used as a guideline [88, 230, 231]. Finally, the individual answers on the questions of TQ and TFI were linked to the ICF model to define the severity of the perceived disability of the patients.

7.3.2.1 Questionnaires

Multiple tinnitus questionnaires are available to describe the perceived disability of a patient's tinnitus. We included the TQ and TFI, since both questionnaires are frequently recommended and

used in trials to objectify the influence tinnitus has on a patients' daily life. The TFI is currently the most recommended. The TQ is a little older, but was selected for our population as it contains a specific somatic subscale [109, 204]. The TQ specifically aims to measure annoyance caused by the tinnitus and consists of 52 questions that are answered on a 3-point scale (ranging from "true" scoring 0, "partly true" scoring 1 to "not true" scoring 2). The total score of the TQ ranges from 0 to 84, with higher scores indicating higher levels of annoyance. The test-retest reliability of the TQ is excellent and the internal consistency, convergent and discriminant validity is high [110, 232]. In addition, the TQ has a somatic subscale with three questions on somatic complaints. It has been hypothesized that patients with somatic tinnitus might have higher scores on this subscale. The TFI is designed to cover a broad spectrum of tinnitus-related complaints [112]. It aims to measure the severity and negative impact of tinnitus and consists of 25 questions that are answered on an 11-point Likert scale going from "no disturbance" to "maximal disturbance". A TFI score of 25 or less indicates relatively mild tinnitus with little or no need for intervention, whereas a score ranging from 25-50 indicates a moderate tinnitus and possible need for intervention [112]. A TFI score above 50 indicates severe tinnitus with a clear need for professional attention [112]. The TFI has good convergent and discriminant validity and also a good reliability [125].

7.3.2.2 Linking procedure

According to the linking rules created by Cieza et al. [88, 230, 231], two researchers (A.v.d.W, J.d.P) independently linked each question of the questionnaires to the ICF model, using the English digital version of the ICF browser [233]. Before starting the actual linking process, both authors acquired appropriate knowledge of the domains, chapters and categories of the ICF classification.

The following steps were made during the linking process: First, each question of the questionnaires was classified to one of the four corresponding ICF domains: impairment in body functions/structures, limitation in level of activity, restriction of participation and personal and environmental factors (step 1). Then, the corresponding chapter within the domain was chosen (step 2). After that, the adequate category was indicated (step 3). For example: for the question of the TQ "I wake up more in the night because of my noise", 'maintenance of sleep' is identified as linkable concept (B1342). The steps in the ICF browser for this question are described below and shown in figure 2.

Step 1: domain B (body functions)
Step 2: chapter B1 (mental functions)
Step 3: category B1342 (maintenance of sleep)

If a question encompassed more than one linkable construct, each construct was linked. During a consensus meeting, inconsistencies were discussed and discrepancies eliminated.

If a question could not be linked to the ICF, this was noted. After linking each question to the specific ICF category, the number of questions linked to a predefined ICF category of each questionnaire

were counted and represented by a percentage of the contribution to the total score. For example, looking at the abovementioned category 'maintenance of sleep', two questions of the TQ were linked to this category. So, two of the fifty-two questions means that 'maintenance of sleep' covered 4% of the total score of the TQ.

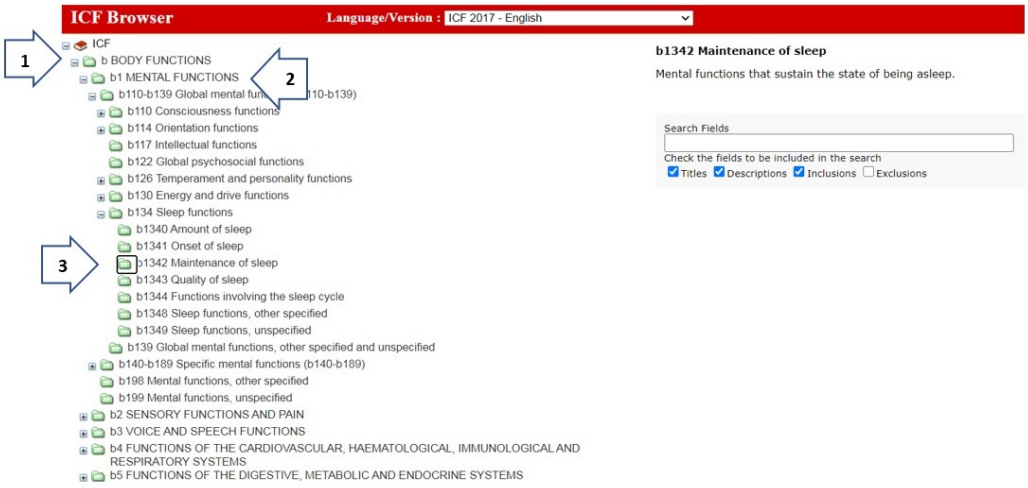

Figure 7.2: Screenshot of the ICF browser. 1: domain B (body functions) 2: chapter B1 (mental functions) 3: category B1342 (maintenance of sleep).

7

7.3.2.3 Determination the severity of impairment

To determine the severity of perceived disability and health status of our patient sample, for each patient, each question was scored as: no impairment (score of 0 points on TQ and 0-2 points on TFI), mild impairment (score of 1 point on TQ and 3-5 points on TFI) or severe impairment (score of 2 points on TQ and > 5 points on TFI). This allowed us to compare both questionnaires each using a specific scoring system.

Afterwards, a count-based method was used to calculate the severity of the impairment for each question. Then, per ICF category, the percentage of patients reporting 'no impairment', 'mild impairment' and 'severe impairment' was calculated.

7.4 RESULTS

7.4.1 Study population

Data from 80 patients was used in the analysis. All patients suffered from a moderate to severe somatic tinnitus. The average baseline TFI score was 52 points (SD 16) and the average baseline TQ score was 36 points (SD 16). From this group of 80 patients, 36.8% had hearing loss and 82.5% were diagnosed with myalgia according to the Diagnostic Criteria of Temporomandibular Disorders [61]. More information about the general patient characteristics are shown in table 7.1.

Table 7.1: Description of the study population

Characteristic	
Gender male/female (n)	42/38
Mean age in years (SD)	45 (±14)
Mean duration of the tinnitus in months	64 (±86)
Mean TQ-score (SD)	36 (±16)
Mean TFI-score (SD)	52 (±16)
% patients with hearing loss	36.8%
% diagnosed with TMD myalgia	82.5%
% diagnosed with both myalgia and arthralgia	25.0%
% only oral parafunctions	17.5%

7.4.2 Linked categories

Each question of the TFI and TQ could be linked to a predefined category of the ICF model as shown in table 7.2 to 7.4. The overlap in the domains and chapters between the two questionnaires is shown in figure 3. A total of 77 questions were linked to 36 different categories. The domain 'body functions' could be linked to 20 categories; 13 questions were linked to 'activity and participation' and 3 questions were linked to 'environmental factors'. No items were linked to the domain 'body structures'.

7.4.2.1 ICF domains covered by the TFI

In the TFI, questions covering the domain 'body functions' could be linked to a total of 14 categories: 10 categories of the chapter 'mental functions' and 4 categories of the chapter 'sensory functions and pain' (table 7.2). The TFI measures 9 categories of the domain 'activity and participation'. Two specific ICF categories are most represented: 'regulation of emotion' (4 questions) and 'recreation and leisure unspecified' (3 questions). The chapters 'domestic life', 'interpersonal interactions and relationships' and 'major life areas' are only measured by the TFI.

7.4.2.2 ICF domains covered by the TQ

In the TQ, questions concerning the domain 'body functions' covered the chapters 'mental functions' (with 13 categories), 'sensory functions and pain' (with 4 categories) and 'neuromusculoskeletal and movement-related functions' (with 1 category) (table 7.2). The category 'content of thought' is most represented (17 questions). The domain 'activity and participation' is measured in 3 chapters with 5 categories. In this domain, the category 'communication' is only covered by the TQ. The 'environmental factors' are also only covered by the TQ with one question that is linked to 3 categories of the ICF.

7.4.3 Prevalence and severity of impairments

The prevalence of impairments identified by the TFI and TQ are presented in table 7.2 respectively. Patients show severe impairments in 'mental functions' (between 28.1% and 62.5% on TFI and between 11.5% and 53.8% on TQ) and 'sensory functions and pain' (between 27.5% and 68.8% on TFI and between 14.1% and 67.5% on TQ). Looking closer to the TFI data, between 45.0% and 62.5% of the patients have severe impairments in 'sleep functions' (B134). This percentage is lower on the TQ, where between 20.5% and 53.8% of the patients has severe impairments in 'sleep functions'. Additionally, the percentage of patients with a severe impairment on 'content of thought' (B1602) is also higher on the TFI in comparison with the TQ (43.8% on TFI and 25.3% on TQ).

