Hearing in early old age

Current perspectives

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ABSTRACT

Age related hearing loss is a public health concern that restricts the possibilities of older persons to lead a healthy, social and active life. The present thesis aims to provide contemporary perspectives on age related hearing function and hearing loss in the general population, in early old age. The thesis is based on data from the Gothenburg H70 Birth Cohort Study, a prospective epidemiological investigation of ageing, in which representative segments of the older population are examined with a wide-ranging test protocol covering multiple aspects of health. The four papers, on which the thesis is built, examine various hearing parameters in a recent birth cohort of 70-year-olds, born in 1944. The results from **Paper I** demonstrated that the prevalence of hearing loss has decreased significantly among 70-year-olds in Gothenburg, across a time period of nearly five decades (1971-2014). Reductions in exposure to occupational noise is probably one of the most important factors explaining the findings. In **Paper II,** auditory function was investigated in detail based on a comprehensive audiological test battery performed in a subsample. The results demonstrated that cochlear pathology is the predominant cause of hearing loss at age 70, but that early neural ageing is present, leading to poorer speech recognition in some individuals. In **Paper III,** a comparison was made between automated and conventional pure-tone audiometry in 70-year olds and 85-year olds (born in 1930). The results indicated that automated pure-tone audiometry is a valid test method in the majority of older persons, and that age, hearing loss and cognitive status did not affect the outcomes. Finally, in **Paper IV** it was demonstrated that poorer hearing is associated with poorer cognitive function, but only when considering pure-tone and speech measures, and not self-report. Hearing aid use was associated with better cognitive scores. In conclusion, hearing loss - of various underlying pathology - is a prevalent condition in early old age that is associated with poorer cognition. Given the rapid ageing of populations in Sweden, and worldwide, efforts of prevention, early identification and rehabilitation of age related hearing loss should be considered a public health priority.

Keywords: Age related hearing loss, presbycusis, prevalence, cross-sectional, secular trends, cognitive function

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SAMMANFATTNING PÅ SVENSKA

Åldersrelaterad hörselnedsättning är ett angeläget folkhälsoproblem som begränsar äldres möjligheter till ett hälsosamt, socialt och aktivt liv. I takt med att andelen äldre i befolkningen ökar alltmer, är det av yttersta vikt med studier inom ämnet. Målet med följande avhandling är att presentera aktuella perspektiv på åldersrelaterad hörselfunktion och hörselnedsättning hos den ”yngre” äldre befolkningen. Avhandlingen är baserad på data som samlats in inom ramen för den storskaliga populationsstudien H70, vilken undersöker en rad olika hälsofaktorer hos representativa urval av den äldre befolkningen i Göteborg. De fyra delarbetena som utgör avhandlingen beskriver hörseln ur olika perspektiv hos en ny födelsekohort bestående av 70-åringar födda 1944. Resultaten från **delarbete I** visade att förekomsten av hörselnedsättningen har minskat signifikant bland 70-åringar i Göteborg, under en tidsperiod som sträcker sig över nära fem decennier (1971-2014). Minskad exponering för skadligt buller på arbetsplatsen är en trolig förklaring till fynden. I **delarbete II** studerades den auditiva funktionen i detalj baserat på ett mer omfattande testbatteri, hos ett mindre urval av födelsekohorten. Resultaten visade att cochleär patologi utgör den huvudsakliga orsaken till åldersrelaterad hörselnedsättning vid 70-års ålder. Vidare sågs även tidiga tecken på neuralt åldrande, vilket ledde till försämrad taluppfattning hos vissa individer. I **delarbete III** genomfördes en jämförelse av hörtrösklar uppmätta med antingen automatiserad eller konventionell tonaudiometri. I denna studie inkluderades även ett urval av 85-åringar födda 1930 som genomgått motsvarande undersökning. Resultaten antydde att det automatiserade testet hade god mätnoggrannhet för majoriteten av äldre, samt att ålder, grad av hörselnedsättning och kognitiv status inte påverkade fynden. Slutligen, i **delarbete IV** visades att försämrad hörsel är associerat med sämre kognitiv funktion. Dessa resultat erhölls dock endast då ton- och talaudiometri beaktades och inte för självrapporterade data. Vidare sågs bättre kognitiv funktion hos deltagare som uppgav att de använde hörapparat. Sammanfattningsvis visade avhandlingen att hörselnedsättning –av varierande orsaksfaktorer – är ett vanligt förekommande tillstånd i tidig hög ålder som är förenat med sämre kognitiv funktion. Med hänsyn till att antalet och andelen äldre ökar i befolkningen, såväl i Sverige som världen över, bör åtgärder som förebygger, upptäcker och behandlar åldersrelaterad hörselnedsättning prioriteras i folkhälsoarbetet.

