Hearing symptoms in children and adolescents

Tinnitus and temporary threshold shift

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Ale Tryckteam

To my entire family

Felix qui potuit rerum cognoscere causas
Vergilius 490 A.D.

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ABSTRACT

This thesis has assessed the prevalence of spontaneous tinnitus (ST), noise-induced tinnitus (NIT) and temporary threshold shift (TTS) in children and adolescents as well as investigated some of the audiometric, medical and psychological characteristics of young subjects with tinnitus. Additionally, long-term effects of noise exposure were examined in relation to ST, NIT and TTS. The methods employed included hearing measurements, tinnitus specific questionnaires to assess the prevalence of ST, NIT and TTS and Hospital Anxiety and Depression Scale to assess symptoms of mood disorders. Paper I reported the prevalence of ST as 46% and NIT as 53%, among 274 investigated schoolchildren (ages 9-16 years; 135 girls, 135 boys). Secondly, the characteristics of 95 consecutive young patients (55 boys and 40 girls) with tinnitus were also explored in Paper I. The onset of tinnitus was most often sudden and, in 54% of the subjects, preceded by noise exposure, predominantly music. The severity of tinnitus correlated to a deterioration in high frequency pure tone average of hearing thresholds and to possible depression or anxiety (r+p). Paper II reported the tinnitus prevalence in 756 seven-year olds as 40.8% among the normal hearing population and 58% among children with hearing loss. Paper III investigated 1105 16-17 year old students in their first and their last year of high school. Results demonstrated NIT in 55% of the students and ST in 33% of the students in the first, and 37% in the last year. Those with tinnitus reported higher scores for HAD-anxiety. The leisure activity most associated with ST, NIT and TTS was playing instruments and attending concerts. This thesis has presented results demonstrating the connections between tinnitus in children and adolescents, signs of incipient hearing impairment, particularly in the high frequency regions, noise exposure (predominantly from live and amplified music) and anxiety symptoms.

Keywords: Adolescent, child, tinnitus, hearing loss, noise, stress, anxiety
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LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I. Holgers, K. M. and J. Juul. The suffering of tinnitus in childhood and adolescence. Int J Audiol 2006;45: 267-272.

II. Juul J, Barrenäs ML, Holgers KM. Tinnitus and hearing in 7-year-old children. Arch Dis Child 2012;97:28-30.

III. Juul J, Holgers KM. Tinnitus in adolescents – intrinsic and extrinsic factors. In manuscript, submitted

CONTENT

1 ABBREVIATIONS

BDI	Beck Depression Inventory
BYI	Beck Youth Inventory
CANS	Central auditory nervous system
dB (HL)	decibel Hearing level
dB (SPL)	decibel Sound pressure level
HADS	Hospital Anxiety and Depression Scale
HI	Hearing impairment
MADRS	Montgomery-Åsberg Depression Rating Scale
NIHL	Noise induced hearing loss
NIT	Noise induced tinnitus
OAE	Otoacoustic emissions
PRO	Patient Report Outcome
PTA	Pure tone average (mean hearing thresholds)
$PTA_{0.5,1,2}$	PTA for the frequencies 0.5, 1 and 2 kHz
$PTA_{3,4,6}$	PTA for the frequencies 3, 4 and 6 kHz
SNHL	Sensorineural hearing loss
SOM	Secretory otitis media
ST	Spontaneous tinnitus
STAI	State and Trait Anxiety Inventory
TSQ	Tinnitus severity questionnaire
TTS	Temporary threshold shift

2 INTRODUCTION

Why do research? Already as a little girl, I was interested in how the body works. I was an inquisitive (my parents would say nosy) child. I used to prepare smelly concoctions in our basement, which were then administered to my teddy bears by injection using needles from a hospital, where my grandmother worked as director of the paediatric department. Maybe the concoctions were poisons, maybe vaccines; maybe it was a question of dosage. Several years later, this interest is as strong as ever with the only difference being that my work tools are more refined.

In our clinical work, we physicians often meet people with ailments, which we cannot alleviate. Often, even when a cure is lacking, patients seem satisfied with only an explanation of disease pathophysiology and how the disease affects their life. How can this be? Moreover, even with our explanations and research, to what extent is the information we impart valid? Why do so many people complain of a symptom when it appears that so few characteristics unite them? In addition, if the proposed treatments span from physiotherapy to medication to acupuncture, are we even talking about the same illness? Alternatively, if so, what are the mechanisms involved? It was this starting point, which made me interested to learn more about tinnitus and motivated me to join the tinnitus research, led by my tutor, Kajsa-Mia Holgers. I wanted to know more about how we can understand this symptom and why this wide range of management strategies could fit one symptom. In our department, children seeking medical help for tinnitus became increasingly frequent. Within the specifics of childhood, this symptom was not particularly emphasized and the topic therefore seemed both interesting and challenging.

Tinnitus is very common, with 10-15% of the population experiencing it notably, whilst only 2-4% seek medical attention. What we call “tinnitus” in the everyday language is somewhat different than when we consider tinnitus in a medical setting. Even within the medical field, different approaches and symptom perspectives exist. There are different aspects of tinnitus that have to be considered. A major shortcoming hampering result comparisons is that the topic concerns a subjective symptom, with various definitions used throughout the medical field. In the background section, I present some of these definitions and specify which one has been used in our approach.

Many hypotheses exist regarding the pathological mechanisms of tinnitus, both in terms of why it presents but also why it persists and becomes a problem. As each study needs to limit the number of observed variables, we see many different mechanisms and correlations being proposed. Hearing loss, noise exposure, alterations in the central nervous system, neural mapping, neuroendocrine imbalance, personality traits are some of the suggested areas. This thesis aims to present several of them.

3 BACKGROUND

Tinnitus can present in both adults and children, but more studies on tinnitus in adults have been done, than in children and/or adolescents.

When performing a literature search in Medline and Scopus for tinnitus studies including children, using the MESH term "Tinnitus" and the filters "Humans" and "Child: birth-18 years" the yield was 782 hits from1965 to January 2013. Narrowing it down to Tinnitus as a major MESH-term resulted in 446 hits. Since the focus of this thesis and the conducted studies presented herein is on subjective tinnitus, a term which will later be presented in detail but which has been used ambiguously for the past 50 years, it required manual control of each hit, to exclude studies on objective tinnitus. Further exclusions were case reports, validations of questionnaires, populations only including patients aged 18 years and older, unavailable abstracts, correlations to sudden deafness and specific auditory or neurological disease. Following this procedure, the number of relevant articles addressing subjective tinnitus was 126. Studies of a more general character, concerning the unselected population of young people reporting tinnitus, turned out to be not more than 40, going back to 1965. Some of these references are included further down in the text and the reference list.

3.1 Tinnitus as a sensation

In 1953, Bergman and Heller performed a classic experiment, where 80 individuals with no prior reports of tinnitus, were asked to sit in a sound proofed room for 5 minutes, under the pretext of a hearing test. The subjects were asked to report on any sounds that might be heard. Concentrating on hearing potential sounds, unbeknown to them, they were subjected to 5 minutes of total silence. Ninety-three per cent reported hearing buzzing, pulsating, whistling sounds in the head or ears identical to those reported by tinnitus sufferers.

This experiment demonstrates that tinnitus, as a sensation, can be harmless and even physiological. The difficulty arises in the distinction between the "tinnitus" that is a physiological sensation and the tinnitus that at some point should be considered pathological.

Consequently, the definition of tinnitus is a problematic issue and will be further described in this thesis. The different risk factors reported for developing tinnitus will be expanded upon.

3.2 Definitions and pathophysiological mechanisms

When we want to conduct a study, we have to begin with the most basic questions. What populations should we study? What criteria should we use? It has been shown that individuals, young or adult, with inner ear pathology have a much higher risk of developing tinnitus than individuals with normal hearing (1-5). On the other hand, the proportion of individuals with hearing impairment is very low among the population as a whole. Among adults, tinnitus surely increases with age but adults are not the focus of this thesis. A Swedish study with a large population sample of 18-year olds demonstrated that 14% of subjects did not pass the screening audiometry criteria of achieving at least 20 dB thresholds on all measured frequencies (6). Another study followed a cohort longitudinally at 7, 10 and 13 years of age, demonstrating that the proportion of subjects presenting with a hearing impairment at all three times or at least both of the last measurements, did not exceed 7% (7).

Prevalence studies of tinnitus in the young population vary considerably, depending on whether it is an unselected or selected population, with regards to hearing status of the study population.

Even without predisposing factors, such as hearing impairment, we are all at more or less risk of acquiring tinnitus, through the adverse effects of noise. Noise has early been identified as one of the etiological factors in tinnitus (8-10). Nonetheless, many individuals who have not been exposed to elevated sound levels suffer from tinnitus and some even have more severe symptoms compared to those with a higher noise exposure.

It has also been increasingly apparent that there is a psychological/psychiatric comorbidity in tinnitus (11, 12). From depression to anxiety and to increased perceived stress (13), more and more scientists report on the close correlation between tinnitus and decreased psychological well-being. We herein approach several neurological models (14) and neuroendocrine models (15-17), explaining the interactions between the auditory pathway and both higher cognitive functions and unconscious reactions from the limbic system. The models are supported by recent discoveries (18, 19).

3.2.1 Subjective hearing symptoms

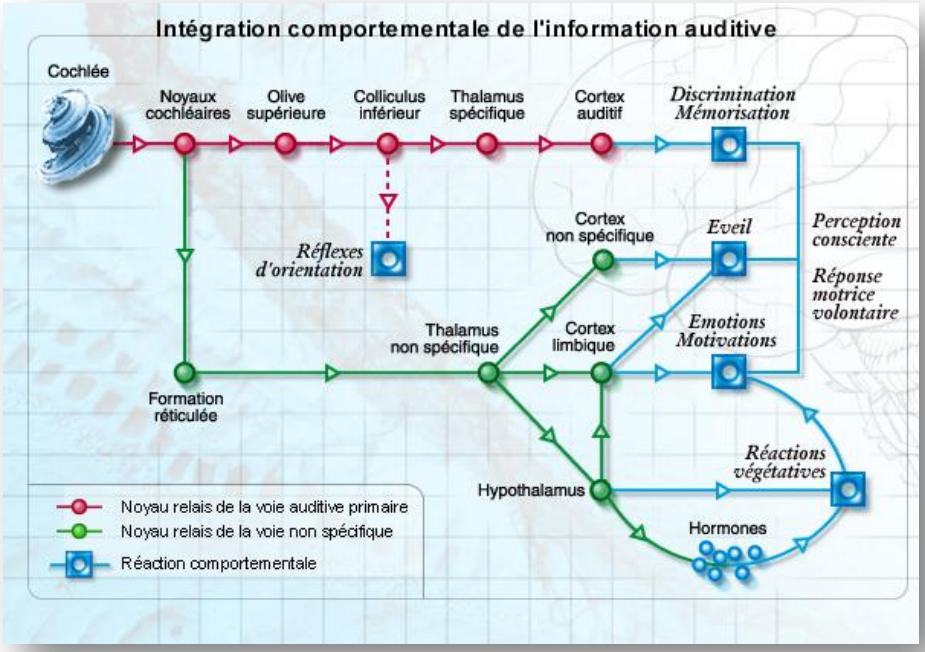
There are several aspects of dysfunctional hearing. Some are easier to define and measure than others. Hearing loss, in the strictest meaning, is a reduction of the hearing thresholds, traditionally measured with psychoacoustic audiometry using pure tones (20). However, there are other facets of the auditory sense, which can become diminished and lead to a decline in perception of the desired sound. Tinnitus, hyperacusis, diplacusis, dysstereoacusis and difficulty in distinguishing complex sounds in noisy environments are all symptoms, which can be described with varying precision but not objectively measured. With subjective hearing symptoms we mean such sensations or loss thereof, which are acutely experienced but not yet quantifiable or interpersonally comparable (21).

The conscious awareness of sound takes place near the surface of the brain, when a pattern of electrical activity traveling up the hearing nerve from the ear reaches the auditory cortex. The electrical signal contains information on spectral and temporal distribution and differs slightly between the sides of the head, resulting in additional information regarding directionality of sound. These electrical patterns are then analysed with respect to the different aspects of the information along the auditory pathway.

There are other parts of the neural signal to be analysed than just the strictest sound components. A large number of signals are sent outside the auditory system to the limbic system and areas responsible for memory, feelings, arousal, awareness, conditioned response. Besides interpreting the meaning of what we hear, we can remember the context in which we last heard it and what emotion it evoked. This process then influences what response we create.

Even weak patterns of sound, if significant to the individual, can be detected by subconscious filters along the pathway (22). The response can be both conscious and autonomous, such as perspiration or raised blood pressure due to a link to the autonomous nervous system as well. This theory has been supported in children by two experimental studies described by Matheson (23). Figure1 summarises the main pathways and links to the limbic system.

Figure 1. *A schematic over the central auditory pathways, both primary (red), secondary (green) and vegetative (blue). "Eveil" means awakening, "noyaux"-nucleus, "motrice" – motor, other terms are self-explanatory. Illustration by S. Blatrix from "Journey into the World of Hearing" www.cochlea.org by Rémy Pujol et al., NeurOreille, Montpellier, by permission.*



The current response is also logged by the memory, which significantly speeds up future responses to similar signals. The process is, however, open for conscious modulation or re-training (24), which can be exemplified by the following: If we have once been in a road-traffic accident, we can, aided by a relevant therapy, disconnect the now automatic response of fear and sweating evoked by the sound of screeching wheels, back to a more normal and neutral response of taking a step back.

3.2.2 Definitions of tinnitus (emergence vs. annoyance)

The word tinnitus is derived from the Latin "tinnire", which means to ring. The colloquial language describes tinnitus as a perception of a ringing, buzzing, beeping or humming sound. However, such descriptions have different meanings for different individuals and therefore are not particularly useful. From a scientific viewpoint, there have been many attempts at

defining the symptom. A criterion frequently used requires the phenomenon to last for a minimum of five minutes (25). This is nevertheless difficult to assess objectively and is subject to recall bias, especially when interviewing younger children as their perception of time can vary.

Objective and subjective

The symptom can be subdivided into 'objective' and 'subjective' tinnitus according to the triggering factor. This division is occasionally inconsistent with classifications such as 'pathological', 'temporary', 'extra-auditory 'or 'associated tinnitus'. The vast majority of tinnitus sufferers experience subjective tinnitus, which only is audible by the tinnitus patient. Generally when the word 'tinnitus' is used, this implies subjective tinnitus. Objective tinnitus, on the other hand, is described as having an acoustic source, a response to an actual sound produced within the body. Examples include spasms in the musculus tensor tympani or stapedius muscle, audible spontaneous otoacoustic emissions or venous hums from a vessel near the middle ear. These sounds are measurable and may even be audible to other people. The source could also be electrical, i.e. experimentally evoked tinnitus using a weak electrical stimulation of the hearing canal through a saline solution.

The subjective tinnitus, however, lacks an identifiable sound source. Subjective tinnitus "is only perceived by the sufferer and the problems for the patients who have a subjective symptom differ from those having symptoms that can be measured. If auditory hallucinations are excluded, tinnitus may be described as genuine tinnitus. It has been suggested that only subjective tinnitus should be regarded as tinnitus and the term 'objective tinnitus' should not be used and, instead, the origin of the sound should be described" (26). Figure 2 shows a schematic presenting the distinctions between objective and subjective tinnitus.

Troublesome

The systematization continues, now with regard to how troublesome the symptom is. The symptom can be categorized by how frequent it is, degree of disturbance and impact on daily life. Does it hamper a person's working capability or mental capacities, such as memory and concentration or contribute to psychological suffering?

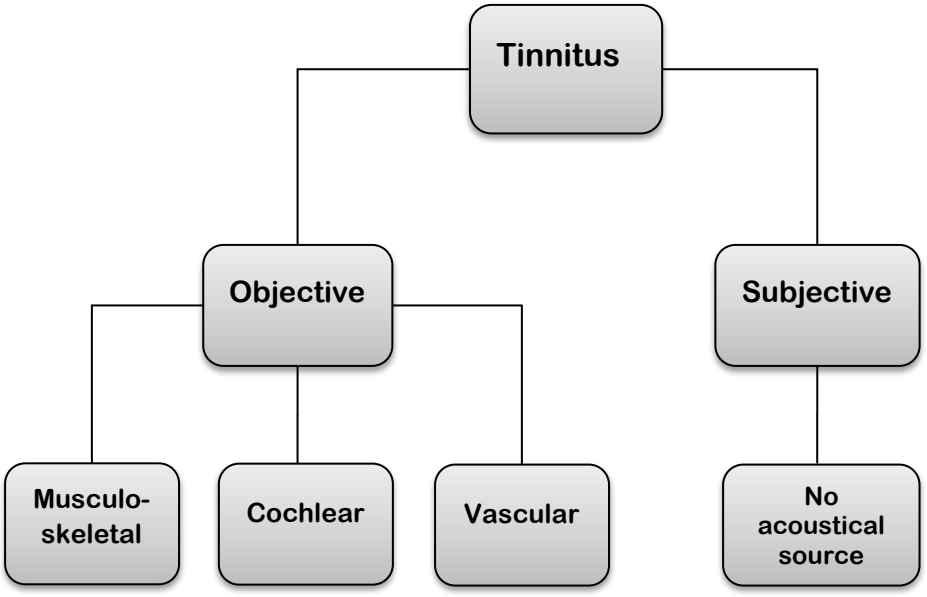
A classic tinnitus grading scale was described by Klockhoff & Lindblom in 1967 (27). The scale classifies the symptom depending on how frequently it is perceived as disturbing (sometimes, always present but not disturbing, always present and always disturbing) and is not related to aetiology.

Another method of classification has been presented by Holgers (26), proposing an aetiological model that distinguishes between the mechanisms

of tinnitus awareness and those mechanisms involved in the suffering. This model can then be used to tailor tinnitus treatment based on the most important causes of the suffering of tinnitus in the individual patient. It comprises three main categories: somatic tinnitus, depression-anxiety-related, and audiological tinnitus. Employing this classification, tinnitus related to a temporo-mandibular disorder would be considered somatic, whereas one related to noise-induced hearing loss would be considered audiological. Combinations of the three classifications may exist naturally, which have to be considered in the management of the patient.