Legend
B1: mental functions
B2: sensory functions and pain
B3: voice and speech functions
B4: functions of the cardiovascular, haematological, immunological and respiratory systems
B5: functions of the digestive, metabolic and endocrine systems
B6: genitourinarty and reporductive functions
B7: neuromusculoskeletal and movement-related functions
B8: functions of the skin and related structures

D1: learning and applying knowledge
D2: general tasks and demands
D3: communication
D4: mobility
D5: self-care
D6: domestic life
D7: interpersonal interactions and relationships
D8: major life areas
D9: community, social and civic life

E1: products and technology
E2: natural environment and human-made changes to environment
E3: support and relationships
E4: attitudes
E5: services, systems and policies

S1: structures of the nervous system
S2: the eye, ear and related structures
S3: structures involved in voice and speech
S4: structures of the cardiovascular, immunological and endocrine systems
S5: structures related to the digestive, metabolic and endocrine systems
S6: structures related to the genitourinary and reproductive systems
S7: structures related to movement
S8: skin and related structures

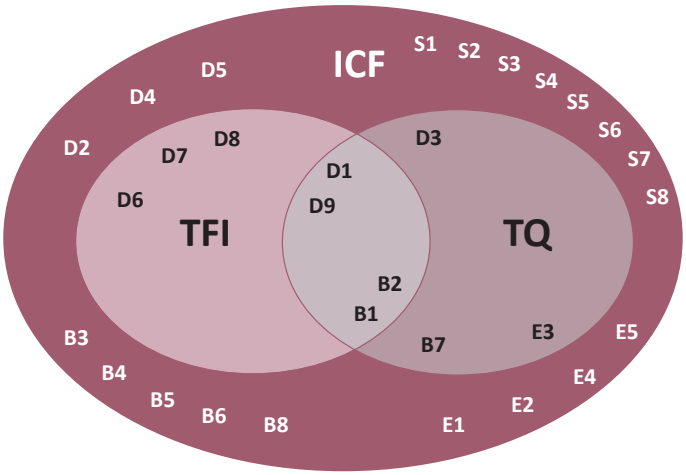

Figure 7.3: The overlap in the domains and chapters between the TFI and TQ. TFI: Tinnitus Functional Index. TQ: Tinnitus Questionnaire.

Table 7.2: The prevalence and severity of impairments identified by the Tinnitus Functional Index and Tinnitus Questionnaire.

Chapter	TFI						TQ					
	ICF category	Number of questions	Contribution to total score	No impairment	Mild impairment	Severe impairment	ICF category	Number of questions	Contribution to total score	No impairment	Mild impairment	Severe impairment
B1: Mental functions							B1266: confidence	1	2%	64.1%	24.4%	11.5%
							B134: sleep functions	1	2%	39.7%	24.4%	35.9%
	B1340: amount of sleep	1	4%	15.0%	32.5%	52.5%						
	B1341: onset of sleep	1	4%	15.0%	22.5%	62.5%	B1341: onset of sleep	1	2%	32.1%	26.9%	41.0%
	B1342 Maintenance of sleep	1	4%	15.0%	22.5%	62.5%	B1342 Maintenance of sleep	2	4%	53.2%	26.3%	20.5%
	B1343: Quality of sleep	1	4%	15.0%	40.0%	45.0%	B1343: Quality of sleep	1	2%	28.2%	17.9%	53.8%
	B1400: sustaining attention	1	4%	18.8%	38.8%	42.5%	B1400: sustaining attention	2	4%	24.4%	51.3%	24.4%
	B1401: shifting attention	1	4%	18.8%	47.5%	33.8%	B1401: shifting attention	1	2%	15.4%	42.3%	42.3%
	B:1521: regulation of emotion	4	16%	18.8%	34.1%	47.2%	B:1521: regulation of emotion	3	6%	55.6%	23.9%	20.5%
	B1522: range of emotion	1	4%	30.0%	41.3%	28.1%	B1522: range of emotion	2	4%	33.3%	29.5%	37.2%
							B1560: auditory perception	2	4%	37.2%	33.3%	29.5%
							B1601: form of thought	1	2%	25.6%	44.9%	29.5%
	B1602: content of thought	1	4%	12.5%	43.8%	43.8%	B1602: content of thought	17	33%	42.2%	32.4%	25.3%
	B1643: cognitive flexibility	1	4%	5.0%	35.0%	60.0%	B1643: cognitive flexibility	2	4%	41.0%	46.8%	12.2%

B2: sensory function and pain	B2300: sound detection	1	4%	2.5%	28.8%	68.8%						
	B2301: sound discrimination	1	4%	46.3%	26.3%	27.5%	B2301: sound discrimination	1	2%	44.9%	15.4%	39.7%
	B2304: speech discrimination	2	8%	42.5%	26.3%	31.3%	B2304: speech discrimination	1	4%	61.5%	24.4%	14.1%
	B2400: ringing in ears or tinnitus	1	4%	1.3%	31.3%	67.5%	B2400: ringing in ears or tinnitus	3	6%	28.2%	38.0%	33.8%
							B28010: pain in the head and neck	2	4%	64.7%	16.0%	19.2%
B7: neuromusculoskeletal and movement related functions							B7350: tone of isolated muscles and muscle groups	1	2%	23.1%	38.5%	38.5%

Table 7.3: The prevalence and severity of activity limitations and participation restrictions identified by the Tinnitus Functional Index and Tinnitus Questionnaire.

Chapter	TFI						TQ					
	ICF category	Number of questions	Contribution to total score	No activity limitation or participation restriction	Mild activity limitation or participation restriction	Severe activity limitation or participation restriction	ICF category	Number of questions	Contribution to total score	No activity limitation or participation restriction	Mild activity limitation or participation restriction	Severe activity limitation or participation restriction
D1: Learning and applying knowledge							D160:focusing attention	1	2%	65.4%	25.6%	9.0%
	D1601: focusing attention on the environment	1	4%	1.3%	36.3%	62.5%	D1601: focusing attention on the environment	1	2%	42.3%	42.3%	15.4%
	D163: thinking	1	4%	26.3%	42.5%	31.3%						
D3: communication							D3600: using telecommunication devices	1	2%	64.1%	25.6%	10.3%
D6: domestic life	D649: household tasks	1	4%	41.3%	33.8%	25.0%						
	D660: assisting others	1	4%	41.3%	33.8%	25.0%						
D7: interpersonal interactions and relationships	D7100: respect and warmth in relationships	1	4%	36.3%	35.0%	28.8%						
	D729: general interpersonal interactions	1	4%	48.8%	30.0%	21.3%						
D8: major life areas	D839: education unspecified	1	4%	41.3%	33.8%	25.0%						
	D850: remunerative employment	1	4%	41.3%	33.8%	25.0%						

D9: community, social and civic life							D9202: arts and culture	2	4%	59.0%	37.2%	3.8%
							D9208: recreation and leisure, other specified	1	2%	12.8%	51.3%	35.9%
	D9209: recreation and leisure, unspecified	3	12%	5.5%	21.3%	73.3%						

7.4.4 Prevalence and severity of activity limitations and participation restrictions

The severity of activity limitations or participation restrictions based on the TFI and TQ are shown in table 7.3. Looking at the TFI, severe activity limitations or participation restrictions were present in 62.5% of the patients in 'focusing attention' (D160). This is in contrast with the scores of the TQ were only 9.0% of the patients stated to have severe activity limitations or participation restrictions in 'focusing attention' (D160). Additionally, on TFI 73.3% of the patients had severe activity limitations or participation restrictions in 'recreation and leisure' (D920) while on TQ only 3.9% and 35.9% indicated to have severe restrictions.

7.4.5 Influence of environmental factors

Only the TQ registered the influence of environmental factors (table 7.4). Three categories of the ICF were asked in one question (i.e. "I wish someone understood what this problem is like"). Around 40% of the patients indicated severe influence of environmental factors on 'immediate family' (E310), 'friends' (E320) and 'acquaintances, peers, colleagues, neighbors and community members'.

Table 7.4: The prevalence of influence of environmental factors identified by the Tinnitus Questionnaire.

Chapter	ICF category	Number of questions	Contribution to total score	No influence of environmental factors	Mild influence of environmental factors	Severe influence of environmental factors
E3: support and relationships	E310: immediate family	1	2%	26.9%	33.3%	39.7%
	E320: friends	1	2%	26.9%	33.3%	39.7%
	E325: acquaintances, peers, colleagues, neighbors and community members	1	2%	26.9%	33.3%	39.7%

7.5 DISCUSSION

The first aim of the study was to investigate which domains of the ICF are measured by the TFI and TQ. In general, the two questionnaires cover most of the domains and chapters. The chapter 'mental functions' was questioned most, 52% (or 13 questions) on TFI and 71% (or 36 questions) on TQ. Additionally, the categories within the domain 'body functions' were linked most (20 of the total 36 categories). 'Body functions' are described in the ICF as 'physiological functions of body systems' and represent chapters as 'mental functions' and 'sensory functions and pain' which are, in most cases, affected in patients with tinnitus. Since tinnitus is a conscious perception of an auditory sensation, it is understandable that most limitations are found in 'body functions'. No questions were linked to the ICF domain 'body structures' that encompasses 'anatomical parts of the body such as organs, limbs and their components'. This seems logical, since tinnitus and TMD are rarely linked to disturbances in the patient's anatomy [8, 61].