LIST OF PAPERS

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

I. Hoff, M., Tengstrand, T., Sadeghi, A., Skoog, I., & Rosenhall, U. (2018). Improved hearing in Swedish 70-year olds-a cohort comparison over more than four decades (1971-2014). Age and ageing, 47(3), 437–444. https://doi.org/10.1093/ageing/afy002

II. Hoff, M., Tengstrand, T., Sadeghi, A., Skoog, I. & Rosenhall, U. (2020). Auditory function and prevalence of specific ear and hearing related pathologies in the general population at age 70. International Journal of Audiology, 59(9), 682-693. https://doi.org/10.1080/14992027.2020.1731766

III. Hoff, M., Göthberg, H., Tengstrand, T., Rosenhall, U., Skoog, I., & Sadeghi, A., (2020). Accuracy of Automated Pure-tone Audiometry in Population-based Samples of Old Persons.
Under review in the International Journal of Audiology.

IV. Hoff, M., Skoog, J., Hadarsson Bodin, T., Tengstrand, T., Rosenhall, U., Skoog, I. & Sadeghi, A. Hearing loss and cognition in early old age – comparing objective and subjective hearing measures.
Manuscript

CONTENT

ABBREVIATIONS

β	Beta (standardized linear regression coefficient)
μPa	Micropascal
μV	Microvolt
ABR	Auditory Brainstem Response
CANS	Central Auditory Nervous System
CAPD	Central Auditory Processing Disorder
CI	Confidence Interval
CT	Computed Tomography
daPa	Decapascal
dB HL	Decibel hearing level
dB nHL	dB HL calculated for a specific click stimulus used to elicit ABR-responses
dB SPL	Decibel Sound Pressure Level
DPOAE	Distortion Product Otoacoustic Emission
f	Frequency
GBD	Global Burden of Disease
ICF	International Classification of Functioning, Disability and Health
IPL	Interpeak Latency
kHz	Kilohertz
L	Level

Mmho	Millimho (1 Mho is the inverse of 1 Ohm)
MMSE	Mini Mental State Examination
MoCa	Montreal Cognitive Assessment
MRI	Magnetic Resonance Imaging
Ms	Millisecond
p	Probability that an observed effect has occurred purely by chance (in statistics)
PTA	Pure-tone Average
PTA4	Pure-tone average of thresholds at 0.5, 1, 2 and 4 kHz
SII	Speech Intelligibility Index
SNHL	Sensorineural Hearing Loss
SNR	Signal-to-Noise Ratio
SPRIN	Speech Recognition in Noise
WHO	World Health Organization
WRS-N	Word Recognition Score in Noise

DEFINITIONS IN SHORT

Hearing loss	Loss of hearing sensitivity in comparison with average sensitivity in a reference group of otologically normal young persons.
Hearing Impairment	A wider term which encompasses impairment or disorder anywhere in the auditory system that alters the perception and interpretation of sounds.
Age related hearing loss	Gradual onset hearing loss of various aetiology that occurs with rising age. The cumulative effect of pure ageing-processes and decay due to environmental factors.
Cohort	A group of persons with a defined set of characteristics.
Epidemiology	A branch within Medicine that aims at identifying risk factors and protective factors that determine health outcomes in the general population (McNeil, 1996)

1 INTRODUCTION

The world's older population is growing at an unprecedented rate, due to significant advancements in medical care, public health, and general living standards. Population ageing is a global phenomenon that affects nearly every country of the world, and the trend is projected to continue for many decades to come. As a consequence, the number of persons affected by chronic disease and age-related disabilities will rise significantly, bringing challenges for social and health care services (United Nations & Affairs, 2019). Age related hearing loss (ARHL) is one of the most prevalent health conditions among old persons. It has a major impact on the physical and mental health, and quality of life of those affected and their families, and has been linked to an increased risk of all-cause dementia. Furthermore, in the latest update of the Global Burden of Disease Study, *GBD 2019* (Vos et al., 2020), ARHL was ranked among the top ten leading causes of global disease burden for persons aged 50 years and above, confirming that ARHL is a major public health concern, and an important area of research.

1.1 OVERVIEW

The present thesis will focus on epidemiological aspects of ARHL in early old age in a contemporary birth cohort of 70-year old persons from Gothenburg, Sweden. Seventy is an age marked by many positive features, such as still being in relatively good health, the freedom of not having to work, the lack of child-rearing responsibilities etc. At the same time, it is a period where many age effects start to emerge, affecting individuals in different ways and at different rates. ARHL, which is already manifest in septuagenarians, could stand in the way of healthy ageing, especially if left unaddressed. The ambition of the present thesis is to contribute knowledge that can promote good hearing health, by studying ARHL through an epidemiological framework.