Tinnitus can further be described as temporary or persistent, yet not describing to what extent it is a problem for the individual at hand. Of those who do experience persistent tinnitus, population studies have shown that approximately 85% do not find it intrusive, disturbing or anxiety provoking. It seems that neither the quality nor loudness of the tinnitus signal differs between those that suffer from tinnitus and those that can shift their attention away from it – but rather what emotional attachment we assign to the signal (28). It may be harder to maintain an unbothered state of mind if our endurance is diminished by comorbidity or if tinnitus interferes with sleep and recovery (3). There are also indications that our personality, prior to the emergence of tinnitus influences how bothersome it will be (29, 30).

Figure 2. *Schematic over the difference between objective and subjective tinnitus*



Since tinnitus is experienced and described in different manners, there is no national or international consensus on which scale or definition to use. There is no "state of the art"-measurement that covers all aspects of tinnitus. There may be different approaches or different points of interest when measuring results of certain interventions. Hence, it is often the main focus of a question that determines which tool is used in practice.

Over the years, several scales have been created, each covering a specific set of dimensions of tinnitus suffering. Scales include Tinnitus Severity Questionnaire (TSQ) (31), Tinnitus Reaction Questionnaire (TRQ) and Tinnitus Handicap Questionnaire (THQ) (32). These questionnaires have different foci, such as quality of life (TSQ), distress and impact on work and leisure activities (TRQ) as well as social, emotional and physical behaviour (THQ).

Throughout this thesis, the definition of tinnitus in terms of subjective tinnitus will be that of an aberrant perception of sound unrelated to an acoustic source of stimulation, internal or external.

3.2.3 Definitions of temporary threshold shift

A threshold shift is a change in a person's hearing thresholds and encompasses both improved and worsened variances. The shift can be transient and then normalised or it can be permanent, signifying a permanent hearing impairment. It is difficult to find a unifying definition of temporary threshold shift (TTS). One major criterion within an experimental setting is that the hearing threshold established prior to the selected exposure (e.g. noise or medication or both), is altered by the study variable. Logically, as opposed to permanent threshold shift, it should return to its original level within a certain amount of time, yet that time-period is not always specified by study protocols, nor is it always evident that normalised thresholds have been verified.

Traditionally, measurements are collected immediately or 1-2 minutes after exposure, with repeated measurements according to specified protocol. In experimental studies on humans, the last measurement is usually finished after 30-120 minutes (33) but some animal studies collect continuous data over months (34)). In animal models, the thresholds can be measured by evoked potentials or electrocochleograms (35). In humans they are often measured by brain stem audiometry, otoacoustic emissions, auditory evoked magnetic fields, or psychoacoustic audiometry - manual or computerized sweep frequency (Békésy). In humans, the very short-term (<5min) TTS can be difficult to verify due to methodological problems, since audiometry, even sweep frequency, takes a few minutes to complete. Axelsson for instance

describes the time for the Békésy audiometer to reach the high frequency area as 5.8 min (36).

In a clinical setting, the majority of physicians employ the term TTS, which refers to an objective or subjective transient increase of the hearing thresholds in any or all frequencies following noise exposure. Additionally, the hearing should fully recover to its pre-exposure levels, if the thresholds shift is to be considered temporary (37). The time span of the temporary damage can be several days or even weeks after noise exposure. The transient component appears to be a swelling of both afferent and efferent nerve endings (38). The concomitantly observed changes in the central signalling in subjects, both human and animal, could be a result of the swelling or some other mechanism, which has not yet been histopathologically described. Spoendlin noted an increase in the number and size of liposomes, mainly in the outer hair cells, as the only morphological correlation to TTS after longer periods of the phenomenon (39). A comprehensive summary of the findings from animal studies is provided by Clark (40).

The experimental studies all have a stimulation of some sort in common, which may be chemical or acoustic. Interestingly, the TTS can occasionally show a lowering of thresholds or an increased tolerance to noise using either chemical substances or sound conditioning (34, 35). Salicylic acid can induce tinnitus via NMDA-receptors (N-methyl-D-aspartate) in the cochlea and inferior colliculus (41, 42) but does not appear to influence TTS (43). Nicotine, on the other hand, does influence TTS (44) and a prophylactic effect of magnesium has also been confirmed (45).

3.3 Epidemiology adult vs. young

The subject of comparative epidemiology of tinnitus is difficult, mainly due to differing definitions and varying study populations. In the adult general population, tinnitus prevalence has been reported as approximately 10 to 15%. For all ages, the prevalence varies between 4.4% and 16.6%, but increases with age and the male gender. More men than women report tinnitus and in 1 to 2%, tinnitus is severe enough to significantly impair daily life (13, 46, 47). The increase with age, with a slight overrepresentation in the male population is observed due to increasing overall hearing impairment (HI) and in the male subgroup – increasing HI due to noise exposure in the work field (46). Over the last few years, this gender skewing is no longer obvious, as an equal number of women now report HI to The Swedish Work Environment Authority (Arbetsmiljöverket). This could be the effect of vigorous noise reduction and hearing preservation programs in the industry, possibly with simultaneously weaker implementation of such preservation programs in the public sector, where many women are employed.

When comparing the studies on tinnitus in children, the prevalence ranges from 6 to 66%. In contrast to research on adults, where researchers can benefit from large population databases and gather questionnaires from respondents in the tens of thousands, scientists focusing on children often have to make due with children already present in the health service. It therefore follows that studies on paediatric tinnitus are smaller in size and on selected populations, such as children in schools for the hearing impaired or children presenting to the ENT-department with any otolaryngological complaint.

Historically, children are also often considered somewhat unreliable witnesses and many attempts have been made to maximize the credibility of children's responses. Researchers have assessed the child's overall reliability, by asking questions unrelated to the hearing subject and accepting tinnitus reports only if the child had shown enough maturity. With this method, Stouffer estimated the prevalence of tinnitus to be 6 or 13% (depending on the criterion for response consistency) (48). The numbers originally presented in each study are not always easy to extract and compare immediately, because they are presented for a subgroup of diagnoses, hearing impairment levels or listening habits.

A summary of tinnitus prevalence in children, recorded in studies dating back from 1972, is listed in Table 1. Some of the studies were conducted on children presenting with any otologic diagnosis, some on children with known hearing impairment, others still on children within a hearing screening context. Some studies focused on how tinnitus was described or its laterality, whilst others explored the relationship between tinnitus and noise exposure. This resulted in a very heterogeneous group of populations and focal points. In order for some systematisation to be made, the original data from the studies was extracted and re-calculated to follow the same presentation, i.e. if the original study compared tinnitus in children with mild hearing impairments to children with severe HI and/or deafness, these numbers were added and related to the entire study group of children from schools for the hard of hearing. Unfortunately, trying to fit data already presented in one form into a different mould, will in some cases result in lack of information.

Table 1. Prevalence or occurrence of tinnitus in children, with the original numbers extracted and re-calculated as to allow the easiest comparison between them all. Studies marked with an asterisk are presented in this thesis.

Authors (year of publication)	**n**	**Age range**	**Prevalence of tinnitus (any kind) % within group**		
			Normal hearing	**Any HI**	**Hearing tests not performed**
Nodar (1972)	2000	10-18	13		
Graham (1979)	92	12-18		66	
Graham (1981)	66	12-18		29	
Mills and Cherry (1984)	110	4-17	44	30	
Nodar (1984)	56	?		55	
Mills et al (1986)	93	?	29		
Viani (1989)	102	6-17		23	
Martin and Snashall (1994)	67	2-16	50	50	
Aust (2002)	1420	5-17			7
Holgers (2003)	964	7	13	9	
Holgers and Pettersson (2005)	671	13-16			53
Holgers and Juul (2006)*	274	9-16			46
Aksoy et al (2007)	1020	6-16	15		
Savastano (2007)	1100	6-16	26	8	
Coelho et al (2007)	506	5-12	38	45	
Raj-Koziak et al (2011)	60212	7	32	43	
Figueiredo et al (2011)	100	15-30	18		
Juul et al (2011)*	756	7	41	58	
Giles et al (2012)	145	19-26			15
Bartnik et al (2012)	59	7-17	44	56	

3.4 Theoretical models of mechanisms

The Bergman-Heller experiment illustrates that the majority of us are capable of registering background electrical activity present throughout the auditory pathways and interpret it as a sound. Not every neuron is equally active, but they all contribute to some extent to the final perception of tinnitus. These background electrical signals are always present and represent a baseline activity. Both an increase and a decrease may be interpreted as sound. Changes in this electrical activity along the pathway can be a result of a natural process of ageing or an intense or prolonged noise exposure. Structural damage to the hair cells can sometimes be visualised but it can just as well be a misrepresentation of a neural signal in the higher parts of the brain.

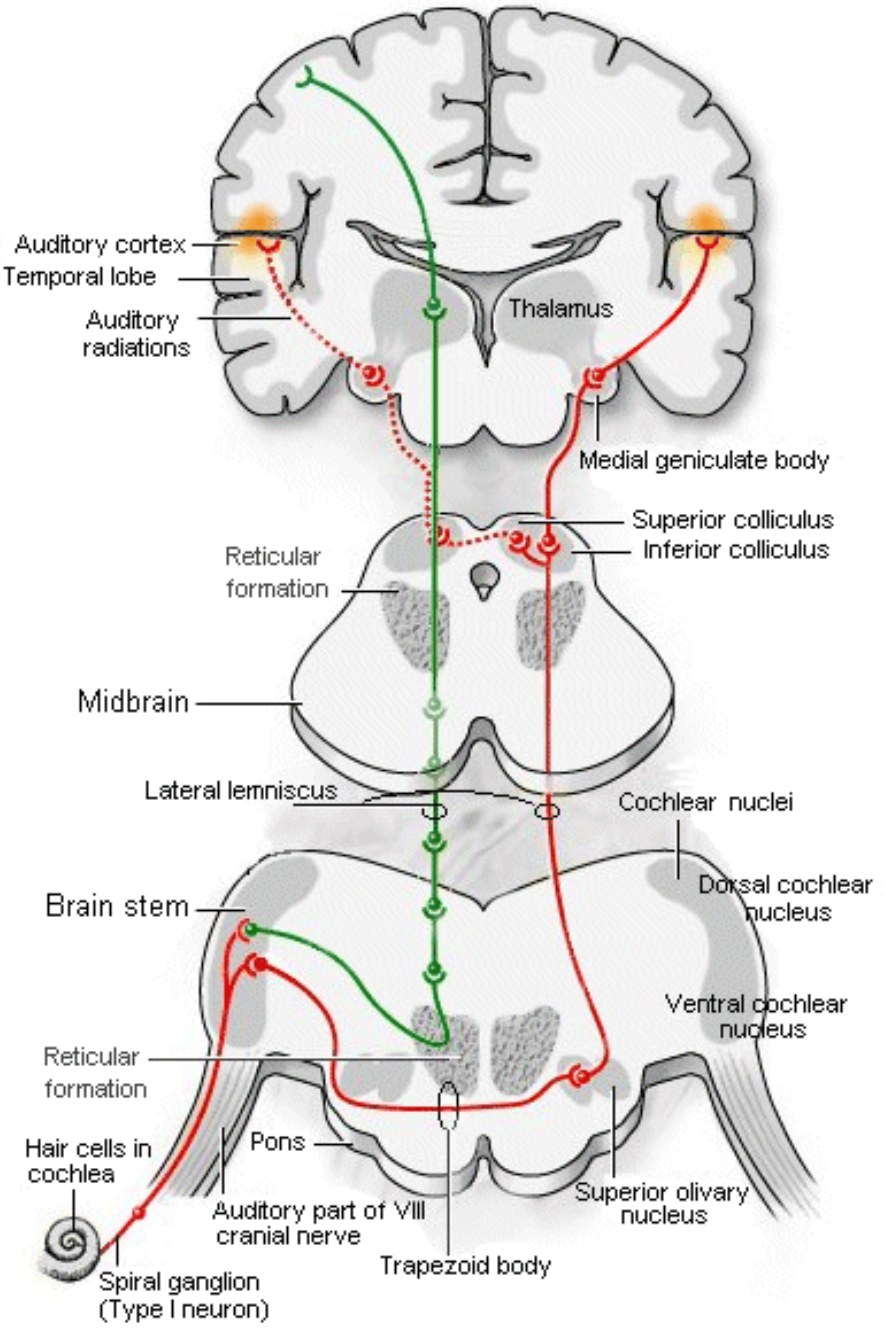
The normal condition for the auditory pathway is a spontaneous, base-line activity in the afferent neurons. In a quiet surrounding, the afferent neurons discharge in an irregular chaos. When presented with a sound, the firing pattern changes from stochastic to regular and is therefore interpreted as a sound. The principal response patterns include the following: 1) primary-like response, an initial spike preceded by a steady response until the stimulus changes; 2) “chopper” post-stimulatory response, an extremely rapid oscillatory neural response to the stimulus; 3) the onset response, a solitary initial spike; and 4) the pauser response, similar to the primary-like but ending soon after the initial spike and resuming a graded response. Additionally, there is a build-up response, where the cell fires increasingly throughout the entire presentation of the stimulus (49).

As sound intensity increases, so will the firing rate of many of the auditory fibers in the brainstem. Besides the intensity coding, which is not described in detail here, the signals contain information on the temporal aspects and the frequencies represented in the stimulus.

3.4.1 Neurological pathways – central and peripheral

The central auditory nervous system (CANS) is anatomically defined as beginning at the cochlear nucleus (CN) and ending at the auditory cortex. However, the endpoint of the CANS might be different depending on the type of acoustic stimuli or task to be completed and thus, physiologically rather than anatomically defined (49). Figure 3 presents a schematic over the primary and secondary auditory pathways.

Figure 3. *A schematic presentation of the primary and mostly contralateral (red) pathway and secondary, mostly ipsilateral (green) pathway. Illustration by S. Blatrix from "Journey into the World of Hearing" www.cochlea.org by Rémy Pujol et al., NeurOreille, Montpellier, by permission.*



The afferent system

Briefly, this pathway is short with few relays and rapid owing to its large myelinated fibers. It carries information from the cochlea and each relay nucleus is responsible for a specific part of decoding and integration.

As described in the Textbook of Audiological Medicine (21), the CN consists of three principal sections: the anterior ventral cochlear nucleus (AVCN), the posterior ventral cochlear nucleus (PVCN), and the dorsal cochlear nucleus (DCN), all three dominated by different cell types. At this level an important decoding of the basic signal occurs: duration, intensity and frequency.

From the CN in the cerebellopontine angle, the signals divide and continue along an ipsilateral and a contralateral path. The primary pathway crosses over to the contralateral superior olivary complex and via the lateral lemniscus, continues to the inferior colliculus in the pons, which contains both auditory and somatosensory fibers. The fibers within the inferior colliculus yield extremely sharp tuning curves, suggesting a high level of frequency resolution. Other neurons present in the inferior colliculus are time- and spatial-sensitive, suggesting an important role in sound localisation. There is significant crossover of signals to the other side but the major part continues upward to the medial geniculate body (MGB), residing on the surface of the thalamus. Here are cells, which respond to both acoustic and somatosensory stimulation, which makes the MGB a multisensory arousal system. It also interacts closely with the reticular formation. As with the inferior colliculus, many neurons in the MGB are sensitive to both binaural stimulation and interaural intensity differences. At this last relay before the cortex, an important integration occurs, namely - preparation of a motor response (e.g. vocal response).

From then on, the signals reach their final destination on the surface of the auditory cortex. Here, the message, already largely decoded during its passage through the previous neurons in the pathway, is recognised, memorised and perhaps integrated into a voluntary response (50).

The secondary pathway runs ipsilaterally and via many synapses. Here, the auditory information is integrated with all other sensory modalities to be prioritised along the way.

Throughout the primary auditory pathway, all structures maintain a tonotopic representation, but this feature is still flexible enough to allow for plasticity if there is a lack of input at a given frequency range.

The efferent system

The Textbook of Audiological Medicine describes the efferent system that carries modulating information back from the cortex to the cochlea and divides it into two section, the olivo-cochlear bundle and the rostral system. The olivo-cochlear bundle (OCB) has been studied but the details of the rostral system remain obscure. The rostral pathway starts at the auditory cortex and descends to the inferior colliculus via the medial geniculate body. Its onward path remains unclear but excitatory and inhibitory signals have been detected in the lower regions, upon stimulation of the auditory cortex.

The OCB has two main tracts where the lateral tract originates from pre-olivary cells and via unmyelinated fibers synapses on ipsilateral dendrites of the inner hair cells (IHC). The medial tract crosses via faster, myelinated fibers and connects directly to the outer hair cells (OHC). The medial system appears to mainly have a suppressive effect, best visualised by contralateral acoustic stimulation of the ear, which then reduces the amplitudes of otoacoustic emissions.

Discrimination in noise is mainly dependent on function of the OCB, probably utilising the ability to trigger the expansion or contraction of OHC, thereby enhancing or damping basilar membrane activity (49).

There is also evidence suggesting that the processing of acoustic information is different in children than in adults and that the central auditory pathways may be travelled by slightly different routes in children (51).

3.4.2 Tinnitus-specific theories

Dyssynchronicity

Under normal, silent conditions, the spontaneous firing activity from the afferent neurons is completely stochastic. The healthy CANS perceives this as “silence”. An external acoustic stimulus will increase the firing rate and change the action potential pattern from irregular to regular. When tinnitus arises, the theory states that firing rate and/or pattern is altered from irregular (silence-pattern) to regular (sound pattern). This altered neural activity simulates the presence of an acoustic signal where there is none. Tinnitus is thus a consequence of an abnormal synchronised action potential pattern of the background spontaneous activity within the CANS (52).