The two questionnaires show overlap in the domains and chapters covered. However, the linked categories differ between the TFI and TQ. First, the category 'content of thought' (B1602) is linked to far more questions in the TQ than in the TFI (33% compared to 4%). This means that the focus of the TQ is more on the measurement of mental and psychological coping compared to the TFI. The fact that the TQ is more suitable to measure the psychological impact of tinnitus, is reasonable because the TQ was originally designed to be used in studies on psychologically based treatments [108, 137]. This difference between the two questionnaires was also pointed out by Jacquemin et al. [137]. Second, looking at the domain 'activity and participation', the TFI measures 9 categories of this domain compared to 5 categories measured by TQ. Additionally, both questionnaires cover different chapters and categories of the domain 'activity and participation' which means that they measure different components of the same domain. Where the TQ is better suited to measure the psychological impact of the tinnitus, the TFI covers a broader spectrum of ICF categories which makes this questionnaire more suitable to measure a more general impact of tinnitus [112]. These results are consistent with the findings of other studies [137, 234, 235].

Overall, the TQ and TFI cover different categories of the ICF. The TFI can be used identifying a broad spectrum of problems in the domains 'body functions' and 'activity and participation'. The TQ, on the other hand, is more applicable for measuring the psychological impact of tinnitus, particularly in the category 'content of thought'.

The second aim of the study was to describe the health status and perceived disability of patients with somatic tinnitus in terms of the ICF. Both TFI and TQ can be linked to the ICF to describe patients' health status and perceived disability. A broad set of impairments in the domains of body functioning, activities and participation is present. Most severe impairments were found in 'mental functions' and 'sensory functions and pain'. Specifically, in the categories 'onset of sleep' (severe impairments in between 41.0% and 62.5% of the patients) and 'sound detection' (severe impairments in 68.8% of the patients). This is in line with a previous research where impairments of speech comprehension, high impact of cognition and sleep quality were found in patients with tinnitus [236 - 239].

Furthermore, there was a discrepancy between the questionnaires in the severity of activity limitations or participation restrictions within our group of tinnitus patients. Looking at the TFI, between 62.5% and 73.3% of the patients scored severe activity limitations or participation restrictions on 'focusing attention' and 'recreation and leisure'. This is in contrast with the TQ where between 9.0% and 35.9% of the patients stated to have no or mild limitation or restriction in these categories. A reason for these differences in severity of limitations between the two questionnaires might be that the TQ uses a 3-point scale to rate each question, while the TFI uses an 11-point Likert scale. Thus, the TQ has limited options to choose from as a patient [137]. A second reason might be that both questionnaires are based on self-report by the patient, but they do differ from each other in the way the questions are prepared. For example, one of the questions about concentration of the TFI is "over the past week, what was your ability to concentrate?". The TQ, on the other hand, formulates a question about

concentration as follows: “the noises have affected my concentration” which might be interpreted differently.

It must be noted that the influence on environmental factors is only measured by one question (i.e. “I wish someone understood what this problem is like”) of the TQ, covering the domain ‘support and relationships’ of the ICF. About 40% of the patients reported to have severe influence on these environmental factors because of the tinnitus. Measuring the influence on environmental factors can be important to gain information about the support at work and at home. Since these factors play a role in maintaining work and a patients’ experience of their mental health, it also influences the persistence and severity of a condition [240, 241].

017, as part of the COMIT study (i.e. Core Outcome Measures in Tinnitus study), several scientists, health professionals and patient representatives stated that determining the best core outcome set in patients with chronic subjective tinnitus is difficult and depends on the intervention [4, 242]. So before starting a clinical trial, it should be clear which specific tinnitus-related complaints are critical to evaluate [4]. However, in the COMIT study only sound-based interventions, psychology-based interventions and pharmacology-based interventions were evaluated. So, orofacial treatment, which is often the treatment for patients with somatic tinnitus complaints, was not analyzed in the study. Looking at our data of somatic tinnitus patients, the chapters ‘mental functions’, ‘sensory functions and pain’, ‘sleep functions’, ‘learning and applying knowledge’ and ‘community, social and civic life’ are important to measure. In general, it is likely that somatic tinnitus patients have a higher score on the chapter ‘sensory functions and pain’ in comparison with other tinnitus patients, since somatic tinnitus is often accompanied by pain in the neck and temporomandibular area. So, future studies should investigate which specific ‘outcome domains’ for patients with ST are necessary. The second step will be to develop an evaluative measurement tool, based on these outcome domains.

Another possible difference is that the patients in our dataset had no or limited hearing loss. As hearing loss might have influence on the answers given on some of the questions (i.e. “how much has your tinnitus interfered with your ability to hear clearly?”, “how has your tinnitus interfered with your ability to understand people who are talking” and “I have more difficulty following a conversation because of the noises”), it is unknown if our results can be generalized to all tinnitus patients. Therefore, future studies should explore the perceived disability in patients with other etiologies of the tinnitus, such as massive hearing loss.

In conclusion, the TQ and TFI questionnaires cover different domains and categories of the ICF and can be used complementary or solely depending on the research question. The TFI is the best option to choose for identifying problems in the domains ‘body functions’ and ‘activity and participation’ since it covers a broad spectrum of ICF categories. The TQ, on the other hand, provides more information about the psychological impact of a patient’s tinnitus on daily life. Somatic tinnitus

patients have impairments and disabilities in all domains of the ICF, particularly in the categories 'onset of sleep' and 'sound detection'.

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ETHICAL APPROVAL

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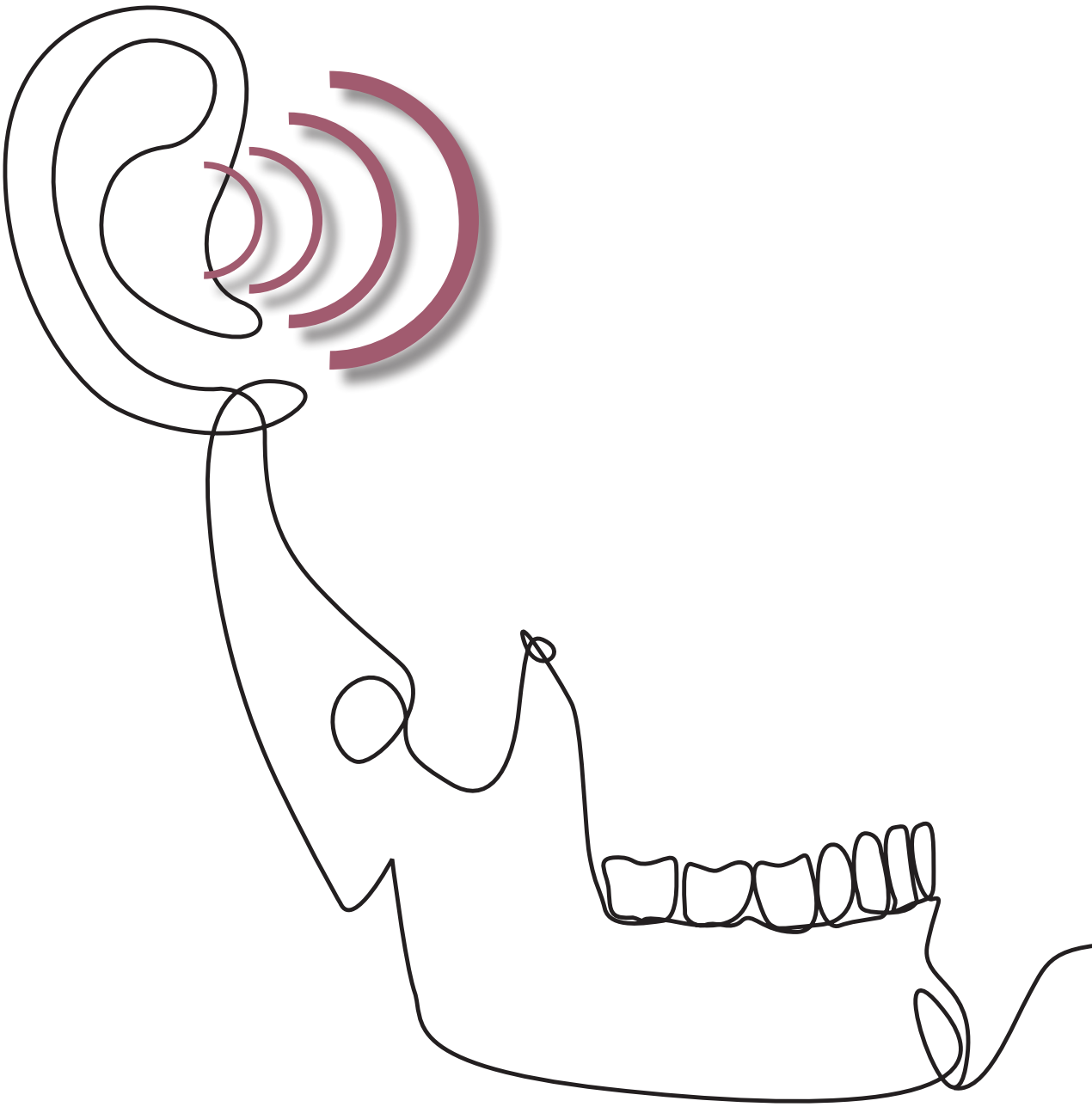
CONFLICTS OF INTERESTS

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.