The first chapter of the introduction provides a brief overview of the field of ageing research, including definitions, theories and demographic aspects. The second chapter describes the hearing sense, by describing its anatomy and physiology, methods for measuring hearing function, and classifications of hearing loss. In chapter 3, the literature regarding ARHL is reviewed with a focus on pathophysiological mechanisms, prevalence, aetiology and risk factors, consequences, and rehabilitation. In the last chapter, a brief overview of cognitive functions and their relation to auditory processing and hearing loss is covered.

1.2 AGEING

1.2.1 AGEING THEORIES

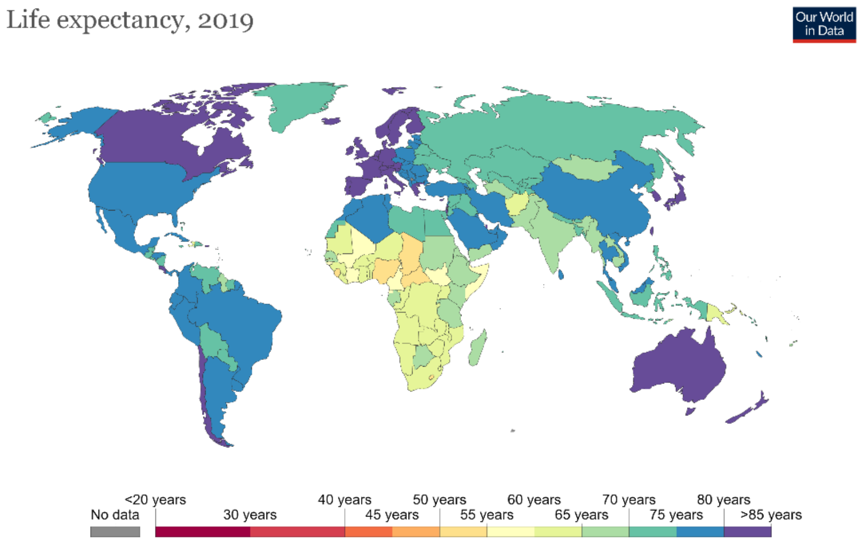
In a wide sense, ageing can be described as a gradual process of decay, which continues throughout life until death. The process of ageing may be viewed from multiple perspectives, why distinctions often are made between for instance chronological ageing (the passing of time), biological ageing (the degeneration of cells and molecules) and social ageing (altering social roles in different stages of life) (Balcombe & Sinclair, 2001).

A natural consequence of ageing is the increased prevalence of chronic diseases and disabilities. Theoretically, these constitute two distinct change processes. Hayflick (2000), a pioneer within the field of ageing science, states that ageing ought to be distinguished from disease owing to the fact that these two concepts differ in a number of respects. Importantly, Hayflick argues, ageing occurs in virtually all species and in all members of a species. Furthermore, unlike disease, ageing is irreversible and invariably ends with death. The scientific study of biological ageing (Biogerontology) can thus be separated from the study of age-related diseases (Geriatric medicine) – at least in theory. In practice, it is complex or even impossible to separate what constitutes *pure* ageing versus disease, since these processes are intertwined in several ways. Therefore, it may be an advantage of viewing ageing and disease as a common process (Bulterijs et al., 2015). In recent times, a new interdisciplinary scientific field has emerged, which combines epidemiological and experimental evidence to understand the interaction between ageing and chronic age-related diseases, known as *Geroscience* (Franceschi et al., 2018).

Moreover, the increasing possibilities of old persons to retain good health and active lifestyles, has led to an interest in the concept of *successful ageing*. Successful ageing was described by Rowe and Kahn (1987) as consisting of three components: absence of disease and disability (and associated risk factors); maintaining physical and mental functioning; and active engagement with life.

1.2.2 DEMOGRAPHICS

One of the triumphs of the previous century is the global increase in life expectancy. In fact, the maximum life-span has been demonstrated to increase by a whole year for every four years that have passed since the mid-1800s (Oeppen & Vaupel, 2002). In the countries with the highest life expectancy of the world, such as Sweden, Japan, Singapore and France, average life expectancy at birth is in the excess of 80 years in men and 85 years in women (Roser, 2013). Figure 1 provides an overview of life expectancies at birth in different regions of the world, showing that this figure varies significantly between countries. Historically, improvements in life expectancy were mainly caused by reductions in mortality among infants and children, but in the last 50 years the main driving force has been falling mortality rates among older persons, especially in high income countries (Mathers et al., 2015). Factors explaining the continuously improving survival rates include improvements in health care, economy and nutrition.


Life expectancy, 2019

Source: Riley (2005), Clio Infra (2015), and UN Population Division (2019) OurWorldInData.org/life-expectancy • CC BY
Note: Shown is period life expectancy at birth, the average number of years a newborn would live if the pattern of mortality in the given year were to stay the same throughout its life.