How this pathological change in firing pattern can arise is also subject to different explanatory models. One such model states that abnormal influx of Ca^{2+} ions (due to ion channel dysfunction in the inner hair cells (IHC) or damage to the hair cell cilia) causes the altered signalling, which fits well

with the mechanism of ototoxic drugs and noise-induced trauma. It does not, however, explain why tinnitus can also be present without any apparent hearing loss and vice versa.

Sensorineural hearing loss (SNHL) is usually accompanied by damage of the outer hair cells (OHC). The activity of OHC is modulated by the efferent system, originating from the superior olivary complex. Together with the efferent system, the IHC, the OHC and the vestibulocochlear nerve, the superior olivary complex forms a feedback system. It functions to modulate the micromechanics of the cochlea. Modulating the motility of the OHC, the IHC are rendered more sensitive. In silence, the afferent input is very limited. If the OHC are damaged, the efferent system may try to activate the remaining OHC at the edge of hair cell loss, in order to increase the afferent auditory input. This will lead to hyperactivity in the OHC close to the damaged frequency area, which in turn increases the firing rate from the IHC in the area, creating a false signal. There is evidence suggesting that OHC-damage may be present in tinnitus patients even without concurrent IHC-damage (53). Several studies have confirmed that the efferent system of patients suffering from unilateral tinnitus seems to be less efficient than on the contralateral side (54, 55). This mechanism can be used in the opposite way, stimulating the cochlea with sound (matched to the hair cell loss or not, matched to the tinnitus pitch or not), and using the loop to downgrade the efferent activity (56). This is sometimes called the masking phenomenon.

Dysregulation of somatosensory input

As for chronic pain, which can be considered analogous with tinnitus in that they both are subjective and often continuous sensations, tinnitus can be relieved, masked or totally suppressed by suitable inputs. Suppression longer than the alleviating stimulus is called residual inhibition. The overall concept behind this stipulates that different fiber systems are relayed together within a gate control system, which regulates the input from the peripheral to the central auditory nervous system. If the input is increased due to damage of hair cells, the “gate” will stay open longer as a result of adaptation (52).

It has been observed that many tinnitus patients can modulate their tinnitus with head and neck contractions. One study compared the effect of such movements on tinnitus and non-tinnitus patients alike. A large majority of the subjects who had on-going tinnitus at the time of testing could change their perception of tinnitus with muscle contractions and relaxations. More interestingly, nearly 60% of those with no tinnitus at the time of testing could elicit a tinnitus-like auditory percept with the same head and neck contractions, probably the mechanism behind tinnitus related to temporo-mandibular disorders (57).

Previous studies have shown that stimulation of somatosensory pathways using the effects of trigeminal nucleus stimulation results in immediate suppression or enhancement of subsequent acoustically evoked discharges. Suppression predominates in the healthy auditory system and damage to the auditory input pathway leads to enhancement of excitatory somatosensory inputs to the cochlear nucleus (58). One study showed that while noise exposure resulted in a temporary threshold shift in auditory brainstem responses it also created a persistent increase in spontaneous and sound-evoked firing patterns in the dorsal aspect of the cochlear nucleus. The long-term somatosensory enhancement of sound-evoked responses was strengthened while suppressive effects diminished in noise-exposed animals, especially those that developed tinnitus. This confirms the role of noise exposure in tinnitus generation, via triggered compensatory long-term synaptic plasticity of somatosensory inputs (59).

Weakest point

The strongest promoter for neural plasticity is deprivation of input, which could explain why tinnitus often occurs together with hearing loss or injury to the auditory nerve (60). This does not appear to have a clear correlation to what frequency region has been damaged. Some researchers have seen a correlation between the perceived tinnitus pitch and the area of maximum HI (61) or where the audiometric slope is the steepest (62, 63), while others have not been able to reproduce these findings (64, 65). It is also possible that a relationship between pitch and audiogram is present only in certain subgroups.

Limbic and auditory brain areas are thought to interact at the thalamic level. While a tinnitus signal originates from lesion-induced plasticity of the auditory pathways, it can be tuned out by feedback connections from limbic regions that block the tinnitus signal from reaching the auditory cortex. If the limbic regions are compromised, this "noise-cancellation" mechanism falters, and chronic tinnitus results (66).

Neural networks

A neural network consists of several interconnected elements, often representative of a neural mechanism. The connections can be weighted and are excitatory or inhibitory in nature. A specific feature, often used in the construction of different models, is called the lateral inhibition network, which is where a neuronal element inhibits its neighbouring elements via inhibitory connections. For example, reduced inhibition in the central

auditory structures can lead to hyperexcitability and in turn to tinnitus generation.

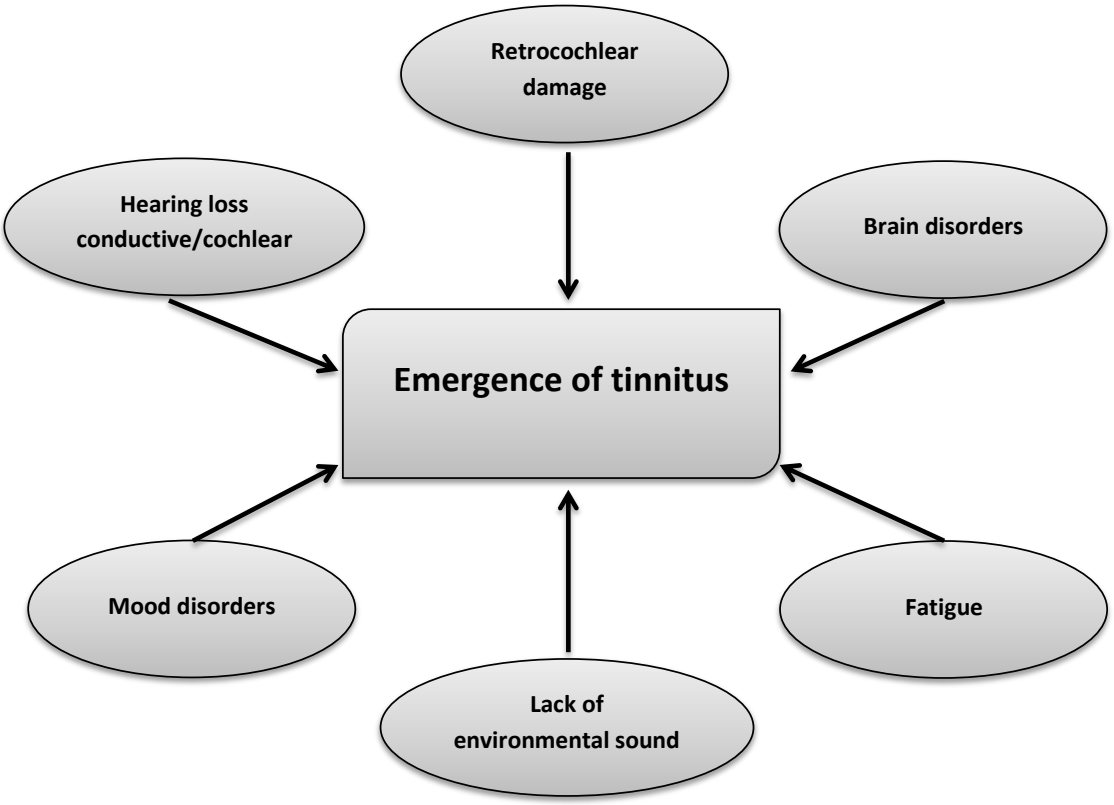
Many proposed models use the same paradigm of lateral inhibition networks, but apply it to different structures, such as the cochlea, the DCN, the inferior colliculus, the thalamus and the primary auditory cortex (67). Recent studies using PET/fMRI imaging techniques indicate several brain regions, including the somatosensory, limbic and motor regions, simultaneously implicated in the tinnitus generation and modulation (68). A dysregulation of limbic and auditory networks in tinnitus has been proposed (69). Confirmatory studies using auditory training suggest that neural changes related to tinnitus alter how neural plasticity is expressed in the region of primary but not non-primary auditory cortex. Auditory training did not reduce tinnitus loudness but a small effect on the tinnitus spectrum was detected, confirming the effect on the pathway (18).

Neurochemical vulnerability

Many tinnitus patients seeking help at an audiology clinic present with concurrent or previous depressive or anxiety disorders (12). Since the presence of the neurotransmitters dopamine and serotonin has been detected throughout the auditory pathway (70-72), the possibility of common neurochemical dysfunctions between tinnitus and mood disorders has been intensely discussed and subject to many studies (15, 73). Serotonin in particular has been attributed a role in the generation of tinnitus and as a mediating factor in severe tinnitus suffering (3). Even oestrogen receptors have been detected in the cochlea (74) and may well be incorporated into future noise protection strategies. The role of NMDA receptors in the cochlea has also been discussed and an involvement in synaptic repair after excitotoxicity has been suggested, opening up for potential treatment approaches (75-77).

It should be stressed that these theories are not mutually exclusive. The mechanisms described could very well all be active and contributing to the generation or sustaining of tinnitus at different stages or in different individuals. Figure 4 presents currently known triggering factors.

Figure 4. *Different etiological factors in the development of subjective tinnitus, revised after Holgers(78)*



3.5 Risk factors

3.5.1 Hearing disorders

Tinnitus is much more frequent in individuals with already established hearing impairments (46). As described in the Epidemiology section, tinnitus prevalence in adults is approximately 10- 15% and increases with age, as hearing deteriorates. Hearing disorders associated with tinnitus in the adult population are most commonly sensorineural hearing losses - either spontaneous, hereditary or due to noise exposure, Ménière's disease, otosclerosis (79), medication related (ototoxic drugs or adverse effects) and tumours of the vestibuloacoustical nerve.

In children, the hearing loss is most often of temporary nature and due to secretory otitis media (SOM). Many children report tinnitus in conjuncture with SOM (80). It has been demonstrated that children with hearing loss of any kind experience more tinnitus if the degree of HI was mild to moderate and not severe to profound (81).

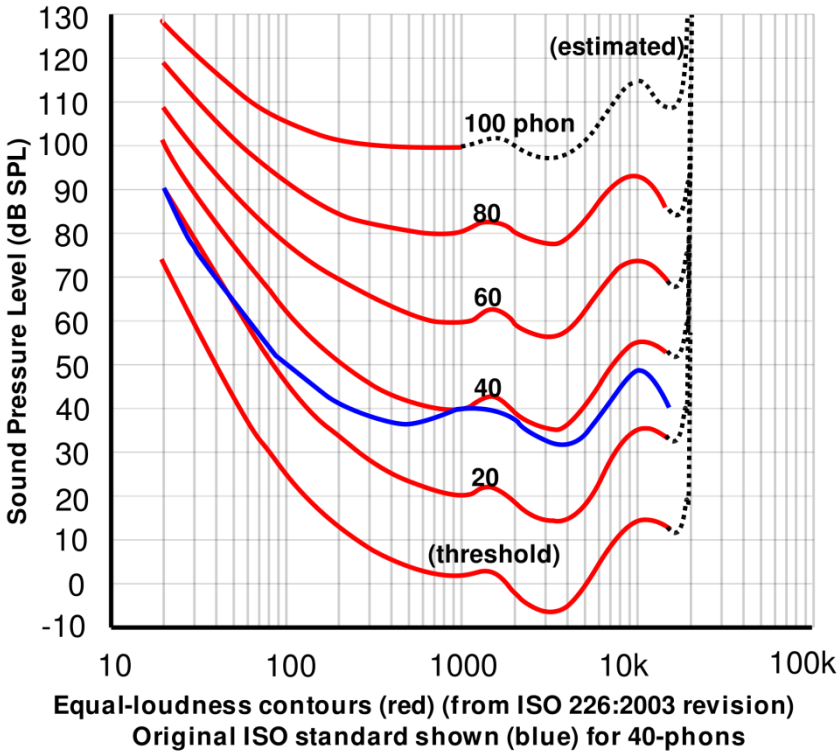
Although there are reports of Ménière's disease in children as young as 4-7 years, it is infrequent in children under 15 years of age (82, 83). Otosclerosis is rarer still, but not unheard of in the paediatric population (84) and, similar to the adult population, is also a cause of tinnitus. Furthermore, multiple sclerosis has been identified in children, with tinnitus as the first and only manifestation of the disease, yet is a disease presenting mostly in young adults (85). Meningitis is still a reoccurring cause of HI in children and often accompanied by tinnitus (86). Head injury in children can lead to tinnitus (87) and children are more prone to head injury, due to their increased physical activity and lesser degree of coordination and vestibular maturation.

3.5.2 Noise

Loudness of sound is measured in decibels (dB), a mathematical unit expressing sound pressure levels along a logarithmic scale. It does not represent an independent scale but is relative to another expression of loudness. The scale always compares a certain reference value of a chosen unit to the one we are measuring in this moment. When measured against atmospheric pressure, zero decibel Sound Pressure Level (dB SPL) corresponds to 20µPa.

When using dB Hearing Level, the loudness is compared to a set level of standardized median normal hearing thresholds in a large population (ISO 389). Humans do not perceive low- and high-frequency sounds as well as sounds near 2,000 Hz, as shown in the equal-loudness contour curves in Figure 5. Because low frequency sounds require higher energy levels to be detected by the human ear than medium range frequency, the reference level is not fixed evenly across the spectrum but varies related to the median normal hearing threshold. A sound attributed the value of 0 dB(HL) at 20Hz corresponds roughly to 75 dB(SPL), whereas at 1kHz both scales are set to 0.

Figure 5. *Equal loudness contours (red) from ISO 226:2003 revision. Original ISO-standard for 40 phons shown (blue). Illustration by Lindosland 2005.*



A logarithmic transformation has been chosen to better fit the large dynamic range of the human ear. An increase of 3 dB represents approximately a doubling of sound pressure and an increase of 10 dB represents a 10-fold increase. A 20 dB increase represents a 10^2 increase of pressure; 40 dB means 10^4 increase. As the frequency response of human hearing changes with amplitude, three weightings for measuring sound pressure have been established: A, for sound pressures levels up to 55 dB; B for levels between 55 and 85 dB, there and C for measuring sound pressure levels above 85 dB.

The 0 dB(HL) sound level is set as the faintest sound perceived by humans in in general. A step of 1 dB(HL) is considered to be the smallest sound pressure difference that a human can distinguish. A normal conversation is at approximately 45-50 dB(HL), a radio at 70 dB and an orchestra at 90 dB.

The Swedish Work Environment Authority (Arbetsmiljöverket) has issued regulations in the Work Environment Act (AML), specifying the accepted noise level in the working place as below 80 dB for a 40-hour workweek and

not exceeding 85 dB for transient noise. In 1990, the scope of the Work Environment Act was expanded so as to include pupils at all levels in the educational system. Rules concerning pupils' safety delegates were added. In the meantime, noise during leisure time has not been regulated in the same manner. The National Board of Health and Welfare (Socialstyrelsen) has issued Provisions on Noise (SOSFS 2005:7) (88) in public places, in- and outdoors, where loud music is played, e.g. discotheques, concert halls or gymnasiums, but these are only guidelines and not legally binding regulations.

Mechanisms

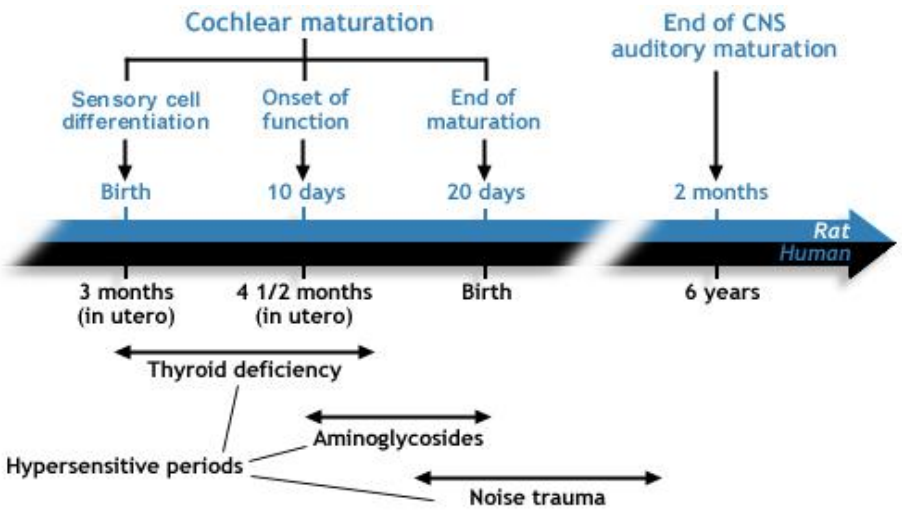
Noise causes harm to the inner ear by several mechanisms. One such mechanism is the mechanical shearing of hair cells located on the basal membrane, whilst another is the toxic effect of the sudden and abundant release of glutamate from the bottom of the hair cells on both adjacent neurons as well as the hair cell itself.

Our present knowledge on the harmful effects of noise are based on exposure tests on laboratory animals (38, 39, 89) and on human studies on adults with long experience of working in noisy environments without protective measures (90). These reports, additional follow-up studies and very large databases (ISO 7029) have been used to calculate recommended maximum noise exposure levels in the industry to prevent permanent hearing impairment (91).

The risk of acquiring HI is higher with prolonged exposure and so is the risk of developing tinnitus (92). Many western countries now adhere to the proposition that, when assuming a 40-year employment, limiting the noise exposure levels to less than 80 dB_{LAeq} (equivalent continuous sound level, A-weighted), limits risking individuals developing NIHL.

In children however, there is only circumstantial evidence suggesting they are more susceptible to cochlear damage than adults. Animal studies on mice, which show higher sensitivity in younger animals make comparisons between the ages of mice and the relative ages of humans, hypothesising that 20 days in a mouse corresponds to the first year of human life, 60 days to early post-puberty and 180 days to adulthood (93), see Figure 6. Accepting that premise would imply that the sensitivity to noise is higher in toddlers than schoolchildren and higher in children than adults. Additionally, ototoxic substances were found to be more harmful to younger rodents than older (89).