Chapter 8

General discussion and conclusions

This doctoral thesis was divided in three main parts covering the research objectives. Part one consists of studies that investigate the effect of multidisciplinary orofacial treatment for patients with temporomandibular related somatic tinnitus. It consists of a study protocol, a randomized controlled trial and a mediation analysis. Part two presents prognostic indicators that can predict a positive outcome for this treatment. In this context, the term 'somatic tinnitus (ST)' in this discussion and conclusions section, refers to the specific temporomandibular related form of somatic tinnitus. Part three concerns the impact of tinnitus on patients' functioning and disability in terms of the International Classification of Functioning, Disability and Health (ICF). In this part we wanted to explore which domains of the ICF are covered by the Tinnitus Questionnaire (TQ) and Tinnitus Functional index (TFI) and to describe the health status and perceived disability of patients with ST in ICF terms. These three parts, contain in total seven chapters, in which we addressed the following research questions:

1. What is the effect of multidisciplinary orofacial treatment on somatic tinnitus complaints in patients with ST?

2. To what extent does a decrease in TMD pain contribute to the overall reduction of tinnitus severity after multidisciplinary orofacial treatment?

2. Which prognostic indicators predict a positive outcome after multidisciplinary orofacial treatment?

4. What is the impact of tinnitus on patients in their functioning and disability in terms of the International Classification of Functioning, Disability and Health (ICF)?

8.1 SUMMARY OF MAIN FINDINGS

8.1.1 The effect of orofacial treatment on somatic tinnitus severity

The primary goal of this thesis was to examine the effect of orofacial treatment on tinnitus severity in patients with ST. A significant and clinically relevant decrease in TFI-score was found between the treatment group and control group, indicating a positive effect of TMD treatment on tinnitus severity. This is in line with several other RCT's and cohort studies that found positive effects of orofacial treatment on subjective tinnitus complaints [80-82, 96, 243-246].

Our study adds to the literature because it differs from the forementioned studies on the following aspects: setting, sample, outcome measures and treatments.

First, regarding the **setting and sample**, we included patients with somatic tinnitus in a tertiary clinic, where tinnitus was the primary complaint. This is in contrast with the study of Buergers et al [96] who included patients with a primary TMD complaint accompanied with tinnitus in a dentistry clinic. Attanasio et al [246], on the other hand, included patients with a primary subjective tinnitus complaint, but not all of them had accompanying TMD. When studying a treatment for patients with tinnitus however, we believe it is important to recruit patients where tinnitus is the primary tinnitus complaint. This to allow that the results are transferred to the tinnitus population. By recruiting in this setting and by selectively recruiting our sample with tinnitus and TMD, we are confident that we minimized the selection bias in our study.

Second, we used valid **outcome measures** such as the TQ and TFI to assess the impact tinnitus has on a patient. A variety of measuring tools is used in the literature. The Visual Analog Scale (VAS), Numerical Rating Scale (NRS) and Global Perceived Effect (GPE) are most frequently reported, alongside questionnaires such as the Tinnitus Handicap Inventory (THI), TFI and TQ. Since the VAS and NRS only measure the overall intensity and severity of a patient's tinnitus and they are not specific in measuring the impact of the tinnitus in daily life, we used the TQ and TFI questionnaires that explore a broader spectrum of a patient's tinnitus.

In our RCT a statistically significant difference between both groups was only found using the TFI. The fact that the TQ and TFI cover different domains and categories of the ICF might explain the differences in treatment outcome in our RCT. The TQ, in which we found no significant difference in reduction between the treatment group and the control group, covers more the psychological impact of the tinnitus (i.e. the category 'content of thought'). In our study, however, the treatment was targeted on the reduction of TMD and bruxism, not the psychological aspect of a patient's tinnitus. For example, 33% of the questions of the TQ cover the category 'content of thought'. Specific questions of the TQ that we classified in this ICF category were "It is unfair that I have to suffer with my noises" and "it will be dreadful if these noises will never go away". Since the TMD treatment was not focused on changing disturbing thought patterns of a patient and practicing new coping skills, it

is likely that a patient's cognition after TMD treatment remains unchanged and a smaller decrease in general TQ-scores can be expected.

Third, in our RCT we used a combination of orofacial therapy and an occlusal splint as **treatment** which is currently the best-evidence treatment for TMD [61, 74]. In the abovementioned studies, however, several other treatments modalities were described such as acupuncture, an educational program and manual therapy. So, the used treatment approaches in other studies were often different compared to the treatment performed in our study and not always based on the best-evidence treatment for TMD.

Finally, most previous studies [80-82, 96, 243, 246] showed a high **risk of bias** due to a lack of comparison between groups, selective reporting and incomplete presentation of the data [85]. Looking at the PEDro scale, we believe the risk of bias of our study is low with lack of blinding of the subjects and therapists being the only source of bias [247]. Blinding is an established methodological procedure in RCT's, but in the design of our study, blinding of patients and health care providers (i.e. physical therapists and dentists) was not possible owing to the type of intervention we used (i.e. physical therapy in combination an occlusal splint).
Overall, our study contributes to the current state-of-the-art by providing evidence for the effect of TMD treatment on tinnitus complaints for patients with ST. It is one of the first studies where patients are thoroughly examined on multiple influencing factors before inclusion in a chronic ST sample.

8.1.2 Mediation analysis

The secondary goal of this thesis was to provide insight in the degree to which a decrease in TMD pain actually contributes to the overall reduction of tinnitus severity. In our mediation analyses we calculated that 35% of the overall reduction in tinnitus severity can be attributed to a decrease in TMD pain. This implicates there is another 65% yet to be explained. This thesis did not aim to investigate other potential mediating factors, but some assumptions can be made. First, treatments such as general relaxation exercises and sleep hygiene advices are often included in orofacial therapy, to relax the jaw muscles and decrease clenching and grinding the teeth during the night. These exercises however, can also have an immediate effect on tinnitus severity, due to the general relaxation effect, as has been suggested by Rademaker et al. [248], who concluded that mindfulness based exercises can decrease tinnitus distress. Second, in the mediation analysis we used the TMD pain screener as outcome measure to analyze the mediating effect of reduction in TMD pain. Given that 17.5% of our included patients had only bruxism or other excessive oral parafunctions and thus no actual TMD pain, it would have been interesting to investigate if a reduction of bruxism and/or oral parafunctions could explain another part of the remaining 65%.

8.1.3 Prognostic indicators for a positive treatment outcome

The third goal was to search for prognostic indicators that can predict a positive outcome in tinnitus severity and tinnitus annoyance after multidisciplinary orofacial treatment. Via logistic regression

analysis we found that a 'shorter duration of tinnitus' was a positive prognostic indicator for clinically relevant improvement on both TQ and TFI. The average tinnitus duration of the group of patients who benefited from our treatment was 39 months, compared to 96 months of the patients who did not benefit. Patients with a longer tinnitus history can suffer from a more complex form of tinnitus. They might have multiple maintaining factors that are currently unknown which can make them more therapy resistant.

Besides gender, age and duration of the tinnitus a "good performance on the speech-in-noise test" (SPIN) was also a prognostic indicator for a positive treatment outcome. A better score on the SPIN is an indication for better hearing [117]. Thus, other factors, such as increased somatosensory information due to TMD or excessive bruxism, can have more influence on a patient's tinnitus. This can explain the higher chance of a positive treatment outcome. This prognostic indicator however, does require a specific audiological assessment that is currently not part of the standard assessment of patients with tinnitus. Nevertheless, in clinical practice it can be used by audiologists as indicator for a positive treatment outcome.

In both the prognostic indicator study and the gender study we found that women were more likely to benefit from TMD treatment than men. Since the risk for developing TMD is twice as high in women than in men [208, 249], we hypothesize that the proportion of true TMD pain sufferers in our sample was higher in females compared to males. For this reason, we reanalyzed our sample of patients. We found that the number of patients with only bruxism (thus without TMD pain) was higher in men compared with woman (25% and 12% respectively). This is in line with a study of Vielsmeier et al. who also found that patients with tinnitus and TMD were more frequently female [172]. It is important, though, that the fact that women are more likely to benefit from orofacial treatment, does not implicate that male patients should be excluded from the therapy, since men can also suffer from TMD. Additionally, gender is not the only influencing factor, as previously mentioned. Our multivariate model based on the TQ, for instance, showed that "shorter duration of tinnitus" and a "higher initial score on the TQ somatic subscale" correctly predicts 68.5% of the outcome on the TQ. So, in this model, these factors were more important than the influence of gender.

In conclusion, we found various prognostic indicators that can be used to increase the clinical success rates of TMD treatment. Keeping in mind these prognostic indicators in the clinic might avoid unnecessary treatment.

8.1.4 Health status and perceived disability of patients with somatic tinnitus

The fourth aim of our study was to describe the health status and perceived disability of patients with ST in terms of the ICF.

First, we investigated which domains of the ICF are measured by the TFI and TQ. Our results showed that the TFI identifies a broad spectrum of impairments and disabilities (i.e. in the domains 'body

functions' and 'activity and participation') and the TQ covers more the psychological impact of a patient's tinnitus (i.e. in the category 'content of thought'). Thus, the two questionnaires cover distinct domains of the ICF. This difference between the two questionnaires was also pointed out by Jacquemin et al [137] and Boecking et al [250] who investigated the convergent validity of the Dutch and German subscales of the TQ and TFI. Both studies found a poor agreement between the two questionnaires suggesting that the specific subscales measure different underlying aspects of a patient's tinnitus.

Second, we described the health status and perceived disability of patients with somatic tinnitus in terms of the ICF. In our sample, patients had particularly problems in the categories 'onset of sleep' and 'sound detection' which is in line with studies of Asplund and Stephans [251] and Sanchez [252]. To improve the personalized care, it might be necessary to add other treatments to the TMD treatment that specifically targets the dysfunctions of the individual tinnitus patient. In the current literature, several treatment options are described to improve sleep in patients with tinnitus such as CBT, TRT and medication (i.e. melatonin solely or a combination of melatonin and sulodexide) [221, 253-257]. Treatment options to improve 'sound detection' are sound therapies (e.g. hearing aids with sound generator) combined with education and counseling [258]. The value of these therapies in combination with TMD treatment should be investigated in the future.

8.2 STRENGTHS AND LIMITATIONS

Our study had several strengths and limitations regarding recruitment setting, design, treatment and secondary analyses.

8.2.1 Recruitment setting

All participants underwent an extensive tinnitus assessment by a multidisciplinary team. This selective way of recruiting enabled us to identify those patients where the somatic system was the major influencing factor. This probably has contributed to the observed effect since it increased the number of patients that were susceptible to a somatic treatment. It must be noted, however, that an extensive assessment with so many disciplines involved is not always possible in other settings (e.g. primary and secondary care) due to the lack of time and/or number of specialists available in the clinic. On the other hand, patients from a tertiary tinnitus clinic are known to be more therapy resistant than patients from primary and secondary care [259]. Taking this into account we are confident our results can be generalized to non-tertiary settings.

8.2.2 Design

A delayed treatment design has the advantage that all patients can receive the orofacial treatment. Since our RCT was performed in a tertiary tinnitus clinic in which patients have a request for a treatment, we considered that using a waiting group that would receive no treatment was ethically

untenable. A disadvantage of the delayed treatment design however, is the limited time before the control group starts the treatment, that can result in an underestimated treatment effect [260]. In our study, most patients continued to improve after TMD treatment was completed and thus, the largest effect was found after follow up. However, we were unable to compare both groups at this timepoint since, the control group already started the therapy. Another downside of creating a waiting group is that most patients preferred to start with the therapy immediately after inclusion. For this reason, some patients were reluctant to wait for 9 weeks. In future studies a different design in a tertiary tinnitus population is recommended, for example an RCT comparing two treatment groups.

8.2.3 Treatment

For the treatment of TMD complaints, patients received orofacial treatment comprising a combination of physical therapy and an occlusal splint which is currently the evidence-based treatment for the conservative management of TMD [61, 74]. Patients with bruxism alone received the same treatment. However, the current evidence for this type of treatment for bruxism alone is lower that it is for TMD. To date, combinations of treatments of the "multiple-P approach" (i.e. Pep-talk, Physiotherapy, Psychology, Plates and Pills) involving diverse health care professionals has been proposed in the literature, but it is unclear which combination of treatments is most effective. It must be noted, though, that the combination of physical therapy and an occlusal splint, as we performed in our study, is most frequently used [78, 261, 262].

Another benefit of our study is that the orofacial treatment was provided by physical therapists and dentists from inside and outside our clinic which increases the accessibility of the treatment. Prior to the start of our study, all physical therapists were specifically trained to standardize the required treatment. Since differences in the performance of the treatment between individual therapists often exist and might have influenced the results, we performed a post-hoc analysis where we divided the physical therapists from inside and outside the clinic into two groups. However, no significant differences in treatment effect were found. So, the fact that the treatment was performed by different therapists did not influence our results and even increased the external validity of our study.

8.2.4 Secondary analyses

For our mediation analyses, we used the TMD pain screener as an evaluation measurement tool. However, the TMD pain screener is primarily designed as a diagnostic tool for a painful TMD and the responsiveness to change of the TMD pain screener has not yet been described in the literature. Therefore, future studies could investigate the responsiveness of the TMD pain screener or conversely, a mediation analyses can be performed with a measurement tool for TMD where the responsiveness to change is already investigated. For example, the Jaw Functional Limitation Scale that is also recommended in the Diagnostic Criteria of TMD (DC-TMD) [61, 263].

To identify prognostic indicators for a positive outcome after orofacial treatment, data from the RCT (n=80) and an additional cohort (n=21) were used. In a group of 101 patients, generally a maximum

of 10 potential prognostic indicators is used as a rule of thumb. Originally, we started from 30 potential prognostic indicators which we selected based on existing knowledge about potential influence. The number of potential prognostic indicators was reduced before the actual analyses by testing all 30 indicators for multicollinearity and only using the strongest indicators for the logistic regression analysis. This approach reduced the total number of potential prognostic indicators included in the logistic regression analysis to 10. In this way, we could avoid bias due to multicollinearity.

8.3 CLINICAL IMPLICATIONS

Orofacial treatment can decrease tinnitus severity in patients with ST. However, for a clinician it is often difficult to recognize those patients where TMD is the most important influencing factor of the tinnitus. So, correctly identifying and referring patients with ST for treatment can be challenging. For physical therapists, who get patients referred to them, sometimes without extensive tinnitus assessment by an otorhinolaryngologist, it is often difficult to determine the patient's prognosis. Furthermore, dentists are often not aware of the potential connection between TMD and tinnitus. Therefore, we present some important clinical findings and recommendations for ENT specialists, audiologists, physical therapists and dentists, based on the results of this thesis.

First, regarding the **effectiveness of the treatment**. Our results showed that orofacial treatment can decrease tinnitus severity in a chronic tinnitus population. So, patients with temporomandibular related ST can benefit from TMD treatment. In most cases, our treatment reduced tinnitus severity, but it did not disappear completely. In a very limited number of patients, however, the tinnitus almost completely resolved. Since patients from a tertiary tinnitus clinic are known to be more therapy resistant, we expect that the same or even better results can be achieved in primary or secondary care.

Second, specifically "young women" with "a shorter duration of tinnitus" and "a higher score on the somatic subscale of the TQ" are **most likely to benefit** from orofacial treatment. These prognostic indicators can be used by physical therapists to predict a clinical outcome of a treatment and by otorhinolaryngologists and audiologists to increase the clinical success rates by targeted referral. In addition, the questions of the somatic subscale of the TQ (table 8.1) can be used in medical history as an indicator for ST since a higher score on this subscale predicts a higher chance for positive treatment outcome after orofacial treatment.

Table 8.1: Specific questions of the somatic subscale of the Tinnitus Questionnaire.

The noises sometimes give me a pain in the ear or head
Because of the noises, I have tension in the muscles of my head and neck
The noises sometimes produce a bad headache

Third, **questionnaires** such as the TQ and TFI can identify the impact of a patient's tinnitus in daily life. However, both questionnaires measure different domains of the ICF and can be used solely or complementary, depending on the underlying clinical question. The TQ is most suited to evaluate the psychological impact of a patient's tinnitus since it covers specifically the ICF category 'content of thought'. The TFI, on the other hand, identifies a broad spectrum of problems in the domains 'body functions' and 'activity and participation'. In our sample of patients, the TFI showed to be a more responsive evaluation tool since most patients had a clinically relevant improvement after treatment. For this reason, the TFI is currently the best option as evaluation measurement in patients with ST.

8.3.1 Specific recommendations for the otorhinolaryngologist and audiologist

For otorhinolaryngologists and audiologists it might be difficult to determine if a patient suffers from TMD. For these clinicians, the TMD pain screener can be **a helpful diagnostic tool,** since it is a brief and valid questionnaire to detect pain-related TMD [61, 106]. Patients with a score of three points or more are suspected to have a painful TMD and are a likely candidate for orofacial treatment.

Orofacial treatment can be provided by **a skilled physical therapist**. It must be noted, however, that not all physical therapists are specialized in the treatment of TMD. For this reason, we recommend to refer patients suspected from TMD related ST, to a physical therapist that is experienced in treating patients with TMD. Additionally, the TMD treatment can be combined with an occlusal splint (i.e. in case of excessive nighttime grinding) applied by the dentist.

8.3.2 Specific recommendations for physical therapists

An extensive TMD assessment is necessary to detect the presence of TMD. So, for physical therapists it is important to correctly diagnose the patient and communicate the findings with the referring physician. For the orofacial assessment, **the DC-TMD protocol** can be used since it is valid to detect the most common pain related TMD and is internationally recommended by experts [61]. In this protocol the orofacial assessment comprises the measurement of the movements of the jaw, tenderness on palpation of the masticatory muscles and static and dynamic movement tests. Based on these tests, the assessor is able to identify if the cause of TMD is mainly articular, muscular or combined articular and muscular.