Figure 6. *Linear development of the cochlea and the auditory brain in both human and rat. Illustration by S. Blatrix from "Journey into the World of Hearing" www.cochlea.org by Rémy Pujol et al., NeurOreille, Montpellier, by permission.*



Another possible mechanism explaining the higher noise sensitivity in children stems from the fact that the ear canal in children is slightly different anatomically compared to adults. The young ear canal is shorter and more horizontally oriented. By inference from acoustic studies on the properties of the adult ear canal (94), this could mean that, in children, there is an amplification of higher frequencies than in adults. Noise of higher frequencies is probably more harmful than low frequency noise. Alternatively, the frequency range of 3-6 kHz might correspond to loss of IHC in the basal turn (9-13mm) of the cochlea, which has been speculated to be prone to vascular insufficiencies and mechanical overstimulation (95).

Exposure

The current technology in iPods, mp3s, mobile phones etc. can emit an output level reaching 103 dB. In-ear plugs increase sound exposure by an additional 5.5 dB, compared to conventional outer ear phones. An iPod set to 65% of the maximum volume emits 80 dB whereas 80% gives 90 dB, which is potentially harmful (96, 97).

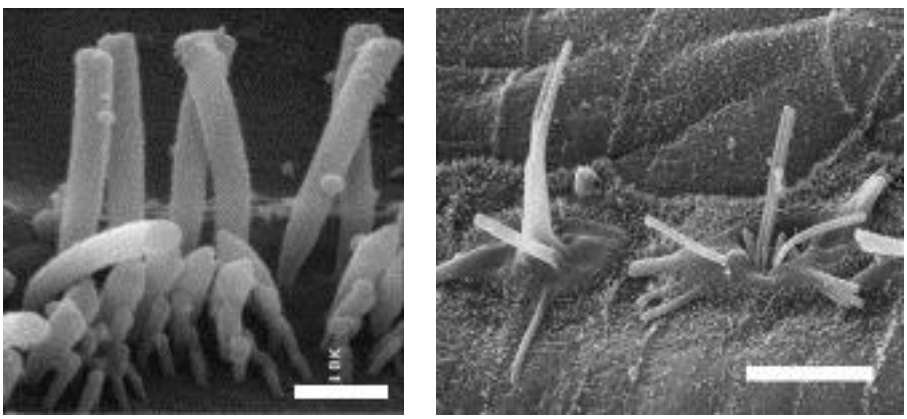
If every increase of 3 dB is regarded as a doubling of the physical sound intensity, the exposure time needs to be cut in half. Prolonged listening can be compared to a shorter exposure but of a higher intensity. One hour a day of 90 dB is equivalent to 80 dB daily for a week. Individuals at risk, apart from workers in environments with constant noise levels (e.g. factory workers), also include people exposed to sudden noise (e.g. day care

environments) and prolonged exposure to medium intensity noise levels (e.g. gym instructors). Since total exposure time includes both work-hours as well as leisure time, all activities need to be taken into account, even hobbies. For example, a day care worker that plays in a string quartet twice a week has a higher total noise exposure than her colleague who plays soccer.

We have a reasonable grasp of the mechanisms of long-term exposure in the industry but as of yet, insufficient information on long-term effects of the sound levels of leisure activities and environments. Some studies have investigated the noise exposure of youngsters by posing questions (98, 99), whilst others have measured the output levels in venue halls and concerts (100). In an experimental setting, listening to one's music of choice has also been shown to cause TTS (101). These studies are of great value but describe results of a pattern that might no longer be valid for the contemporary young generation. There has been a recent shift in listening behaviour towards very long exposures at mid-to-high levels. The previous tradition of listening to music at home or concerts only, has been replaced by today's ever more present constant companionship of personal music players and telephones.

Our expectancy of, and tolerance for, very intense sound levels is evident in the clubs and stadium venues. In a discotheque and concerts, the sound levels often reach 100 dB and 105 dB, respectively. In Gothenburg, the often referred to concert of 2008 with Bruce Springsteen exposed the cheering crowds to 106 dB, whilst a stunning 113 dB were recorded at later concerts including Metallica and Madonna. Figure 7 shows electron microscope-generated photographs of damaged hearing cells, a result which is not uncommon after noise exposure (38).

Figure 7. *Broken stereocilia. Photo by R. Pujol from "Journey into the World of Hearing" www.cochlea.org by Rémy Pujol et al., NeurOreille, Montpellier, by permission.*



In 2005, the National Board of Health and Welfare (Socialstyrelsen) carried out an oversight investigation in co-operation with 134 local environment administrations, where sound field measurements were done in 471 places were music, live or recorded, was played. The results revealed that 24% of the events exceeded regulation levels. Unsurprisingly, the majority of the violations were found at concerts and festivals, where 42% of events presented sound levels over the stipulated level. As many as 27% of schools were also among the offenders (102).

Due to the cumulative effect of noise, all the sounds we expose ourselves to must be considered. This means taking into account music at home, concerts, mp3's, motorbikes, machine sounds, gym halls etc.

Some individuals are more susceptible than others are and can develop symptoms after an occasional exposure to loud sounds. Unfortunately, we cannot tell in advance, who is more vulnerable until the damage is done and is also often permanent.

There is also evidence that environmental noise exposure in children evokes stress reactions and diminished stress endurance, as established by testing under controlled conditions (103). The harmful effects of noise are thus not only auditive but also systemic and related to cognition and performance.

3.5.3 Mood disorders and anxiety

Mood disorders are a group of diagnoses in the Diagnostic and Statistical Manual of Mental Disorders (DSM IV-TR) classification system where a disturbance in a person's mood is hypothesized to be the main underlying feature. It has previously been termed affective disorder, but the psychiatric community has considered the term "affect" to signify a transient change of emotion, whereas "mood" would signify a more enduring disturbance of the emotional core. Mood disorders are divided broadly into unipolar and bipolar syndromes, based on whether a manic or hypomanic episode has ever been present. The condition commonly called "clinical depression" is, using DSM-IV-TR terminology, termed "major depressive disorder". It is a condition dominated by anhedonia (lack of lust/joy), which is more than an ordinary state of misery or grief (104). In Europe, its prevalence is 8.5%, with a gender ratio 2:1 women to men (105).

Anxiety disorder is a term gathering several different forms of psychiatric disorders characterized primarily by excessive rumination, worrying, uneasiness, apprehension and fear about future uncertainties based either on real or imagined events. Up to 18% of Americans and 14% of Europeans may be affected by one or more forms of anxiety disorders (106).

Depression is more prevalent in adults than in the young population, whereas anxiety is more common in youngsters than in adults (106-108). Tinnitus is a symptom often correlated to anxiety or depression. In the beginning of tinnitus research, this correlation was considered to be cause-effect related – suffering from tinnitus was considered the cause of depression in these patients (109), or possibly, there could exist a bi-directional relationship. The early findings of serotonergic circuits in the auditory pathway (70) prompted researchers to instead view this as co-morbidity where pathological mechanisms were potentially shared. Zöger described shortly thereafter that a large majority of tinnitus patients suffered from depression and/or anxiety prior to their tinnitus onset (12).

In adults the correlation with depression is stronger than with anxiety, but overall psychiatric morbidity, both simultaneous and life-time incidence, appears to be more prevalent in tinnitus sufferers (12, 110). Proposed mechanisms are neuro-endocrine changes and formation of specific neural circuits in both tinnitus and depression (15, 111). As discussed previously, concurrent depression can be regarded as a predictor for debilitating tinnitus (3).

Several studies have shown that tinnitus loudness and annoyance are not necessarily congruent and should be assessed separately. It is the psychological factors that correlate to annoyance, not the specifics of the tinnitus signal itself (112-114). There is also evidence pointing to some personality traits being correlated to the severity of tinnitus (115).

Mood disorders and anxiety in youngsters

The prevalence of depression in teenagers is reported to be 5–6 % and in the younger children and pre-adolescents approximately 1 % (116), although different screening methods can yield different figures. According to a thesis by Olsson, screening for depression with Beck Depression Inventory using adult cut-off values for moderate depression resulted in a prevalence of 10% and 4%for severe depression (117). Olsson describes further that childhood depression often starts with dysthymia and transforms into major depression in adolescence. These symptoms should not be regarded as the norm and should require action, so that they do not transform into a reduced global functioning. Anxiety disorders are more frequent than depression in youngsters. In adolescent community studies, 17% have been found to suffer from anxiety and slightly fewer (14%) among younger children. More than 40% of adolescents with depression have a concurrent anxiety disorder. Comorbid diagnoses in children and adolescents are more the rule than the exception (118).

There is no certain data demonstrating if the depression prevalence in adolescents has changed over time. Gender differences exist in presentation of symptoms (117), as well as in prevalence in different age groups. When seeking psychiatric help, boys are more often in the prepubertal age, whereas girls peak around 15 years (119). Rates of depression are low before puberty, but rise from the early teens, especially among girls (120). Anxiety disorders appear equally frequent in boys and in girls prior to puberty, but from teenage and onward, anxiety is more prevalent amongst girls (121, 122), landing on an incidence ratio of 2-3:1 in adulthood. The reasons for this are probably both biological and social. For some of the anxiety disorders, there seems to be a gender related difference in both symptomatology and progress (118).

Boys with mood disorders seem to have poorer coping strategies and suffer more from the same degree of symptoms than the girls, an effect that is visible even after remission (123). Longitudinal studies have demonstrated that the chance of childhood anxiety or depression symptoms being transient is substantial. However, in case of persistent or recurrent symptoms, it is feasible to assume that genetic factors may play a greater role in their stability. Genetic factors may be correlated with environmental risk or could interact with an environment. In case of persistent symptoms, in addition to addressing environmental factors, therapy should focus on individual characteristics that could maintain the symptoms (124). It is important to address these issues early, to avoid a negative development. Untreated anxiety disorders in the young can develop into chronic (125). In addition to medication and family support, cognitive behavioural therapy has shown good effects (126).

When specifically focusing on tinnitus and mood disorders, there is always the question which symptom precluded the other. In a study from South Korea, 940 students aged 10-12 were interviewed with regard to tinnitus, its difficulty and the subjects' current mood state and their mood trait (30). The results showed that tinnitus was correlated to the trait anxiety, not the state anxiety. The interpretation follows that any concurrent acute anxiety state should not be regarded as a trigger for the tinnitus. Additionally, tinnitus is not necessarily responsible for the acute anxiety.

Similar results were obtained from a study on randomly selected subjects that were confirmed to have tinnitus. The 256 subjects answered questions on tinnitus distress, anxiety sensitivity (AS) and anxiety/depression symptoms using the Hospital Anxiety and Depression Scale (HADS). Anxiety sensitivity is described in psychological research as an individual tendency to fear bodily sensations associated with anxious arousal and it is believed that heightened AS does not directly lead to the development of anxiety disorders, but rather to a maladaptive avoidance due to fear of anxiety-related

symptoms. This study showed a stronger relationship between anxiety sensitivity and tinnitus distress than the HADS-subscales, which code for present symptomatology (127).

The two above-mentioned studies point to a possible vulnerability in individuals with an “anxious readiness” and not necessarily requiring a concurrent affective pathology.

The validity of the suggested mechanism does not contradict the need for intervention. A prospective study of 6215 Swedish working adults showed a direct and long-term association between tinnitus severity and depression, where a decrease in depression was associated with a decrease in tinnitus prevalence, and even more markedly with tinnitus severity (128).

It should be stressed that, when discussing mood disorders or anxiety with respect to tinnitus, we should not single out those with the former symptoms with a sole purpose of treating the psychological comorbidity, but instead search for mood disorders and anxiety as it may be indicative of underlying tinnitus pathology.

4 AIM

The overall aims of this thesis are to increase our knowledge of subjective tinnitus in children and adolescents and to study possible common factors in children and young people seeking help for tinnitus.
Additional aims include to study the prevalence of tinnitus in an unselected paediatric population and, if possible, to identify factors that trigger or contribute to tinnitus in children and adolescents.

- The aim of paper I was to
  - explore the point prevalence of tinnitus, both spontaneous and noise-induced, in an unselected paediatric population;
  - investigate some of the audiometric and medical characteristics and mood disorders of children seeking medical attention for tinnitus.

- The aim of paper II was to investigate the prevalence of spontaneous and noise-induced tinnitus in a large community sample, together with hearing data.

- The aim of paper III was to examine noise exposure, audiometry and mood disorders in relation to ST, NIT and TTS.

4.1 Ethical considerations

The studies were approved by the Ethical Committee in Gothenburg and performed according to the Helsinki declaration. The major ethical concern was interviewing children without the presence of a guardian and on possibly sensitive matters such as a perception of something that had not before been the focus of the child's attention. The risk was thus that the questions could awake a hitherto dormant attention towards sensations from the ear. There is also the issue of prompted response vs. spontaneous report, where the former might result in positive answers describing an existing but very low-level sensation, which in some situations might be considered physiological. On the contrary, awaiting spontaneous report could result in a serious underestimation of the prevalence and leave certain individuals unaided.

The potential drawbacks of being interviewed were considered being compensated for by the extensive information on the auditive system and its sensitivity to noise, as well as instructions on noise preventive measures. Therefore, the subjects were considered better prepared to act in situations hazardous to hearing.

5 PATIENTS AND METHODS

The main study variable was tinnitus, spontaneous and noise-induced, with the addition of subjective temporary threshold shift. The population of interest was children and adolescents. Table 2 presents the study populations and the methods used in each study.

Our strategy was - the younger the study population, the simpler the questions. The common denominator throughout the studies was a set of two questions, confirming or denying experience of spontaneous or noise induced tinnitus. In the older groups, questions were added regarding increasing level of difficulty, including an assessment of annoyance, general health and well-being, concentration and mood.

5.1 Patients

Table 2. Layout of the study populations and methods used

	Study design	**Subjects**	**Age (years)**	**Instruments used**
Paper I (pilot)	Descriptive, cross sectional	274	9-16	Study specific instruments (Q1-4)
Paper I (help-seekers)	Descriptive	95	8-20	Audiometry, TSQ,HADS, VAS
Paper II	Descriptive, cross sectional	756	7	Study specific instruments (Q1,2,5), screening audiometry, tympanometry
Paper III	Descriptive, cohort, prospective, longitudinal	1105	16-17, 18-19	Study specific instruments (Q1-5), screening audiometry, tympanometry, HADS, health, noise-exposure

Paper I

In paper I (pilot), all subjects were children present the day of the lecture in the selected school, which yielded a total of 274 subjects in the ages 9-16 (139 girls, 135 boys). The study was done in collaboration with the Tinnitus Association in Gothenburg for Tinnitus Sufferers. Children under the age of nine were not included, due to anticipated difficulties in assessing time aspects of tinnitus. After listening to a short lecture on hearing, its function and tinnitus, a short written questionnaire was administered to the attending children, asking about their experience of tinnitus, see Appendix B.

Within the parameters of the first study regarding consecutive help-seeking patients, paper I (help-seekers), all consecutive patients, 20 years or younger, that sought help at the Audiological clinic, ENT-department of Sahlgrenska University Hospital were invited to participate. The youngest subject enrolled was eight years old and the oldest 20.

Paper II

In Gothenburg, all seven-year-old children (~5000 each year) undergo an audiometric 20 dB(HL) screening at the 0.5, 1, 2, 3, 4, 6 and 8 kHz frequencies as part of the regular school health services (129). This study included the first 756 consecutive children (366 girls and 390 boys, born 1999) tested during the year 2006. The same audiologist performed all measurements and the same nurse interviewed all children, directly after the audiometry testing. The same design and tinnitus questions as in 1997 were used.

Paper III

Starting in the year 2004, 1260 high school students in Gothenburg were given the opportunity to participate in a health-screening program during their first and their third/last year of high school, i.e. at the ages 16 and 19 years. The selection of high schools was provided by the School Health Authority of Gothenburg. Of these 1260 students, 155 declined to participate. The young students were enrolled equally from noisy, occupational education programs and less noisy, mostly theoretical programs. The definition of noisy/not noisy was made by the Department of School Health and followed the national guidelines for noise in the work place.

5.2 Measurements

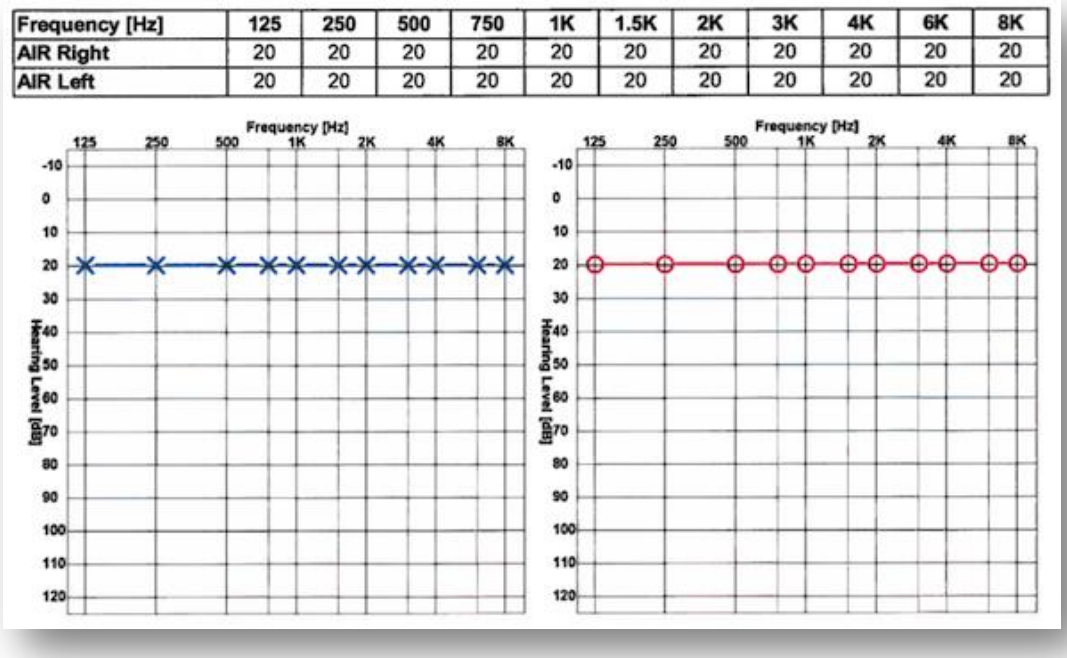
5.2.1 Screening audiometry

Screening audiometry is a psychoacoustic measurement of hearing thresholds to a previously set lowest level of presentation, not to the full extent of the individual hearing. In most countries, the lowest level is 20 dB, in some countries it is 25 or 30 dB. The rationale behind this method is to quickly identify individuals with a need for more extensive hearing investigations and let those with levels considered as adequate pass.