Once the cause of the TMD is identified, **focus should lie on the treatment of TMD,** not on the tinnitus. Since a decrease in TMD pain contributes to a reduction of tinnitus, the treatment should focus on reducing TMD dysfunctions. This point is related to our second advice: **refrain from asking whether the tinnitus change during every treatment session**, since it will increase the patients' focus on the tinnitus. This will result in an increase of related distress associated with tinnitus and thus trigger the limbic, autonomic and auditory system. Thirdly, **do not expect immediate effect of your treatment on tinnitus severity**, since treating TMD symptoms can increase the activity in the somatosensory system and might even worsen a patient's tinnitus at first. Somatosensory afference should be normalized for a longer period before an effect on the tinnitus can be expected. This is

in line with the results of our study where we found that most patients further improved after TMD treatment was completed.

8.3.3 Specific recommendation for dentists

Dentistry interventions, TMD and bruxism can exacerbate tinnitus complaints. For this reason, dentists should be aware of the possible link between the auditory system and the temporomandibular area. If a patient is diagnosed by the dentist with TMD or excessive bruxism, dentists should **ask whether a patient has additional tinnitus complaints**. In case the dentist suspects ST related with the temporomandibular area and other causes or major influencing factors for the tinnitus are excluded by the ENT specialist, a patient can be treated by the dentist and/or physical therapist, dependent on the patients' TMD complaints.

8.4 RECOMMENDATION FOR FUTURE RESEARCH

The studies conducted in this doctoral thesis make several contributions to the current knowledge of somatic tinnitus treatment and the measurement of the health status and perceived disability in patients with ST. Still, several questions remain and need to be investigated in the future.

The results of our RCT showed that 61% of our patients had a clinically relevant improvement in tinnitus severity after TMD treatment. This means that the remaining 39% of the patients still suffer from moderate to severe tinnitus complaints and have a request for help. It might be possible that in some of these patients, an additional influence on the tinnitus was present from subclinical anxiety or depression that might have affected the outcome of our orofacial treatment. Relatively high anxiety or depression scores could be expected in our population, since anxiety and depression are also associated with temporomandibular disorders [65], although patients with a diagnosed anxiety or depression disorder were excluded from the study. In this specific group of TMD patients where psychological problems negatively influence the TMD complaint, a multidisciplinary TMD treatment with psychologist, physical therapist might be more effective [103, 264]. This is in line with the advice of several researchers to use multimodal, interdisciplinary therapeutic trajectories in TMD patients with major psychological problems [123, 265]. So, an RCT could investigate the effect of multidisciplinary TMD treatment applied by psychologist, physical therapist and dentist in ST patients with accompanying influence from anxiety or depression.

For the ST patients without major psychological problems, TMD treatment in combination with another therapy targeted on the particular disability of the patient might be even more successful. Since patients in our population had specific problems in the categories 'onset of sleep' and 'sound detection', a combination treatment with sleep medication and/or sound therapies (e.g. tinnitus masking by hearing aids) could be explored.

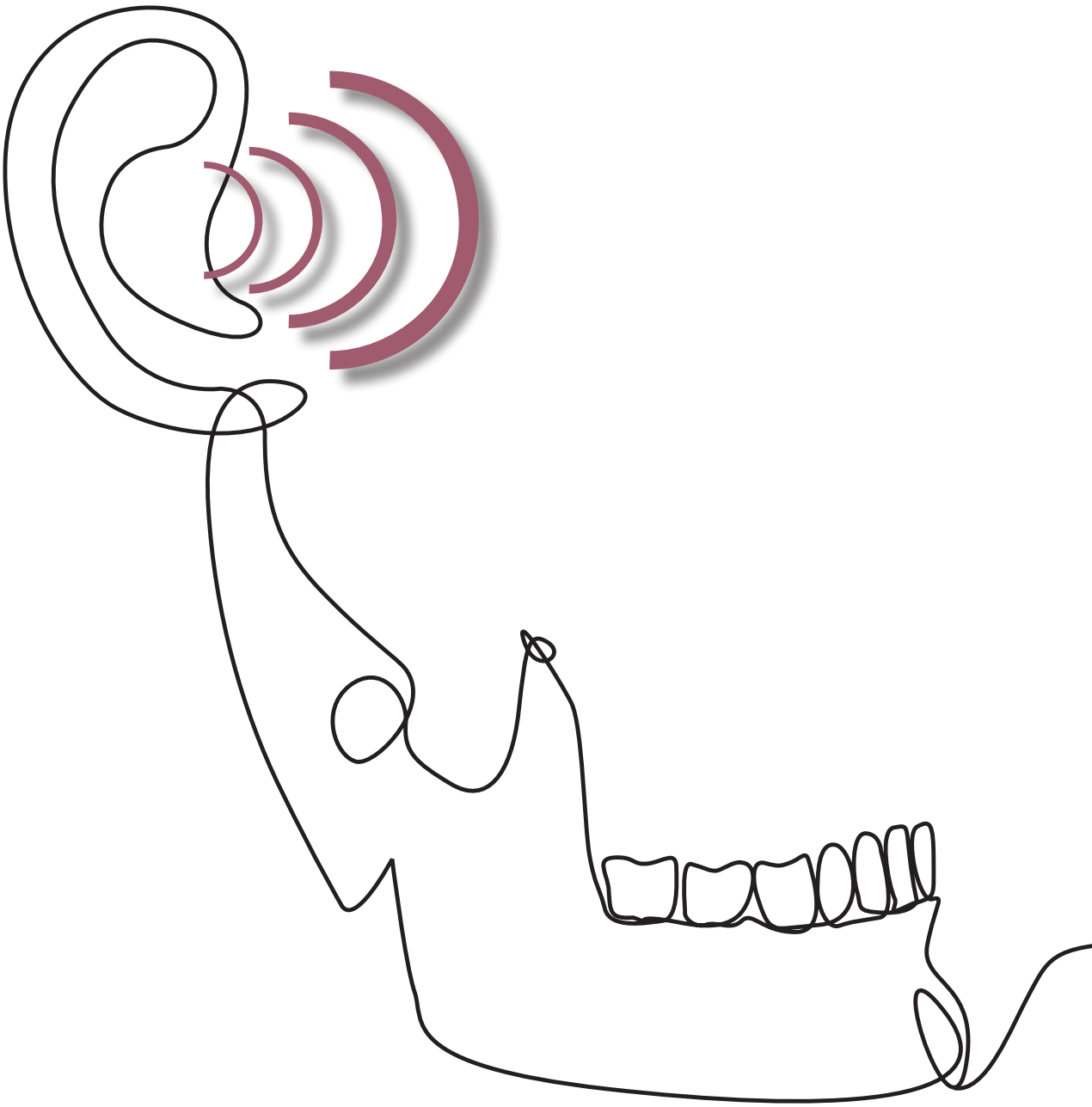
Furthermore, future research could investigate if a quick referral for orofacial therapy can increase treatment success patients. Since "a shorter duration of the tinnitus" is a prognostic indicator for positive outcome after TMD treatment, an early treatment for patients who suffer from chronic tinnitus seems important. However, for general practitioners it is difficult to determine if a patient suffers from ST since the combination of tinnitus and TMD is not always related. Therefore, future research could explore new pathways for chronic tinnitus patients such as a "one stop tinnitus service" where a patient gets an assessment of an ENT specialist, an audiologist, a psychologist, a physical therapist and dentist, in one appointment [259, 266]. After full ENT examination, necessary audiological and psychological tests, and orofacial examination, these specialists can make a management plan together, tailored to the individual needs of the tinnitus patient. In this way, patients can be earlier diagnosed and referred for treatment which might reduce the risk for chronicity.

Determining which tinnitus-related outcome measures are relevant and how the effectiveness of an intervention in patients with ST can be measured, remains difficult [4]. We used two disease specific questionnaires (i.e. the TQ and TFI) to measure tinnitus annoyance and tinnitus severity [267]. Prior to the start of our study, we hypothesized that the TQ would be more responsive to change for a physical therapy intervention than the TFI since it contained a somatic subscale. However, the number of somatic questions asked in the TQ is limited to three which is proportionally small in a total of 52 questions. In general, there is need for intervention-specific standards to objectify a patient's tinnitus that can be used in clinical and research settings [4]. For this reason, a set of core outcome domains was developed for sound-based, psychology-based and pharmacology-based interventions, but no information on outcome domains for physical therapy interventions is available [4]. So, future studies should investigate which specific 'outcome domains' for the evaluation of orofacial treatment are necessary. The second step will be to develop an evaluative measurement tool for patients with ST, based on these outcome domains. Currently, specific questions about somatic complaints are minimally asked in the existing questionnaires, but should be more extensively questioned in patients with ST.

8.5 FINAL CONSIDERATIONS

The findings in this thesis are encouraging for the treatment of somatic tinnitus. By investigating the effect of TMD treatment and prognostic indicators that can predict a positive outcome, this thesis studied some important research questions regarding temporomandibular related somatic tinnitus.

Our results showed that TMD treatment should be considered in patients with temporomandibular related somatic tinnitus. Furthermore, TMD assessment needs to be included in the examination of all patients with subjective tinnitus to investigate if the temporomandibular area is one of the major influencing factors. Given the expertise in this area, physical therapists and dentists can play a role in the assessment and treatment of somatic tinnitus.



Appendices

1. Tinnitus Questionnaire (TQ)
2. Tinnitus Functional Index (TFI)
3. TMD pain screener

1. Tinnitus Questionnaire (TQ)

	Tinnitus Questionnaire	True	Partly true	Not true
1	I can sometimes ignore the noises even when are there			
2	I am unable to enjoy listening to music because of the noises			
3	It's unfair that I have to suffer with my noises			
4	I wake up more in the night because of my noises			
5	I am aware of the noises form the moment I get up to the moment I sleep			
6	Your attitude to the noise makes no difference to how it affects you			
7	Most of the time the noises are fairly quiet			
8	I worry that the noises will give me a nervous breakdown			
9	Because of the noises I have difficulty in telling where sounds are coming from			
10	The way the noises sound is really unpleasant			
11	I feel I can never get away from the noises			
12	Because of the noises I wake up earlier in the morning			
13	I worry whether I will be able to put up with this problem forever			
14	Because of the noises it is more difficult to listen to several people at once			
15	The noises are loud most of the time			
16	Because of the noises I worry that there is something seriously wrong with my body			
17	If the noises continue my life will not be worth living			
18	I have lost some of my confidence because of the noises			
19	I wish someone understood what this problem is like			
20	The noises distract me whatever I am doing			
21	There is very little one can do to cope with the noises			
22	The noises sometimes give me a pain in the ear or head			
23	When I feel low or pessimistic the noise seems to worse			
24	I am more irritable with my family and friends because of the noises			
25	Because of the noises I have tension in the muscles of my head and neck			
26	Because of the noises other people's voices sound distorted to me			
27	It will be dreadful if these noises never go away			
28	I worry that the noises might damage my physical health			
29	The noises seem to go right through my head			
30	Almost all my problems are caused by these noises			
31	Sleep is my main problem			
32	It's the way you think about the noise – NOT the noise itself which makes you upset			
33	I have more difficulty following a conversation because of the noises			
34	I find it harder to relax because of the noises			

35	My noises are often so bad that I cannot ignore them			
36	I takes me longer to get to sleep because of the noises			
37	I sometimes get very angry when I think about having the noises			
38	I find it harder to use the telephone because of the noises			
39	I am more liable to feel low because of the noises			
40	I am able to forget about the noises when I am doing something interesting			
41	Because of the noises life seems to be getting on top of me			
42	I have always been sensitive about trouble with my ears			
43	I often think about whether the noises will ever go away			
44	I can imagine coping with the noises			
45	The noises never 'let up'			
46	A stronger person might be better at accepting this problem			
47	I am a victim of my noises			
48	The noises have affected my concentration			
49	The noises are one of those problems in life you have to live with			
50	Because of the noises are one of those problems in life you have to live with			
51	The noises sometimes produce a bad headache			
52	I have always been a light sleeper			

2. Tinnitus Functional Index (TFI)

TINNITUS FUNCTIONAL INDEX

Today's Date _____ (Month / Day / Year) Your Name _____ (Please Print)

Please read each question below carefully. To answer a question, select *ONE* of the numbers that is listed for that question, and draw a *CIRCLE* around it like this: (10%) or (1).

I **Over the PAST WEEK...**

1. What percentage of your time awake were you consciously **AWARE OF** your tinnitus?

Never aware ► 0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100% ◄ *Always aware*

2. How **STRONG** or **LOUD** was your tinnitus?

Not at all strong or loud ►0 1 2 3 4 5 6 7 8 9 10 ◄ *Extremely strong or loud*

3. What percentage of your time awake were you **ANNOYED** by your tinnitus?

None of the time ► 0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100% ◄ *All of the time*

SC **Over the PAST WEEK...**

4. Did you feel **IN CONTROL** in regard to your tinnitus?

Very much in control ►0 1 2 3 4 5 6 7 8 9 10 ◄ *Never in control*

5. How easy was it for you to **COPE** with your tinnitus?

Very easy to cope ► 0 1 2 3 4 5 6 7 8 9 10 ◄ *Impossible to cope*

6. How easy was it for you to **IGNORE** your tinnitus?

Very easy to ignore ► 0 1 2 3 4 5 6 7 8 9 10 ◄ *Impossible to ignore*

C **Over the PAST WEEK...**

7. Your ability to **CONCENTRATE**?

Did not interfere ► 0 1 2 3 4 5 6 7 8 9 10 ◄ *Completely interfered*

8. Your ability to **THINK CLEARLY?**

Did not interfere ► 0 1 2 3 4 5 6 7 8 9 10 ◄ *Completely interfered*

9. Your ability to **FOCUS ATTENTION** on other things besides your tinnitus?

Did not interfere ► 0 1 2 3 4 5 6 7 8 9 10 ◄ *Completely interfered*

SL **Over the PAST WEEK...**

10. How often did your tinnitus make it difficult to **FALL ASLEEP or STAY ASLEEP**?

Never had difficulty ► 0 1 2 3 4 5 6 7 8 9 10 ◄ *Always had difficulty*

11. How often did your tinnitus cause you difficulty in getting **AS MUCH SLEEP** as you needed?

Never had difficulty ► 0 1 2 3 4 5 6 7 8 9 10 ◄ *Always had difficulty*

12. How much of the time did your tinnitus keep you from **SLEEPING** as **DEEPLY** or as **PEACEFULLY** as you would have liked?

None of the time ► 0 1 2 3 4 5 6 7 8 9 10 ◄ *All of the time*

 08.15.08

TINNITUS FUNCTIONAL INDEX PAGE 2

Please read each question below carefully. To answer a question, select *ONE* of the numbers that is listed for that question, and draw a *CIRCLE* around it like this: (10%) or (1).

A	**Over the PAST WEEK, how much has your tinnitus interfered with...**	*Did not interfere*									*Completely interfered*
13.	Your ability to **HEAR CLEARLY**?	0	1	2	3	4	5	6	7	8	9	10
14.	Your ability to **UNDERSTAND PEOPLE** who are talking?	0	1	2	3	4	5	6	7	8	9	10
15.	Your ability to **FOLLOW CONVERSATIONS** in a group or at meetings?	0	1	2	3	4	5	6	7	8	9	10
R	**Over the PAST WEEK, how much has your tinnitus interfered with...**	*Did not interfere*									*Completely interfered*
16.	Your **QUIET RESTING ACTIVITIES**?	0	1	2	3	4	5	6	7	8	9	10
17.	Your ability to **RELAX**?	0	1	2	3	4	5	6	7	8	9	10
18.	Your ability to enjoy "**PEACE AND QUIET**"?	0	1	2	3	4	5	6	7	8	9	10
Q	**Over the PAST WEEK, how much has your tinnitus interfered with...**	*Did not interfere*									*Completely interfered*
19.	Your enjoyment of **SOCIAL ACTIVITIES**?	0	1	2	3	4	5	6	7	8	9	10
20.	Your **ENJOYMENT OF LIFE**?	0	1	2	3	4	5	6	7	8	9	10
21.	Your **RELATIONSHIPS** with family, friends and other people?	0	1	2	3	4	5	6	7	8	9	10

22. How often did your tinnitus cause you to have difficulty performing your **WORK OR OTHER TASKS**, such as home maintenance, school work, or caring for children or others?

Never had difficulty ► 0 1 2 3 4 5 6 7 8 9 10 ◄ *Always had difficulty*

E **Over the PAST WEEK...**

23. How **ANXIOUS** or **WORRIED** has your tinnitus made you feel?

Not at all anxious or worried ► 0 1 2 3 4 5 6 7 8 9 10 ◄ *Extremely anxious or worried*

24. How **BOTHERED** or **UPSET** have you been because of your tinnitus?

Not at all bothered or upset ► 0 1 2 3 4 5 6 7 8 9 10 ◄ *Extremely bothered or upset*

25. How **DEPRESSED** were you because of your tinnitus?

Not at all depressed ► 0 1 2 3 4 5 6 7 8 9 10 ◄ *Extremely depressed*

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3. TMD pain screener

TMD-pain screener

1. In de last 30 days, how long did any pain last in your jaw or temple area on either side?
    a. No pain
    b. Pain comes and goes
    c. Pain is always present