The test protocol is as follows. First, the child is tested at the frequencies 500-6000 Hz at 20 dB. If the child responds correctly to all frequencies, the test is finished and the result noted as "passed". If the child misses any frequency, the test continues to determine the individual hearing thresholds, now including 8000 Hz. The ears are inspected and an impedance measure performed. The audiologist then decides whether to redo the test after six weeks or refer to an ENT-clinic at once. Figure 8 exemplifies how a so-called "normal" result is transcribed.

Figure 8. *Example of transcribing the results of normal screening audiometry set at 20dB. Possible better result with thresholds below 20dB will not be noted.*

Frequency [Hz]	125	250	500	750	1K	1.5K	2K	3K	4K	6K	8K
AIR Right	20	20	20	20	20	20	20	20	20	20	20
AIR Left	20	20	20	20	20	20	20	20	20	20	20



The equipment used is a mobile audiometer for screening purposes and in our studies it was a Tegnér Audiometer PTA-8 with Sennheiser headphones HD A 200, shown in Figure 9. The equipment is calibrated according to the clinical guidelines. The measurement is carried out in the school nurses office.

Figure 9. *Portable equipment for screening audiometry.*

All but the participants of paper I (pilot), (i.e. paper I (help seekers), papers II and III) underwent audiometry, screening or full thresholds. Subjects having failed the screening audiometry underwent an additional tympanometry.

The 95 subjects in paper I – help seekers, were clinical tinnitus patients and therefore able to have a full threshold audiometry performed on them. The pure tone hearing thresholds were tested in a sound proof test booth with noise levels well below those recommended by ISO 8253-1 (1989). The audiometers used were Interaucoustics AC-30 or Madsen OB-822 using TDH-39 earphones with MX-41/AR cushions.

5.2.2 Patient report outcomes

The concept of patient report outcome (PRO) is defined as any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else. The American Food and Drug Administration (FDA) has presented a set of guidelines for the development, modification and evaluation of self-report instruments used as endpoints in clinical trials, where the concept and the theoretical framework for constructing a PRO are presented (130).

Dealing with symptoms and experiences of illness entails classifying subjective descriptions. It can therefore be argued that the patient providing the descriptions is the only reliable source of such data. In such cases, traditionally used observer-reported measures are not optimal since they are an interpretation of the experience and therefore often affected by inter-observer variability.

Self-report instruments is a method of gathering PRO data that is less time consuming than doing interviews and asking the questions in a standardised manner, facilitating intra- and inter-group comparisons. If the questions are simple enough though, they could be administered verbally with very little variation and a speedy harvest. This method has the advantage of being able to correct or clarify any misunderstanding of the wording of questions.

In summary, the PRO instruments consist of a number of questions or statements (items), grouped together in domains (factors), where the domains measure the same concept. The PRO instrument can be generic or disease specific or it can consist of two parts; one generic and one disease specific. Generic instruments are designed to measure domains of general health, disability or quality of life, while disease-specific instruments measure attributes of symptoms, mental health and functional status relevant to a particular disease. Generic instruments enable comparisons across patient populations and with norm populations. Their weakness lies in responsiveness to disease specific changes that may be clinically relevant. Here, the disease-specific instruments are more responsive to changes in the target condition.

The questionnaires included in the PRO in this thesis are described below.

Tinnitus questionnaire

Tinnitus Severity Questionnaire (TSQ) is a validated tinnitus-specific PRO instrument that has been developed by Coles and co-workers (31) with focus on the psyche, attitude and circumstances of the individual with tinnitus as well as his/her ability to mask tinnitus. The questionnaire was constructed in English and Swedish simultaneously and its ten items cover two major

factors – Tinnitus Affect and Day-vs.-night Intrusiveness. The response options are based on a five-point Likert scale: *"Never or very seldom/Sometimes/Often/Very often/always"* (0 = not affected to 4 = always affected). Total score is the sum of item scores and the maximum score is 40. A higher score indicates greater perceived severity of tinnitus. The questionnaire is designed for self-administration. It is enclosed in its entirety as Appendix C.

HADS

The Hospital Anxiety and Depression Scale (HADS) is an instrument developed for detection of mood disorders in somatically ill patients (131). This scale is a widely used questionnaire that identifies depressive and anxiety disorders in patients with a wide array of somatic disorders and has been validated for adults as well as children and adolescents. HADS consists of 14 items on a four-point Likert scale ranging from 0-3. The summary scale scores for anxiety (7 items) and depression (7 items). The creators have calculated cut-off scores for the adult population, where a scale score < 8 is in the normal range, a score 8-10 indicates possible anxiety or depression, and a score >10 - probable anxiety or depression. When administered to children and adolescents, different cut-off points are recommended. In this age group, the lower cut-off point is recommended to be seven for the depression sub-scale and nine for the anxiety sub-scale. The higher cut-offs of 10 (for depression) and 12 (for anxiety) should be used when the main aim is to avoid false positives (132). In our studies, the focus was not on identifying clinically significant psychiatric illness, but on investigating psychological traits. Therefore, the lower cut-off points were implied, signifying positive signs of depression-related symptoms or anxiety-related symptoms.

The HADS has been used in conjunction with tinnitus (133-135). It was concluded that the concurrent validity of HADS was good to very good (136), when compared to other questionnaires for anxiety and depression in common use, such as Montgomery-Åsberg Depression Rating Scale (MADRS), Beck Depression Inventory (BDI), State and Trait Anxiety Inventory (STAI) and others, The sensitivity and specificity of HADS when used in tinnitus patients were analysed by Svedlund et al, 2004, using the structured clinical interview for DSM-IIIR criteria as the golden standard. Receiver operating characteristic (ROC) curves were used to compare the screening abilities of the HAD subscales for anxiety and depression and the total HAD Scale, and showed that HAD Scale was better at detecting depression than anxiety disorders (134). HADS is short, easy to score and its use in both adults and adolescents gives it an advantage from a health care provider perspective. The questionnaire is enclosed in its entirety as Appendix D.

Study specific questions

Three study specific questions were formed:
Q1. *"After listening to loud music or other loud sounds or noise, have you heard any ringing, buzzing or other sort of sounds in your ear even after that the loud music or noise has been turned off?"* This question was intended to detect experience of noise-induced tinnitus, NIT.
Q2. *"Have you heard a ringing, buzzing or other sort of sound in your ears without first having listened to loud music or other loud sounds?"* This question was intended to detect experience of tinnitus, permanent or temporary, without being induced by noise, ST.
Q5. *"After listening to loud music or other loud sounds or noise, have you noticed that your hearing is worse?"* This question was intended to detect experience of temporary threshold shift, TTS.
The response options were *No, never / Yes, once / Yes, several occasions.*

The same questions covering the experience of ST, NIT and TTS have also been used in previous studies from our research group (137, 138) on a total of 1635 children and adolescents from the year 1997 and onward. The questions have not been formally validated but have been constructed based on previously existing wording in other questionnaires and assessed by the audiologist performing all school entry hearing screenings to be easily understood even by the young children.

Visual analogue scales (VAS) were also used, focusing on the loudness and the annoyance of tinnitus, for the time periods "Today" and "Last Week". The scales were 100 mm with the following end-point sentences for "Loudness": "*I didn't perceive any tinnitus today*" (0 mm) to "*My tinnitus was extremely strong today*" (100 mm) and "*I didn't perceive any tinnitus last week"* (0 mm) to "*My tinnitus was extremely strong last week*" (100 mm). For Annoyance, the scales presented the following end-point sentences: "*My tinnitus did not disturb me at all today*" (0 mm) to "*My tinnitus was unbearable today*" (100 mm) and *"My tinnitus did not disturb me at all last week"* (0 mm) to *"My tinnitus was unbearable last week"* (100 mm). All questions are enclosed as Appendix A.

Specification for each study

Paper I (pilot):
The questionnaire included age and gender and the following items:
Q1. NIT, response option *No/Yes*.
Q2. ST, response option *No/Yes*.
Q3. *"How often do you have tinnitus?"* Never/Seldom/Every day/Always.
Q4. *"Is tinnitus troublesome for you?"* No/Sometimes/Often.
The questionnaire is enclosed as Appendix B.

Paper I - help-seekers:
The following questionnaires were used and distributed immediately before the first visit to the clinic.
1. Tinnitus severity questionnaire (TSQ)
2. Visual analogue scales (VAS) "Loudness" and "Annoyance"
3. Hospital Anxiety and Depression scale (HADS)
At the clinic, the patients were asked about the duration of tinnitus, whether they had or had not been exposed to noise immediately prior to the initial presentation of tinnitus, whether the onset was sudden or gradual and whether the onset was related to noise exposure and the type of noise.

Paper II
Structured interviews were carried out individually by a nurse accompanying the audiologist performing the audiometry, who also made sure that the child had understood the questions.
Q1. NIT, response option (*No, never / Yes, once / Yes, several occasions*)
Q1. ST, response option (*No, never / Yes, once / Yes, several occasions*)
Q5. TTS, response option (*No, never / Yes, once / Yes, several occasions*)
For all these three variables, in order to be regarded as a case, the symptom had to occur at several occasions.

Paper III
The school nurse collected anthropometric data in addition to Q1-Q5. The youngsters responded to questions regarding noise exposure during school and leisure time, their listening habits, more specifically in terms of playing instruments, attending concerts, listening to music on stereos or portables devices, as well as playing computer games, going to the cinema, target shooting, use of mobile phones, with or without hands-free earphones and use of hearing protection devices. Extract from the questionnaire is presented in Appendix E.

5.3 Statistics

In all the studies, the analyses were conducted using the statistical package of SPSS for Windows (versions 13.0 for the first paper and 19.0 for papers II and III). Throughout the studies, a two-tailed *p-value < 0.05* was considered as statistically significant.

Paper I made use of t-tests, Spearman's non-parametric correlation, Mann-Whitney tests and multiple stepwise regression analyses. No variables were normally distributed in the help-seeker cohort.

In paper II, there were three dependent variables: Spontaneous tinnitus (ST), Noise induced tinnitus (NIT) and Temporary threshold shift (TTS). For statistical purposes, all answers were dichotomised, where "*No, never"* and "*Yes, once*" were treated as "*No*" and "*Yes, several occasions*" were treated as "*Yes*". The hearing data were analysed frequency by frequency, as well as dichotomised in some analyses to groups of Hearing loss "*Yes*"/"*No*" (meaning screening audiometry level 20 dB failed or passed). Where applicable, t-tests were performed and logistic regression analysis was used to determine the most influential parameters on the presence of tinnitus.

In paper III, there were three dependent variables: ST, NIT and TTS. Each of the listening activities created one noise-related variable. For statistical purposes, all answers were dichotomised, where "*Never*" and "*Once/Rarely*" were treated as "*No*" and "*Often/Sometimes*" and "*Very often*" were treated as "*Yes*". The hearing data were analysed frequency by frequency, as well as dichotomised in some analyses to groups of Hearing loss "*Yes*"/"*No*" (meaning screening audiometry level 20dB failed or passed).

For each subject, the difference between the results of each variable in 2004 and 2006 was calculated. The created Δ-variables were used where applicable. All the variables were tested for correlations using Spearman's rho or univariate logistic regression. The analyses were conducted identically for all three dependent variables (ST, NT, TTS). The independent variables with significant outcome were put in a multiple stepwise logistic regression analysis. The probabilities attained in the final models were then applied in ROC-curves for calculation of model strength with Area under the Curve (AUC). Variables were tested for, and fulfilled the criteria for normal distribution. Grading of correlation strength was as follows: $0 < |r| < .3$ weak correlation, $3 < |r| < .7$ moderate correlation, $|r| > 0.7$ strong correlation (139).

6 RESULTS

Paper I

Pilot study

Of the 274 schoolchildren investigated (9-16 years; 135 girls, 135 boys), 53% of the children responded yes to Q1, regarding noise induced tinnitus (NIT). The mean age of the group with experience of NIT was higher (12.1±2.2 years) than in the group without experience of NIT (11.4±2.2 years), (*p<0.01*).

Forty six per cent of the children had experienced tinnitus without any noise exposure immediately before the sensation of tinnitus. Age did not significantly differ between the groups with spontaneous tinnitus (ST) (11.9±2.1 years) or without ST (11.8±2.4 years). There was a non-significant (p= 0.17) overrepresentation of girls among the children that had experienced ST, i.e. 57% (n=78) among the girls and 36% (n=48) among the boys. When calculating the two symptoms (ST and NIT) separately, the gender skewing remained only with regard to NIT. Fifty-nine per cent (n=81) of the girls and 47% (n=64) of the boys had NIT, with an almost significant p-value (*p=0.07*). Table 3 presents the percentage of reports signifying a higher degree of occurrence. Subjects reporting that their tinnitus often was annoying were 62 (22.6%).

Table 3. Percentage of tinnitus as represented by how frequently it occurs

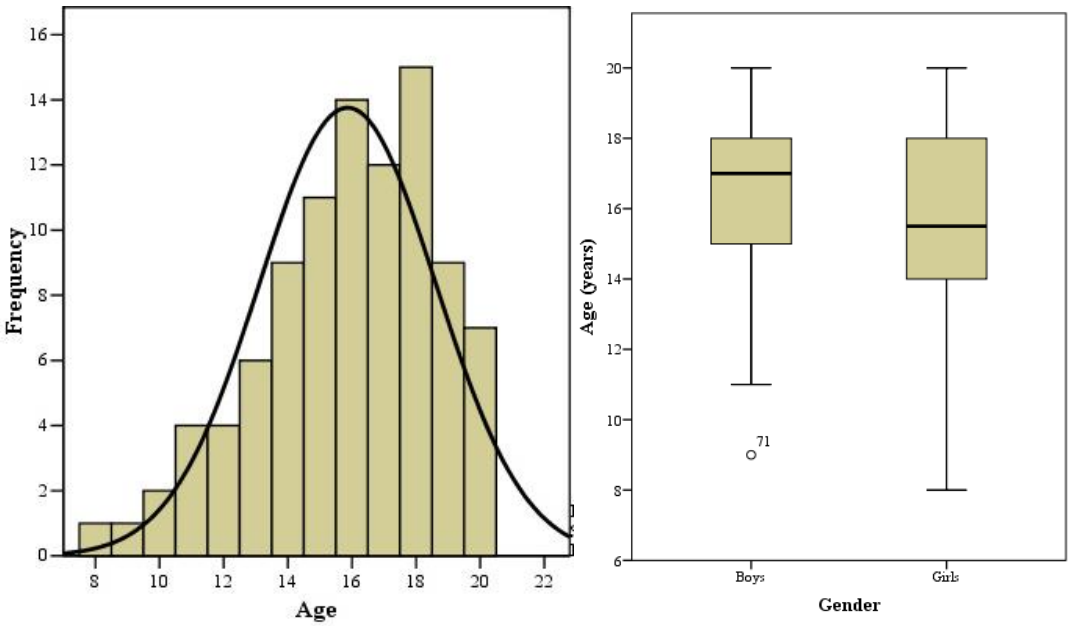
Subjects reporting:	***n***	***% of total***
Tinnitus often	39	14.2
Tinnitus at all times	6	2.2

Age was not a significant factor with respect to the annoyance caused by tinnitus, nor how often it was perceived.

Help-seekers

Ninety-five consecutive young patients (55 boys and 40 girls) with tinnitus were included. The age and gender distributions are shown in Figure 10. For all calculations concerning age, the data was used both as one group and subdivided into two, i.e. children (12 years or younger) and teenagers (13 years or older).

Figure 10. *Distribution of age amongst subjects seeking help for tinnitus, n=95, median=15.8 years and distribution of age with respect to gender.*



The onset of tinnitus was twice as often sudden than gradual. In 54% of the subjects, tinnitus had started after noise exposure, most commonly music (girls: 94% and 66% boys, *p=<0.001*). Those who developed their tinnitus gradually had higher scores on the HAD scale for both anxiety (Mann-Whitney, Z= -2.223, *p= 0.023*) and depression (Z= -1.974, *p= 0.048*), but no difference was found between the degree of suffering as measured by TSQ. Type of onset was not significantly correlated to hearing parameters.

However, several significant correlations between the severity of tinnitus and tinnitus loudness as well as annoyance during the day or week, were demonstrated using Spearman's non-parametric correlation test (see table 4). Such correlations were observed between the pure tone average of hearing thresholds at 3, 4, 6 kHz ($PTA_{3,4,6}$) and TSQ scores and also between $PTA_{3,4,6}$ and all four visual analogue scales.

Table 4. Correlations (Spearman's rho) with two-tailed significances.

Independent variables		Total TSQ-score	VAS loudness		VAS annoyance	
			day	week	day	week
Total TSQ-score	r=		0,450	0,410	0,561	0,555
	p=	.	*<0.001*	*<0.001*	*<0.001*	*<0.001*
Possible depression	r=	0,367	0,343	0,248	0,381	0,329
HAD-D >7, no/yes	*p*=	*0,001*	*0,001*	*0,026*	*<0.001*	*0,003*
Possible anxiety	r=	0,269				
HAD-A >9, no/yes	*p*=	*0,013*	*n.s.*	*n.s.*	*n.s.*	*n.s.*
PTA $_{0.5,1,2}$	r=			0,231		
continuous variable	*p*=	*n.s.*	*n.s.*	*0,048*	*n.s.*	*n.s.*
PTA $_{3,4,6}$	r=	0,283	0,265	0,250	0,404	0,303
continuous variable	*p*=	*0,011*	*0,021*	*0,032*	*<0.001*	*0,009*
Age	r=				0,213	
continuous variable	*p*=	*n.s.*	*n.s.*	*n.s.*	*0,044*	*n.s.*
Teen no/yes	r=	0,333			0,238	
dichotomous variable	*p*=	*0,001*	*n.s.*	*n.s.*	*0,024*	*n.s.*

This table highlights the significant correlations between TSQ and possible depression and anxiety (as defined by the lower cut-off levels of HADS), as well as the high degree of correlation between TSQ and all VAS-subscales. In this material, the majority of the subjects were in their teens. The teenagers scored higher on VAS annoyance during the day and on the TSQ but they did not differ in their HADS-scores compared to the younger children.

Regression analysis

Out of the five different variables measuring tinnitus (TSQ and the four visual analogue scales), we selected VAS annoyance/week and VAS loudness/week as the variables most likely to cover the aspects of tinnitus that make the perception a suffering. We then performed multiple stepwise regression analysis with VAS annoyance/week as the dependent variable and the independent variables age, gender, HADS, $PTA_{3,4,6}$, the remaining VAS-scales and TSQ. This resulted in a model highlighting VAS loudness/week, TSQ score and possible anxiety as factors with the greatest influence (adjusted R^2 =0.773).

The corresponding calculation using VAS loudness/week as a dependent variable pointed out the remaining visual analogue scales, again together with possible anxiety (adjusted R^2=0.836).

Mood disorders

Thirty-two per cent of the patients scored above the cut-off level for possible anxiety disorder for adolescents, and 14.5% scored above the cut-off level for possible depression. More girls than boys reported symptoms of anxiety (40% and 26% respectively, *p=0.017*), but there was no gender difference observed with respect to depressive symptoms. There was no difference in the duration of tinnitus in patients with or without anxiety symptoms, but the patients with depressive symptoms had experienced tinnitus for a longer duration (24 months vs. 17 months, *p=0.017*).

Paper II

The study population consisted of 756 seven-year olds. Children with normal hearing were 706 and children having failed the screening audiometry and considered having a hearing impairment (HI), were 50. In the group with normal hearing, 288 children (40.8%) reported having experienced tinnitus in some form. The corresponding prevalence among the 50 children with HI was 58.0%. Among the 50 children with hearing impairment (HI) (32 boys and 18 girls, i.e. 7% of the total sample), the most common configuration was a high frequency loss, and the left ear was more commonly affected than the right. Table 5 presents the figures for all symptoms separately, and subjects are categorised with respect to if they report only ST, only NIT, only TTS or which combination of the three symptoms is reported. Table 6, however, presents the overall prevalence of tinnitus of any kind, using the figures from Table 5.

Hearing loss

In this sample, hearing loss was not a significant factor for tinnitus. In the group with no tinnitus, the mean pure tone average $PTA_{0.5,1,2}$ was 20.2 dB and for the high frequencies $PTA_{3,4,6}$ 20.3 dB, compared to $PTA_{0.5,1,2}$ 20.6 dB and $PTA_{3,4,6}$ 21.0 dB in the group with tinnitus (t-test not significant). A majority of children with both ST and HI had their hearing loss in the left ear (*p=0.043* for high frequencies; non-parametric test).

Table 5. Distribution of interview data according to hearing. Figures represent numbers and per cent recorded of ST, NIT and TTS (n=756).

	Normal hearing	***% within group***	***% of total***	**Hearing loss**	***% within group***	***% of total***
No tinnitus or TTS	368	*52,1*	*48.7*	19	*38,0*	*2.5*
ST only	108	*15,3*	*14.3*	11	*22,0*	*1.5*
NIT only	53	*7,5*	*7.0*	3	*6,0*	*0.4*
Both tinnitus forms	43	*6,1*	*5.7*	6	*12,0*	*0.8*
TTS	34	*4,8*	*4.5*	2	*4,0*	*0.3*
TTS and ST	16	*2,3*	*2.1*	1	*2,0*	*0.1*
TTS and NIT	28	*4,0*	*3.7*	3	*6,0*	*0.4*
ST, NIT and TTS	40	*5,7*	*5.3*	5	*10,0*	*0.7*
Incomplete answers	16	*2,3*	*2.1*	0	*0,0*	*0*
Total	**706**	***100,0***		**50**	***100,0***	

In Table 6, all reports regarding ST from Table 5 have been pooled into one category and all reports of NIT have been pooled into another. The category of tinnitus of any kind has been constructed so that there are no overlaps, i.e. no individual is included twice.

Table 6. Overall prevalence of ST and NIT among 7-year olds, according to hearing results.

	Normal hearing (n)	**% within group**	**Hearing loss (n)**	**% within group**	**Total (n)**	**% of total**
ST	207	*29,3*	23	*46,0*	230	*30,4*
NIT	164	*23,2*	17	*34,0*	181	*23,9*
Any kind	288	*40,8*	29	*58,0*	317	*41,9*

Paper III

In the first year, 1105 students participated in the investigation, covering nine major high schools in Gothenburg. More boys than girls selected the occupational education programs and more boys with pre-existing hearing loss entered these programs rather than the quieter theoretical programs. The students did not differ in experience of NIT, ST or TTS with respect to the chosen program but girls were overall more likely to report any of these three symptoms.

In the year 2004, 33% of the students (n=368, 37% of the girls and 31% of the boys) reported recurrent ST. Two years later the numbers had risen to 37% (39% of the girls, 36% of the boys). Already present hearing loss at the first audiometry in 2004 did not demonstrate significant statistical correlation to ST, NIT or TTS but heredity of hearing loss did correlate significantly (*p=<0.001)*.

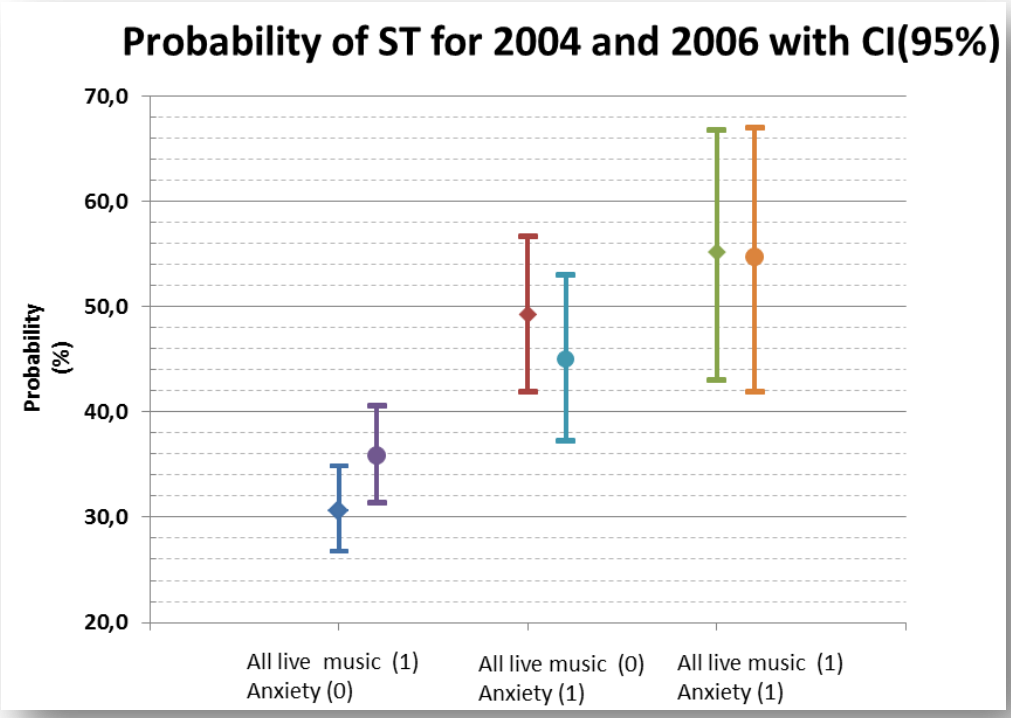
In the third year, many students had dropped out from school (26%), mostly within the theoretical programs, reducing the observed number from 1105 to 816. When calculating with the dichotomised variable Hearing loss (meaning audiometry screening passed or failed at 20 dB), there were no significant differences between the sufferers and non-sufferers of ST, NIT and TTS. Students affected with ST scored significantly higher on both the anxiety and depression parts of the HADS.

Correlations and probabilities
When performing logistic regression analysis, we entered the variables describing the students' noise exposure, specified by activity. The students reported whether they played any instrument, attended concerts, discotheques, played computer games etc. The variables for playing instruments and attending concerts were pooled into one variable, called "All Live Music", which was separate from "Recorded Music", including personal music players, mp3 or stereo.

ST: These variables were entered in a logistic regression analysis, which resulted in a number of significant factors influencing ST, such as All live music, Anxiety and Depression. After inserting the significant factors into a multiple stepwise regression analysis, the overall model for the probability of developing ST contained only All live Music and Anxiety.

Figure 10 illustrates the fitted model, producing probabilities for getting ST if the subject is positive for one variable (1) or negative (0). The three possible configurations (All live music (1)+Anxiety (0); All live music (0)+Anxiety (1); All live music (1)+Anxiety (1)) are separated from each other and presented with results for the year 2004 on lines with diamonds and for the year 2006 on lines with circles. The confidence intervals at 95% for each calculated probability are also presented. For example, playing an instrument or attending concerts (All live music) but not scoring above the cut-off level for anxiety (0) yields a probability of 31% for getting ST, in the year 2004.

Figure 11. *The probability model for ST containing All Live Music and Anxiety both 2004 (diamonds) and 2006 (circles).*



NIT: Over half of the students, 55% (N=610, 64% of the girls and 50% of the boys) reported recurrent NIT in 2004. Two years later, in 2006, 54% (58% of the girls, 52% of the boys) still experienced the symptom. The same method for calculating multiple stepwise regression analysis as described above was used for NIT. For the year 2004, the strongest correlates were Gender, All Live Music and Anxiety. In comparison, the variables differed slightly in 2006, producing All Live Music, Disco, Handsfree (earphones with mobile phone – positive value) and Anxiety instead in the final model.

TTS: In the first grade, 39% (N=425, 43% of the girls and 36% of the boys) confirmed recurrent TTS. In 2006, the number had increased to 54% (equal gender distribution). Students reporting TTS scored significantly higher on both the anxiety and depression parts of the HADS. Frequent use of cell phones was highly correlated to NIT and TTS, but the use of earphones did not appear to have any protective influence. The multiple stepwise regression analysis showed the strongest variables to be: All Live Music, Mobile, Recorded Music and Anxiety in 2004; and All Live Music, Computer (negative value) and Anxiety in 2006.

7 DISCUSSION

What is so special about tinnitus? It is an interesting cross point of biology, neurophysiology, Ca^{2+}-channels and psychiatry as well as perception of self, attitude, expectations and societal pressure. We expect ourselves to always function at the highest level and have very little acceptance for factors beyond our control that influence our lives. "Life is what happens to you while you're busy making other plans", in the words of John Lennon.

There is no denying that words such as "tinnitus", "noise" and "stress" have come to be an inseparable part of our vocabulary. Our lives, lifestyles and expectations were very different fifty years ago. These changes have come slowly, subtly and in a multitude of fields.

When investigating a specific symptom, the symptom needs to be defined from several aspects. When a symptom is subjective, one could argue that it is more challenging to define, due to lack of objective measurements, compared to other symptoms where objective measurements are available. To evaluate the impact of a symptom on an individual's life, some kind of grading system needs to be defined, with cut-off scores that can be regarded as a "normal" and physiological sensation but also identifies scores that indicate a severe and disabling pathological symptom.

It is an interesting area to explore, the definition of what is a physiological finding and were pathology begins in the perception of tinnitus. There are several models used to describe the aetiology to this development, some of which are presented in this thesis. In addition, several methods exist for grading the studied symptom, with respect to different aspects of tinnitus impact on an individual's life.

Regarding tinnitus, it is interesting to explore the boundaries where a physiological phenomenon becomes a pathological symptom. The reasoning behind physiological findings and severe impact on life quality due to a certain symptom leads us into health care ethics – how much suffering is required for the health care system to acknowledge it as a problem? Most fundamentally, how much suffering do we accept ourselves?

The studies presented in this thesis add to the present knowledge on tinnitus in children by providing a large bank of hearing data that includes parameters we had reasons to believe could, to some extent, explain the severity of tinnitus in children and adolescents. The factors that the presented papers demonstrated to have significant impact on tinnitus were hearing function, noise exposure and symptoms of anxiety. The main results are further

discussed below, as well as the methodological aspects of measuring parameters of assumed importance in the development of tinnitus.

7.1 Importance of hearing tests

The results from the three studies all indicate some form of relevance of the hearing results, but only enough to speculate on the impact of the measured hearing thresholds. With the exception of paper I (pilot), all subjects (in total 2175 young people under the age of 20) were tested by audiometry. A hearing screening combined with a screening for tinnitus symptoms were chosen for the 7 year olds. However, for the help-seekers, thresholds were measured in order to further analyse tinnitus severity correlated to the hearing results. The investigations provided interesting but not always consistent data. In paper I (help-seeker), all subjects were clinical patients with tinnitus. The statistical comparisons of the impact of hearing status on tinnitus could here be made with respect to the severity of tinnitus and not its occurrence, as in papers II and III. Within the help-seeker population, 74% had normal hearing and the remainder had predominantly high frequency hearing impairment (HI) of a mild degree (<30 dB). There were significant correlations of weak to moderate degree between high frequency loss ($PTA_{3,4,6}$) and the degree of tinnitus, as measured by TSQ and all VAS-scales.

In paper II, the large sample consisted of 756 unselected 7-year olds, from the national hearing screening program. This investigation did not show any significant correlations to HI itself, as measured by screening audiometry. However, in the logistic regression model, the presence of HI elevated the probability of having ST from 37% to 76%, depending on confidence intervals and prior experience of TTS. The most common configuration of HI in this sample was high frequency loss and in the left ear. Only 16 children exhibited a possible sensorineural HI, having normal tympanometry. The remaining children with failed screening thresholds showed signs of on-going secretory otitis media (SOM). Other studies have also demonstrated the connection between SOM and tinnitus (80, 140) and it would seem that the presence of SOM could be a stronger trigger for tinnitus than the HI it entails.

Paper III, investigating 1105 teenagers, showed significant correlations between tinnitus and heredity of HI, whereas no significant correlation between tinnitus and HI was found. This raises speculations whether or not individuals with heredity of HI already carry a vulnerability but not yet a visible and measurable HI. Screening audiometry does not detect a minor damage. However, it is possible that subjects with tinnitus have some degree of damage to the hair cells, which could only be identified by other methods. Assuming that tinnitus should be regarded as a sign of minute damage, its

pathology, which is not yet detectable, could prove potentially progressive due to unchanged listening behaviour (141). In clinical practice, it appears to be an increasing number of youngsters complaining of tinnitus or hard of hearing, yet our standard psychoacoustic tests seem too blunt to detect a minor damage. Is there a place for audiometry and especially screening audiometry in tinnitus diagnostics and research? As long as we do not have better tools, they have to suffice and do still provide useful insights into the mechanisms of tinnitus. The ambition to improve the methodology does not negate the results it has brought us so far.

There are on-going international discussions regarding the details of the screening protocol, such as what frequencies it should entail, what cut-off level should be used and what ages are most appropriate (142). Whereas there is agreement on detecting permanent childhood HI of moderate or greater degree, there is less agreement on the need to detect unilateral HI, temporary HI or mild HI. Identification of children with previously undetected, acquired or progressive permanent HI is obviously desirable, but the number of such cases would be relatively small compared to the large number of children with transient conductive hearing loss, such as SOM, in the pre-school age group. This results in low specificity and carrying out the tests in schools, where there is excessive ambient noise, lowers it additionally (143). In addition, in Sweden, there are no national recommendations or guidelines for primary paediatric health care concerning screening for hearing loss, but there are guidelines for school health care providers. The guidelines contain a passage on school entry hearing tests, recommending screening audiometry 500-6000 Hz at 20 dB (144). There had also been a screening point at the age of four, but it has since 1999 been discontinued as a national guideline and exists only subject to local policies (145).

The advantages of the screening audiometry protocol are its simplicity and accessibility, whereas the drawbacks are that tests are performed in less than ideal test conditions, therefore affecting the screening quality. However, the method appears to have high sensitivity and high specificity for minimal, mild and greater hearing impairments (142). Since the focus in this thesis was to identify factors connected to the development of tinnitus and not to detect hearing losses requiring treatment, the actual audiometry testing in papers II and III was deemed sufficient.

Most studies that show any correlation between tinnitus and HI, do so at higher end of the audiometry scale. Some researchers even advocate high frequency hearing tests (10-20.000 Hz) to detect any measurable damage to the cochlea. There has been some research on extended high frequency (EHF) audiometry in conjuncture with noise exposure or tinnitus but the results are not conclusive (146-148). Children over five years of age have

been tested with EHF audiometry with reliable results, whereas younger children tended to respond with elevated thresholds. The latter may perhaps signal younger children's immaturity to perform on such tests (149). In the current situation, my belief is that the method does not yet possess sufficient reliability, to be implemented without further improvements.

Distortion product otoacoustic emissions (DPOAE) have been used with EHF audiometry when comparing tinnitus patients to healthy controls with promising results. This result points towards evidence of damage in the basal regions of the cochlea, but is not visible on standard audiometry (150, 151). One particular variant is the synchronized spontaneous otoacoustic emission (SSOAE). In one study, SSOAE was compared to EHF audiometry and two other variants of otoacoustic emissions (DPOAE and click-evoked, CEOAE), which indicated that the presence of SSOAEs was indicative of an ear with highly normal cochlear function over a broad frequency range (152). It appears that both otoacoustic emissions and EHF audiometry do add to the picture of discrete damage. However, when it comes to which region to focus the measurements on, studies disagree (153). Measuring otoacoustic emissions is also extremely sensitive to background noise and test results are often not possible to interpret.