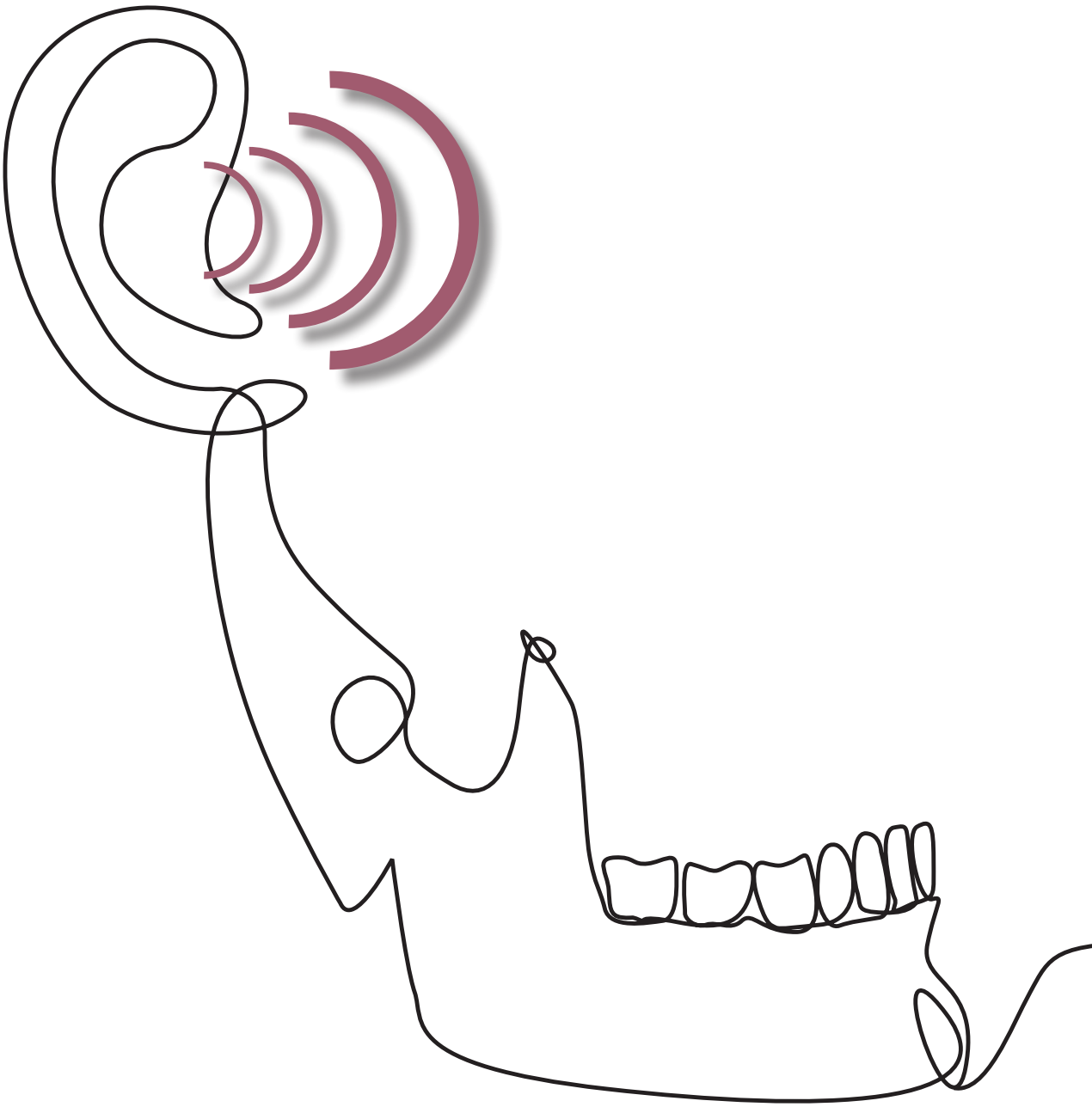
2. In the last 30 days, have you had pain or stiffness in your jaw on awakening?
    a. No
    b. Yes

3. In the last 30 days, did the following activities change any pain (that is, make it better or make it worse) in your jaw or temple area on either side?
    A. Chewing hard or tough food
        a. No
        b. Yes

    B. Opening your mouth or moving your jaw forward or to the side
        a. No
        b. Yes

    C. Jaw habits such as holding teeth together, clenching, grinding, or chewing gum
        a. No
        b. Yes

    D. Other jaw activities such as talking, kissing or yawning
        a. No
        b. Yes



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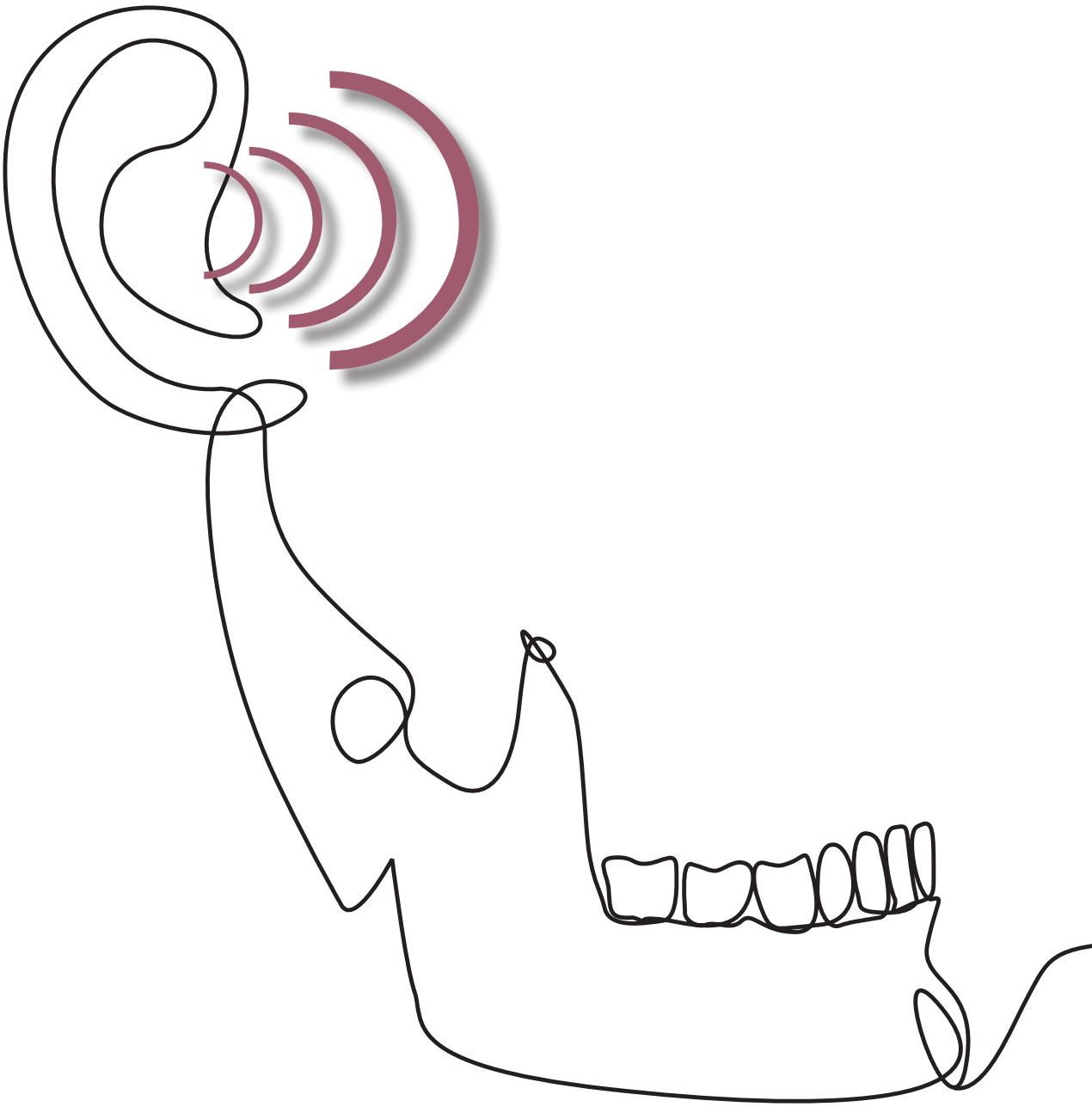

Dankwoord

DANKWOORD

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CURRICULUM VITAE

Annemarie van der Wal was born in Tiel, the Netherlands, on June 23, 1982. After her years at the preuniversity secondary education (VWO) at the Lingecollege in Tiel, she started her study at the International school for physical therapy in Nieuwegein in 2001. She graduated after three years and decided in 2005 to specialize in Manual Therapy at the University of Applied Sciences in Utrecht. After working for several years in private practice as physical and manual therapist, she was asked to teach at the Master Manual Therapy at Utrecht University. Here she met Anton de Wijer, co-founder and first chairman of the Dutch Association Physiotherapy and Dentistry (NVOF), who made her enthusiastic about the field of orofacial therapy. That is why she decided in 2015 to start a second master in orofacial therapy at HAN University of Applied Sciences, where she graduated in 2016.

In 2018 she got the opportunity to do a PhD research on “temporomandibular disfunctions and tinnitus” under the supervision of Prof. Dr. Van de Heyning, Prof. Dr. Willem De Hertogh and Prof. Dr. Sarah Michiels at the University of Antwerp and the University Hospital of Antwerp. One year later, on the Tinnitus Research Initiatives (TRI) conference in Taiwan, she won one of the three best paper awards.

Her ultimate career goal is to continue the combination of patient care, education and research within the field of orofacial physical therapy and somatic tinnitus. To date, Annemarie works as a specialized physical therapist in a private practice in Beuningen and Eck en Wiel and teaches at the University of Applied Sciences in Utrecht. In September 2021, she started to work as an orofacial therapist and teacher at the Academic Centre for Dentistry Amsterdam (ACTA), where she continuous to teach, conduct research and helps patients.

In the spare time, Annemarie rides her horse Indy Sarah at competition level of dressage, and travels around the world with her partner Gijs Timmers.

For a complete overview of her profile, scan the QR-code:

Proefschrift voorgelegd tot het behalen van de graad van Doctor
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