Still, much evidence points to the importance of the higher end of the acoustic spectrum. Thus, at least for statistical calculations, when using conventional audiometric frequency range, it could perhaps be better to use $PTA_{3,4,6}$, rather than $PTA_{0.5,1,2,4}$. Now that interviewing young children about tinnitus has been established by several studies, it could possibly be implemented in the standard audiometric screening. Subjects that confirm experience of tinnitus can then be referred for further audiometry and information regarding hearing preservation. Such a procedure could serve the purpose of targeted intervention.

Laterality

An interesting finding in paper II, was that a majority of the children with HI suffered from HI on their left side. It is a recurring topic of discussion, as some studies have shown a predominance of left-sided tinnitus (46, 154), while others have not been able to see any side preponderance (155). Even HI has been reported to appear more frequently on the left side (7, 156). The left ear has been said to be more susceptible to noise damage, while spontaneous otoacoustic emissions (SOAEs) are more often found in the right ear (157, 158). Whether there is an evolutionary connection to auditory symptoms and left-handedness has been investigated (159, 160). Left- and mixed-handedness is associated with greater bihemispheric representation of cognitive functions than in right-handers, which has given rise to discussions of asymmetric higher cognitive functions and hemispheric dominance (154,

161). Language perception is more often localised in the left hemisphere. Although the connections between the higher areas of cognitive processing are still unclear, there is enough evidence to state that the asymmetric representation of these functions can influence the experience of tinnitus.

7.2 True increase or increase of awareness

When dealing with children we must be careful to ensure that the child understands the question posed and the issue. There are several advocates of the idea that children answer what they think we want to hear from them, not what they actually feel. Some researchers have therefore included test questions unrelated to the issue and whose purpose is solely to ascertain the young subject's credibility when later answering tinnitus related questions. Others accept the children's answers at face value. In our studies, the youngest subjects were asked only three questions, verbally in a standardized manner and leaving room for correction or clarification. The studies where older children were involved, made use of written self-reports and questions requiring a higher degree of self-evaluation.

In the previously described Epidemiology-section, Table 1 presented the combined results of tinnitus prevalence studies on children from the last 40 years. In these studies, the prevalence range varies widely (7-64%) and the disparity between populations is substantial. Within the aggregate of young people with confirmed normal hearing, which for audiological reasons should represent a fairly homogenous group, researchers arrive at a prevalence between 13 and 50%. The most plausible confounding factor is probably differing definitions. Two studies have differentiated between spontaneous tinnitus (ST) and noise-induced tinnitus (NIT), which was an important step in the direction of narrowing down the definitions. Using this distinction, only 2.4% of Swedish 7-year olds in 2003 reported NIT and 12% ST (137). In a study of teenagers the prevalence was definitely higher, 44% for NIT and 32% for ST (138). Subsequent studies from our research group have continued this distinction between ST and NIT, in order to keep these entities separated.

In paper I (pilot), as many as 53% and 46% of the 274 children (9-16 years) reported having experienced NIT and ST respectively. Furthermore, 22% found tinnitus to be annoying, a lower recording compared to the previous study on teenagers, where 53% found their tinnitus to be annoying (138). This difference could reflect the larger age span in the pilot study, where younger children possibly did not fully understand how to relate to the question of frequency of annoyance.

In paper II, the results from 756 seven-year olds demonstrated that 42% of the children had experienced tinnitus in any form. Presenting the figures subgrouped for ST and NIT, the prevalence of ST was 30% and 24% for NIT.

These results are in accordance with several other studies, supporting the notion that tinnitus is more prevalent in individuals with HI. When prior studies have reported on tinnitus prevalence, it has not been clear if this has included only prevalence of ST or both ST and NIT, thus hampering comparison of our results to those available in published literature. Results from our normal hearing sub-group are in the middle of the range of that published in other studies, assuming that the other studies report only ST. However, if any type of tinnitus was accepted in the published studies, our results are instead towards the higher spectrum. It becomes clear that comparing results and evaluating epidemiological trends is not quite possible with the existing information. On the other hand, one recent Polish study has performed the herculean task of gathering both tinnitus reports and screening audiometry data from 60.212 Polish 7-year olds (162). All other 19 reports pooled into one, represent heterogeneous data from 9.542 children. The Polish report has investigated a sample covering 44% of the entire national 7-year old population. Some rather generalising conclusions could be drawn from such a large sample.

The Polish study was carried out in two parts. One questionnaire was presented to children undergoing school-entry audiometric screening. The audiologists performing the screening asked every child whether he or she had experienced sounds in quiet surroundings (ST) and if so, if it occurred sporadically, often or very often. The other questionnaire was sent to the parents of each child, with the question if the child had mentioned experience of ST and if so, how frequently. The first observation was the disparity between the reports of tinnitus prevalence obtained directly from the children vs. the reports gathered from the parents. The prevalence figures based on child responses were 32.6%, whereas the same estimate using parental reports yielded 13.6%. Approximately 18% of these children stated that tinnitus was present often to very often (5.8% of the total sample) and in only 25% of the cases were the parents aware of their child's symptom. Among the sample with normal hearing according to screening audiometry (all frequencies 20 dB(HL)) the prevalence of tinnitus was 31.7%, which is in the same range as the results from paper II. Among the children that did not pass the screening (any frequency >20 dB), the prevalence was 43.1%, compared to 46% in paper II.

Fifteen to twenty years ago, tinnitus in children seemed to be a marginal problem, with numbers presented in the range of 5-10% amongst children with normal hearing. Latest reports, however, circle around the 50% mark for

noise related tinnitus. During this time, there has been some scepticism toward the increasing numbers. Are the children capable of describing the phenomenon? Are they answering positively to please the investigator? If they indeed experience so much tinnitus, why are they not represented in corresponding numbers in the clinics? In my opinion, that query is answered by the results of the Polish study. The figures clearly show that a majority of children, when asked, report tinnitus even of quite disturbing degrees, but simultaneously negate that they have raised the issue with their parents or school health workers. Other studies also support the notion that children do not spontaneously report on audiological problems, regardless of the impact they have on everyday life of the child (163).

In paper III, the prevalence of tinnitus among teenagers in the years 2004 and 2006 was 33-37% for ST and 55-58% for NIT. In comparison, the previous investigation of teenagers and their experience of tinnitus, revealed prevalence figures of 32% for ST and 44% for NIT. An alternative calculation, presenting any of the symptoms, yielded 53%. No comparison with other studies can be done, as there are none specific for this age group.

As previously discussed, comparison is difficult and unequivocal conclusions hard to draw. However, bearing in mind the Polish results, which imply that children can very well suffer from tinnitus and yet not report it, it is my interpretation of the figures from the last 40 years and our results, that the problem of tinnitus in the young population is indeed increasing.

Useful instruments

Other benefits can be drawn from the results of paper I – help-seekers. Here, for the first time, a questionnaire focusing on the degree of disturbance from tinnitus (TSQ) was used in a paediatric population. Since the question used in paper I (pilot) (*"Is tinnitus troublesome for you?")* proved to be a challenge when comparing results with previous studies, TSQ provided a standardized instrument to quantify many of the aspects the aforementioned question was trying to capture. The young patients also had visual analogue scales with which to grade the impact of tinnitus.

To begin with, the results demonstrated a moderate correlation between TSQ and the two HAD subscales (HAD-A, anxiety and HAD-D, depression), as well as between TSQ and all the visual analogue scales. This is most likely due to an overlap of the psychological component of TSQ. Furthermore, the model from the multiple stepwise regression analysis using VAS annoyance/week as a possible major descriptor of suffering pointed out VAS loudness/week, TSQ score and possible anxiety as factors with the greatest influence on suffering (as defined by VAS annoyance/week). Using VAS loudness/week instead, resulted in highlighting out the remaining visual analogue scales, again together with possible anxiety.

These results could be interpreted that the higher one scores on TSQ, answers above the cut-off for possible anxiety and reports the tinnitus sound to be loud - the higher the probability of finding it very annoying (in other words – troublesome, a suffering). Both models showed high degrees of strength (adjusted R^2=0.836 and adj. R^2 =0.773). This means that both TSQ and VAS-scales besides HADS could be useful tools in predicting tinnitus suffering in the paediatric population, as also previously reported in adults (164).

Gender perspective

Paper I (pilot) revealed a majority of girls (57%) reporting tinnitus, while most boys (61%) did not report it. Then again, in the help-seeker part, the boys were in slight majority (55 boys, 40 girls). In paper II, the gender distribution was equal. In paper III, there was a minute majority of girls reporting tinnitus. One can only speculate on the gender skewing visible in the two parts of the first study. Could it be that fewer girls were referred to the ENT-clinic? Were their symptoms estimated to be of lesser degree, did the girls present their symptoms differently than the boys, or did they really find their tinnitus less annoying than the boys did? These questions cannot easily be answered, but it is important to keep a vigilant eye on any potential gender inequality in diagnostics and health service.

7.3 Accumulated noise exposure

Paper III focused on teenagers under the supposition that voluntary exposure to noise increases with age. A previous investigation of teenagers pointed towards higher prevalence of tinnitus and an association to noise exposure in concerts and discotheques (138). By setting up a longitudinal framework, we were hoping to follow any developing hearing problems related to noise at school or noise during leisure activities.

When describing the characteristics of the study population, we saw that youngsters entering the noisier, vocational programs displayed a higher prevalence of already present hearing loss. Noise exposure habits of the adolescents vary, both individually and with socioeconomic background (156, 165). When analysing a subpopulation highly exposed to noise, such as youngsters in technical vocational schools, the question arises whether socioeconomic or hereditary factors might contribute to the noticed HI. The fact remains that socioeconomic status reflects on hearing results (166-168). Additionally, one Swedish study has shown a link between lower socioeconomic status and less precautionary attitudes towards noise and noise protection (169).

In 2003, the Swedish Work Environment Authority measured the sound levels that teachers and pupils in 27 schools nationwide were exposed to in

the course of a school day. Depending on the activities, levels varied greatly during the school day, from silence with average sound levels down to approximately 40 dB(A) to noisier moments with average levels of about 80 dB(A). For the school day as a whole, average levels between 66 and 77 dB(A) were recorded, and for theory lessons alone between 57 and 74 dB(A). There are also indications of elevated noise levels in primary schools and day care centres, leading to varied degrees of discomfort for the staff (170). However, the youngest children who are also exposed to the same sound environment as the staff, are not possible to question. The existing regulation states that places where education is conducted, the total background noise level should not exceed 35 dB(A) (88). Unfortunately, the same text concludes that contributing noise from the activity itself is not included and is not mentioned elsewhere. Paper III wanted to ascertain whether the working environment of the students was sound, at least from the perspective of noise exposure. The results demonstrated that the students did not develop more hearing loss, tinnitus or TTS over the three years in school, which implies that good protective measures are in place.

Secondly, we wanted to know whether varying degrees of voluntary noise exposure in leisure time contributes to tinnitus development. Paper III has demonstrated that every third or every second youth has experienced tinnitus or TTS, mostly after listening to music. A large majority of these youngsters presented with normal audiometry alongside tinnitus. The noise in school did not seem to influence the youngsters negatively, but the following 16 hours of leisure time were of significance. When looking for just one powerful noise impact factor, playing instruments and attending concerts (called All Live Music) were present in all of the analyses. These are activities where shielding one's hearing is controversial and not always possible or wanted. The impact of live music was measurable for all three studied symptoms, namely ST, NIT and TTS, and this influence was present for all study years. Other factors, such as recorded music, mobile phones or discotheques were also present, but of weaker influence in this sample. It is important to underline the potentially harmful effect of live music in this age group, as many other studies done on professional musicians have demonstrated high frequency hearing loss in adults and for different types of music, classical or popular (171-173).

Even though the effect of live music was the strongest, discotheques, mobile phones and recorded music were still significantly correlated with ST, NIT and TTS. The role of discotheques and recorded music is easy to understand, as they both expose the listener to amplified music. The effect of mobile phones in this survey is more difficult to explain as the technology had changed dramatically between the years 2004 and 2006 and mobile phones were beginning to merge with mp3-players. In 2004, only 6.4% students used

earphones vs. 12.4% in 2006, while the number of students reporting use of mobile phones remained constant at 70%.
Unfortunately, we do not know what the students refer to when answering how much they use their mobile phone with or without hands-free earphones. It may be used for phone calls and therefore exposing the teenagers to possibly harmful electromagnetic radiation but it may also be for listening to music and thus exposing them to possible high speaker output levels (96, 174). Many young people do not appear to appreciate the potential harm in a seemingly harmless and fun device. One study conducted physical measurements on preferred listening levels of mp3s in youth. The results indicated that over 25% of the participants were at risk for noise induced hearing loss (NIHL). The mean preferred listening level was as high as 82 dB(A) in quiet, and 89 dB(A) in the presence of background noise (175).

It has also been presented that the attitudes of adolescents towards traditional risk situations correlated with attitudes towards noise exposure. Interestingly, young women judged risk situations generally as more dangerous than young men did, but still behaved in the same way as men (176). A large Dutch study among 12-19 year olds, revealed that 90% of youngsters listened to mp3s and 29% of them were at a direct risk of acquiring NIHL, as they listened to over 89 dB(A) for more than 1 hour daily (177). In addition, the listeners at risk were more likely to come from lesser socioeconomic backgrounds. Similar psychosocial correlates were seen for frequenting discotheques, where the estimated exposure would reach 100 dB(A) for 1.25 hours per week or more (178). In another study, as few as 11% of Dutch medical students confirmed the use of hearing protection in noisy environments (179). It does, however, instil a small sense of hope, when music students display a higher degree of healthy attitudes towards noise (180), as it implies that more information and specific information results in better risk judgement.

Many report tinnitus debut in connection to noise exposure, whilst others deny a specific trigger. Still, we see that the overall exposure to sound has increased in general, with larger and noisier classes in school, music in shops and elevators, continuous listening to iPods, mp3s and mobiles (see Figure 12). The younger generation appears to become used to an uninterrupted sound field accompanying them in many activities. A recent study on rats has shown visible auditory dysfunction following long time exposure to structured noises below 65dB (181). These noises are deemed “safe” and are often present in modern human environments, and yet here they indicate substantial negative auditory consequences. Initially insignificant injury can progress to significant damage. As observed in the industry, tinnitus can preclude noticeable hearing loss by many years (10). Studies have demonstrated the deleterious influence of smoking, lack of exercise and poor diet on the development of NIHL (182), which conversely might imply that

young people can be better equipped to withstand unsuspected noise with better nutrition and overall health.

Figure 12. *Increased listening time.*

Information and particularly repeated information in the classrooms has proved to be an accessible way in promoting hearing health in elementary school students. Interpersonal and interactive educational interventions were more effective and had longer impact than self-directed learning experiences for NIHL and tinnitus prevention (183).

Sound conditioning

Forward and backward sound conditioning is a very interesting effect and the subject of several studies (184-186). Canlon's group specifically has been very active in this field. The sound conditioning paradigm consists of a low-level, long-term, non-damaging acoustic stimulus. The stimulation protects the outer hair cell morphology (fewer missing outer hair cells), as well as physiology (distortion product otoacoustic emissions) compared to an unconditioned group (187). One hypothesis is that antioxidants are primary mediators of the conditioning effect (188), whereas another theory focuses on dopamine or glucocorticoid receptors in the cochlea and hypothalamus (16, 72).

In practice, different kinds of sound have proved effective, including octave band noise, broadband noise, pure tones and music of own choice (101). According to a recent review of the subject (72), within the parameters of the most commonly used setups, test subjects are conditioned for days or weeks prior to exposure of high intensity, which is not very useful if we should ever try to make practical use of the mechanism. However, one study demonstrated a protective effect with only 15 min of sound conditioning before exposure. Others show sufficient effects with sound presentation after the acoustic trauma (185). The mechanism behind this backward conditioning is hypothesised to be an activity-induced change in the cochlear metabolism and an up-regulation of antioxidants, particularly in the stria vascularis. Classical symphonic musicians who, due to the specifics of their work, are exposed long-term to moderately loud music have shown to have significantly more suppression than non-musicians (189). The authors hypothesise that music may have served as a sound conditioning stimulus for strengthening central auditory pathways.

Could we in the future suggest that concerts include a completive phase of cochlear relaxation, comparable to muscle stretching after physical exercise?

7.4 Stress and mood disorders

Loud sound volumes are not only potentially damaging to our hearing, they may also invoke stress reactions. In general, humans have a lower performance with memory impairment and slower decision making after longer periods in noisy environments (190). Perhaps, in the near future, because of the increased noise burden, we might see an increasing number of people with hearing impairment, tinnitus and exhaustion syndromes, not meeting the increasing expectations and decision burdens (103).

Since the study population in paper III consisted of adolescents, who in general are mature enough to perform self-evaluation of their somatic and mental well-being, we wanted to explore any connections between psychological and stress related well-being in connection with ST, NIT and TTS. The population of paper I (help-seekers) allowed for similar queries.

Paper I (help-seekers) showed no differences in the degree of suffering, as measured by TSQ, or any statistically significant correlations to hearing parameters in a comparison with the type of onset. However, 32% of the patients scored above the cut-off level for possible anxiety disorder for adolescents, and 14.5% scored above the cut-off level for possible depression. Additionally, patients with depressive symptoms had experienced tinnitus for a longer period of time as opposed to the group without depressive symptoms. As previously mentioned, a prospective Swedish study

reported that a decrease in depression is associated with a decrease in tinnitus prevalence, and even more markedly with tinnitus severity (128, 135). By addressing the concurrent depression, we can reduce the impact of tinnitus.

In paper III, scoring above the cut-off level for either depression or anxiety was highly correlated to the presence of any hearing symptoms, with odds ratios of 2 to 3 times higher risk for these subjects. Moreover, all probability models from the multiple stepwise regression analyses demonstrated that anxiety was the strongest variable in all hearing symptoms in both 2004 and 2006. To clarify, spontaneous tinnitus as well as strictly noise-induced tinnitus or temporary threshold shift, are all influenced by anxiety symptoms. This result underscores the importance of an active search for symptoms of mood disorder or anxiety, in this young population, as well as in adults, as demonstrated by earlier research (3, 109, 191).

No matter why the young patient with tinnitus displays symptoms of mood disorders, we should be quick to identify them and address them, as the success of our proposed tinnitus rehabilitation relies on covering all aspects. Beliefs and attitudes towards tinnitus play an important role in the process of rehabilitation and even tinnitus severity is significantly related to perceived attitudes (192).

One large epidemiological study of the Swedish adult population showed increasing risk of tinnitus with increasing levels of noise in the work place (13). In parallel, increasing risk of tinnitus was also attributed to stress increase (193). One validated instrument, which would be very interesting to apply in clinical practice to quantify the level of stress in children, is Stress In Children (in Swedish BUS, Barn Under Stress) (194). Mood disorders and anxiety represent one facet of the overall wellbeing and stress has been shown to have both psychological and somatic effects. As discussed previously, noise can induce stress in children (103) and higher stress impact correlates significantly to higher degrees of tinnitus suffering (195). Now that we have the necessary tools, we should endeavour to identify those individuals who might need extended tinnitus rehabilitation and counselling.

Psychological well-being of adolescents is a very important topic. Some countries debate on whether to issue national screening programs on mood disorders, while others have already set them in motion (196). The audiological department has different aims and angles of approach compared to both national psychological surveys and targeted child psychiatric units and may therefore sometimes successfully use instruments, which the latter two institutions would find unsatisfactory. HADS is a screening instrument only, not decisive in whether or not a subject actually meets the criteria for a depression or anxiety disorder. That is its major shortcoming but also its major strength. As an instrument for the non-psychiatric health provider, it is

simple enough to administer and to evaluate. Other more specific instruments, such as BDI or BYI, are sharper tools in terms of diagnosing an individual with a specific ailment. However, as discussed in the Risk factor section, it is not the depression itself we should be looking for, but rather the psychological vulnerability that can turn tinnitus into a major problem. We should definitely strive not to miss a mood or anxiety disorder that so often is present together with tinnitus, but we would probably be helping many more by identifying individual weakness points and thereby tailoring the treatment and prevention strategies.

8 CONCLUSION

This thesis sought to increase our knowledge of subjective tinnitus in children and adolescents.

Although the main difficulty in tinnitus research is the use of differing definitions of the symptom, there is reason to believe that tinnitus is more prevalent than 30 years ago, reaching prevalence figures of over 40%. It is useful to discriminate between spontaneous tinnitus and noise induced tinnitus in order to bring more clarity to the continued study of tinnitus. Youngsters confirm the experience of noise induced tinnitus to be as high as 53%.

Tinnitus may be a sign of damage to the cochlea. Unaltered noise exposure may lead to a permanent hearing impairment and the subjects with already present hearing impairment are more vulnerable and at higher risk for developing tinnitus.

Teenagers that had chosen vocational programs in high school already had a higher prevalence of hearing loss at the beginning of the first year. However, their hearing did not deteriorate during the three years of school.

Prolonged exposure to noise such as via the relatively new habits of portable listening devices, mobile phones, iPods and mp3'-s increase the risk of subjective temporary threshold shift.

This thesis has presented results demonstrating the connections between tinnitus in children and adolescents and:

- signs of incipient hearing impairment, especially in the high frequency regions
- noise exposure, predominantly from live and amplified music
- anxiety symptoms

9 FUTURE PERSPECTIVES

Future research in the field of tinnitus would benefit from a widely agreed upon definition of the symptom. In the field of methodology, future studies could benefit from full pure tone thresholds and perhaps extended high frequency threshold audiometry. It would be very interesting to see stress-gauging instruments implemented in research on young people and their hearing symptoms. Additionally, it would be valuable to further validate HADS as an instrument for clinical use in children with tinnitus.

For the clinicians meeting children with tinnitus, I would wish to see the knowledge regarding symptoms of depression and anxiety spread and implemented independent of the presentation of the problem and of the specialisation of the clinic.

It is my wish that our legislators understand the importance of systematic information on noise effects and preventive measures and of a stricter implementation of regulations on noise, especially in schools and pre-schools.

For our young generation, the following advice might be useful:

- Do not listen to music louder than you can still carry a conversation.
- Think about the total amount of sound you expose yourself to – not just headphones, but also concerts, discotheques, clubs, your own participation in orchestras and bands, afterhours in mechanical workshops with power tools, etc.
- Limit yourself to 1 hour of excessive sound of any kind per day.
- Remember our brain's adaptive capability – just because it doesn't feel as loud after 15 minutes, it doesn't mean it is less harmful. Set an upper limit on your listening device and don't turn it up when you have gotten used to the sound.
- Do not listen to music in noisy environments, such as busses, trams or bikes. Wait until you get home and it is quiet.
- Listen when you want to concentrate on the music, not as a background noise.
- Give yourself time to recuperate and rest from noise.

For all of us, I wish that music would always feel like a blessing, not a curse.

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Q. F. F. F. Q. S.

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DATUM POSNANIAE DIE XV MENSIS DECEMBRIS ANNO MCMXXV

SAMMANFATTNING PÅ SVENSKA

Tinnitus är ett symptom som ibland beskrivs som ringningar i öronen. Själva ljudet som upplevs kan variera i styrka, grad och ljudkvalitet, men det som framför allt kännetecknar tinnitus, är att det inte orsakas av någon yttre eller inre ljudkälla. Orsakerna till att man upplever ett sådant ljudfenomen kan vara många, varför det är viktigt att understryka att tinnitus inte är en sjukdom, utan ett symptom som kan likställas med t.ex. värk. Exempel på orsaker till tinnitus är olika hörselsjukdomar, hörselskador, bullerskador, stress, ångest och utmattning.

Det är ganska vanligt med tinnitus hos vuxna (ca 15%) och på senare år har även studier visat att barn också kan ha tinnitus. Det är tyvärr ganska svårt att veta exakt hur vanligt det är eftersom olika forskare inte definierat tinnitus symptomet på samma sätt, men mycket tyder dock på att förekomsten av tinnitus har ökat hos barn och ungdomar.

Denna avhandling har syftat till att öka kunskapen om tinnitus hos barn och ungdomar och att undersöka möjliga gemensamma faktorer hos de som söker hjälp för sin tinnitus. Vidare har målsättningen varit att undersöka hur vanligt förekommande tinnitus är hos barn och ungdomar i en svensk population och att undersöka möjliga faktorer som kan påverka uppkomsten av tinnitus hos dessa personer.

I avhandlingens tre delarbeten har hörselmätning genomförts och olika frågor har ställts om tinnitus, exempelvis om tinnitus uppstått spontant eller om tinnitus eller tillfällig hörselnedsättning har uppstått i samband med buller. Frågor har även ställts om symptom på ångest och depression samt vilka lyssningsvanor individerna har, dvs om de spelar instrument, om de går på konserter, lyssnar på iPod och mp3 osv samt hur ofta dessa aktiviteter utförs. Sammanlagt har 2230 personer i åldrarna 7-16 år undersökts i olika studier.

I den första studien undersöktes skolelever och så många som 46% av dessa rapporterade att de hade haft spontan tinnitus och 53% att de hade haft bullerutlöst tinnitus. Vidare undersöktes 95 ungdomar som hade sökt hjälp för sin tinnitus på hörselvården på Sahlgrenska Universitetssjukhuset i Göteborg. Hos dessa hade mer än 50% upplevt en plötslig debut av sin tinnitus och den vanligaste utlösande orsaken var musik. Studien visade även att det hos dessa personer fanns ett samband mellan svårighetsgraden av tinnitus, hörselnedsättning i diskantområdet och symptom på ångest och depression. Avhandlingens andra delarbete visade att 40% av sjuåringar med normal hörsel hade upplevt tinnitus och att förekomsten hos barn med

bekräftad hörselnedsättning var så hög som 58%. Den tredje studien undersökte förekomst av tinnitus hos gymnasieungdomar, där 33% av ungdomarna i första ring hade spontan tinnitus och 37% i tredje ring. Förekomsten av bullerutlöst tinnitus var 55% vid de båda mättillfällena och framförallt orsakad av att spela instrument och gå på konserter. Studenter med tinnitus rapporterade också högre grad av ångestsymptom.

Denna avhandling rapporterar att tinnitus är vanligt förekommande hos barn och ungdomar, vidare att det finns samband mellan tinnitus och tecken på hörselnedsättning i diskantområdet, bullriga aktiviteter (särskilt musik) samt psykisk ohälsa som framför allt var i form av upplevd ångest. Det vore önskvärt att minska på ljudnivån av musik man lyssnar på och minska på mängden tid man lyssnar, i syfte till att minska risken för uppkomst av tinnitus.

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APPENDIX

A. Study specific questions

Q1. *"Efter att du lyssnat på starka ljud, hög musik eller andra starka ljud, har du märkt av att det ringer eller piper i öronen, fastän musiken (eller annat starkt ljud) stängts av?";* (Nej, aldrig / Ja, en gång / Ja, flera gånger).

Q2. *"Har du märkt av att det ringer eller piper i öronen, även om du inte lyssnat på starka ljud?"* (Nej, aldrig / Ja, en gång / Ja, flera gånger).

Q3. *" Hur ofta har du märkt av att det ringer eller piper i öronen? "* (Aldrig /Sällan/Ofta /Alltid).

Q4. *"Tycker du att det är besvärande när det ringer eller piper i öronen?"* (Nej / Ibland / Ofta).

Q5. *"Efter att du lyssnat på starka ljud, hög musik eller andra starka ljud, har du märkt av att du hör sämre efteråt?"*, (Nej, aldrig / Ja, en gång / Ja, flera gånger).

VAS

"*Jag har inte märkt av min tinitus idag*" (0 mm) till "*Min tinnitus var extremt stark idag*" (100 mm)

" *Jag har inte märkt av min tinitus förra veckan"* (0 mm) till " *Min tinnitus var extremt stark förra veckan*" (100 mm)

" *Min tinnitus har inte stört mig alls idag*" (0 mm) till "*Min tinnitus var outhärdlig idag*" (100 mm)

" Min tinnitus har inte stört mig alls förra veckan" (0 mm) till *" Min tinnitus var outhärdlig förra veckan"* (100 mm)

B. Frågeformulär pilotstudien

Tinnitus är ett symptom som många människor märker av. Med tinnitus menar man att personen hör ett ljud i örat eller i huvudet utan att det finns en ljudkälla som t.ex en radio, TV, CD eller något annat som är på. Eftersom tinnitus är vanligt vill vi ställa lite frågor till dej om det, och ber att du **ringar** in de svar som gäller för dej.

A. Är du flicka eller pojke?

B. Hur gammal är du?_____

3) Efter att du lyssnat på starka ljud, hög musik eller andra starka ljud, har du märkt av att det ringer eller piper i öronen, fastän musiken (eller annat starkt ljud) stängts av?

☐ Nej ☐ Ja

4) Har du märkt av att det ringer eller piper i öronen, även om du **inte** lyssnat på starka ljud?

☐ Nej ☐ Ja

5) Hur **ofta** har du märkt av att det ringer eller piper i öronen?

☐ Aldrig ☐ Sällan ☐ Ofta ☐ Alltid

6) Tycker du att tinnitus, dvs ljudet du märker av, är **besvärande**?

☐ Aldrig ☐ Sällan ☐ Ofta ☐ Alltid

TACK för att du tog dej tid att svara!

Dina svar är betydelsefulla och tack vare dej ökar kunskapen om tinnitus. Det har vi nytta av när vi möter unga människor som lider av tinnitus.

C. Tinnitus Severity Questionnaire

Sahlgrenska Universitetssjukhuset ÖRON-, NÄS- och HALSSJUKVÅRD

Svårighetsgradering av tinnitus

Namn: ..... Personnr: .....

Adress: .....

Postnr: ..... Postadress: ..... Datum: .....

Försök att besvara alla frågor, kryssa endast för en ruta för varje fråga!

		Litet	Måttligt	Mycket ofta	Pullst.	Vet ej
1	Hur mycket påverkar tinnitus Din livskvalitet, totalt sett?					
2	När Du är vaken och vistas i tyst miljö (men inte försöker sova) hur mycket obehag orsakar tinnitus då?					

		Aldrig	Sällan	Ofta	Mycket ofta	Alltid	Vet ej
3	Hur ofta märker Du tinnitus när Du är vaken?						
4	Hur ofta påverkar tinnitus Din koncentrations-förmåga t.ex. när Du läser?						
5	Hur ofta har Du svårt att somna eller somna om p.g.a. tinnitus?						
6	Hur ofta kan Du förtränga eller "glömma" tinnitus genom någon aktivitet t.ex. att titta på TV eller tala med någon?						
7	Om Du utsätts för vardagsljud t.ex. musik, en klocka, en fläkt, minskar eller överröstar dessa ljud Din tinnitus?						
8	Hur ofta medför tinnitus att Du känner Dig orolig och bekymrad?						
9	Hur ofta medför tinnitus att Du känner Dig spänd och irriterad?						
10	Hur ofta medför tinnitus att Du känner Dig deprimerad och olycklig?						

JP 2013-03-13

D. HADS *Denna del handlar om hur Du känt Dig under den senaste veckan. Besvara frågorna genom att markera det svarsalternativ Du tycker stämmer bäst. Om Du är osäker, markera det som känns mest riktigt.*

1. Jag känner mig spänd och nervös

3 ☐ Mestadels
2 ☐ Ofta
1 ☐ Av och till
0 ☐ Inte alls

2. Jag uppskattar fortfarande saker jag tidigare uppskattat

0 ☐ Definitivt lika mycket
1 ☐ Inte lika mycket
2 ☐ Endast delvis
3 ☐ Nästan inte alls

3. Jag har en slags känsla av att något hemskt kommer att hända

3 ☐ Mycket klart och obehagligt
2 ☐ Inte så starkt nu
1 ☐ Betydligt svagare nu
0 ☐ Inte alls

4. Jag kan skratta och se det roliga i saker och ting

0 ☐ Lika ofta som tidigare
1 ☐ Inte lika ofta nu
2 ☐ Betydligt mer sällan nu
3 ☐ Aldrig

5. Jag bekymrar mig över saker

3 ☐ Mestadels
2 ☐ Ganska ofta
1 ☐ Av och till
0 ☐ Någon enstaka gång

6. Jag känner mig på gott humör

3 ☐ Aldrig
2 ☐ Sällan
1 ☐ Ibland
0 ☐ Mestadels

7. Jag kan sitta stilla och känna mig avslappnad

0 ☐ Absolut
1 ☐ Vanligtvis
2 ☐ Sällan
3 ☐ Aldrig

8. Allting känns trögt

3 ☐ Nästan alltid
2 ☐ Ofta
1 ☐ Ibland
0 ☐ Aldrig

9. Jag känner mig orolig, som om jag hade fjärilar i magen

0 ☐ Aldrig
1 ☐ Ibland
2 ☐ Ganska ofta
3 ☐ Väldigt ofta

10. Jag har tappat intresset för hur jag ser ut

3 ☐ Fullständigt
2 ☐ Till stor del
1 ☐ Delvis
0 ☐ Inte alls

11. Jag känner mig rastlös

3 ☐ Väldigt ofta
2 ☐ Ganska ofta
1 ☐ Sällan
0 ☐ Inte alls

12. Jag ser med glädje fram emot saker och ting

0 ☐ Lika mycket som tidigare
1 ☐ Mindre än tidigare
2 ☐ Mycket mindre än tidigare
3 ☐ Knappast alls

13. Jag får plötsliga panikkänslor

3 ☐ Väldigt ofta
2 ☐ Ganska ofta
1 ☐ Sällan
0 ☐ Aldrig

14. Jag kan uppskatta en god bok, ett TV- eller radioprogram

0 ☐ Ofta
1 ☐ Ibland
2 ☐ Sällan
3 ☐ Mycket sällan

E. Frågor om hörsel, tinnitus, buller och hög musik

1. När du lyssnat på starka ljud eller hög musik, har du då märkt att du hör sämre efteråt?
☐ Aldrig ☐ Ja, en gång ☐ Ibland ☐ Ofta

2. Efter att du lyssnat på starka ljud eller hög musik, har du då märkt att det ringer, piper eller tjuter i öronen fastän ljudet/musiken har stängts av?
☐ Nej ☐ Ja

3. Kan ringningen, pipet eller tjutet, finnas kvar längre än ett dygn?
☐ Nej ☐ Ja

4. Har du märkt av att det kan ringa, pipa eller tjuta i öronen även om du inte lyssnat på starka ljud eller hög musik?
☐ Nej ☐ Ja

Om du svarat NEJ på frågorna 2, 3 och 4 kan du hoppa över fråga 5 t o m 8.

5. Hur ofta märker du att det ringer, piper eller tjuter i öronen?
☐ Sällan ☐ Ofta ☐ Alltid

6. Tycker du att det är besvärande när det ringer, piper eller tjuter i öronen?
☐ Nej ☐ Ibland ☐ Ofta ☐ Alltid

7. Hur började det när det började ringa, pipa eller tjuta i öronen?
☐ Kom plötsligt ☐ Kom smygande

8. Hur länge har du märkt att det ringer, piper och tjuter i öronen?
..…..veckor …….mån

Kryssa för det som stämmer bäst för dig

	Aldrig	Ibland	Ofta	Mkt ofta
Hur ofta använder du hörselskydd vid ”bullriga” sysselsättningar	☐	☐	☐	☐
Hur ofta lyssnar du på musik med mp3,ipod,bärbar CD eller dylikt?	☐	☐	☐	☐
Hur ofta pratar du i mobiltelefon?	☐	☐	☐	☐
Hur ofta använder du ”handsfree” när du pratar i mobilitelefon?	☐	☐	☐	☐

Kryssa för hur ofta du ägnar dig åt nedanstående skriviteter:

	Aldrig	Sällan	6-12 ggr/år	Varannan vecka	Flera ggr /vecka
Går på konsert	☐	☐	☐	☐	☐
Går på disco	☐	☐	☐	☐	☐
Går på bio	☐	☐	☐	☐	☐
Spelar eget musikinstrument	☐	☐	☐	☐	☐
Playstation/dator med hörlurar	☐	☐	☐	☐	☐
Tränar skytte/smäller smällare	☐	☐	☐	☐	☐