Figure 1. *Life expectancy at birth in different parts of the world. Sweden is among the countries with the highest life expectancy. From OurWorldInData.org [retrieved from https://ourworldindata.org/life-expectancy, October 2020].*

An inevitable consequence of people living longer is the increase in the number of old persons and the share of old persons in the population. According to projections carried out by the United Nations (2019), 16% of the world's population will consist of persons aged >65 years in the year 2050, up from 9% in 2019. In Europe and Northern America the proportion of persons aged >65 years is estimated to reach 25% in 2050. Whilst the older segments of the population are expanding, fertility rates have fallen –especially in high-income countries (Ritchie & Roser, 2019). This means that the ratio between old persons and persons of working age increases. This measure is referred to as the *Old age-dependency-ratio*, and is frequently used to assess the financial impact of population ageing and the implications for healthcare services. For example, in Sweden there is currently around 25 retirees (aged 65 and above) to every 100 persons of working age, and this figure is projected to increase (Muszyńska & Rau, 2012).

1.2.3 EPIDEMIOLOGY

Although ageing is universal, it is by no means uniform. Considerable differences in health status or functional level may be found between populations or between individuals of the same age within a population, due to varying exposure to risks throughout the lifespan. In addition to genetic variation, health in old age is determined by environmental and socioeconomic factors, such as education, occupation, income and social support systems (Lu et al., 2019). Figure 1 on the previous page, indirectly illustrates these inequalities in a global perspective, since life expectancy is a good indicator of population health (Stiefel et al., 2010). In epidemiological research, cross-sectional and longitudinal analysis methods are used to study risk factors and protective factors that determine health outcomes in populations (McNeil, 1996). The methodology involves examining cohorts of the population that are followed up longitudinally, which allows for researchers to distinguish between effects caused by *cohort*, *age* and *period*. Cohort effects describe how being born a specific year impacts on health. Age effects, on the other hand, are considered present when a health variable consistently changes with increasing age, regardless of what cohort is being studied. Finally, period effects are age related changes that occur uniformly in all of the population at a given time, regardless of year of birth (Blanchard et al., 1977). Moreover, the study of secular trends – i.e. changes in a health variable that occurs in the population over a long period of time – is made possible when data is available for several birth cohorts sampled in a similar way.

1.3 HEARING

Hearing is described as *“sensory functions relating to sensing the presence of sounds and discriminating the location, pitch, loudness and quality of sound”* (Granberg et al., 2014). It is one of the five traditional senses, enabling us to receive and interpret information about the surrounding environment. Perhaps most importantly, hearing forms the basis of spoken language, which is central to human interactions and social engagement. Further, hearing is important for spatial orientation, and as a mechanism for alerting us to danger. Another important aspect is the ability to hear music, a major source of enjoyment for many that has played an important role in human history, culturally and therapeutically. It is therefore not hard to imagine that the loss of hearing function has a significant impact in many aspects of life (Smith, 2007).

Sounds are small fluctuations in atmospheric pressure, which can be picked up by the ear and converted into nerve impulses that are interpreted by the brain. The most important attributes used to describe sounds are *frequency* and *intensity*. The frequency of a sound refers to the rate of vibration, measured in Hertz (Hz), whereas the intensity of the sound is the amplitude of the vibration, measured in decibels (dB). The decibel unit is logarithmic, meaning that it always relates to a reference value. When measuring a sound pressure level (dB SPL), the reference level is 20 µPa (micropascal), corresponding to the threshold of human hearing. A young healthy ear is able to perceive sounds of a remarkably wide range of frequencies, ranging from 20 Hz up to 20,000 Hz. In terms of sound intensities, the possible range covers approximately 120 dB.

1.3.1 ANATOMY AND PHYSIOLOGY

The auditory system consists of three functionally distinct systems, which can be described as the conductive system, the sensorineural system and the central auditory nervous system, CANS (Gelfand, 2009). The *conductive* system, comprising the external and middle ear, serves to receive, amplify and transfer mechanical vibrations onwards in the auditory system. The *sensorineural* system is made up of the inner ear and the auditory nerve, whose main functions are to convert sounds to sensory impulses, allowing for transmission to and processing by the *CANS*, where auditory perception occurs.

An anatomical overview of the auditory pathways is illustrated in Figure 2. The *peripheral* auditory pathway stretches from the external ear up to – and inclusive of – the auditory nerve, while the remainder (from the cochlear nuclei onwards) is labelled the *central* auditory pathways. Sound waves, initially received by the funnel shaped pinna, travel onwards through the external auditory meatus (ear canal), which ends with the tympanic membrane (eardrum). The oscillating sound wave is further transmitted through the three ossicles in the middle ear, the innermost being attached to a further membrane (the oval window). This sets the fluid (endolymph) within the spiral-shaped inner ear (cochlea) in motion, causing sensory cells along the basilar membrane within the organ of Corti to bend. As the cells deflect, an electrochemical response lead to the excitation of associated auditory neurons.

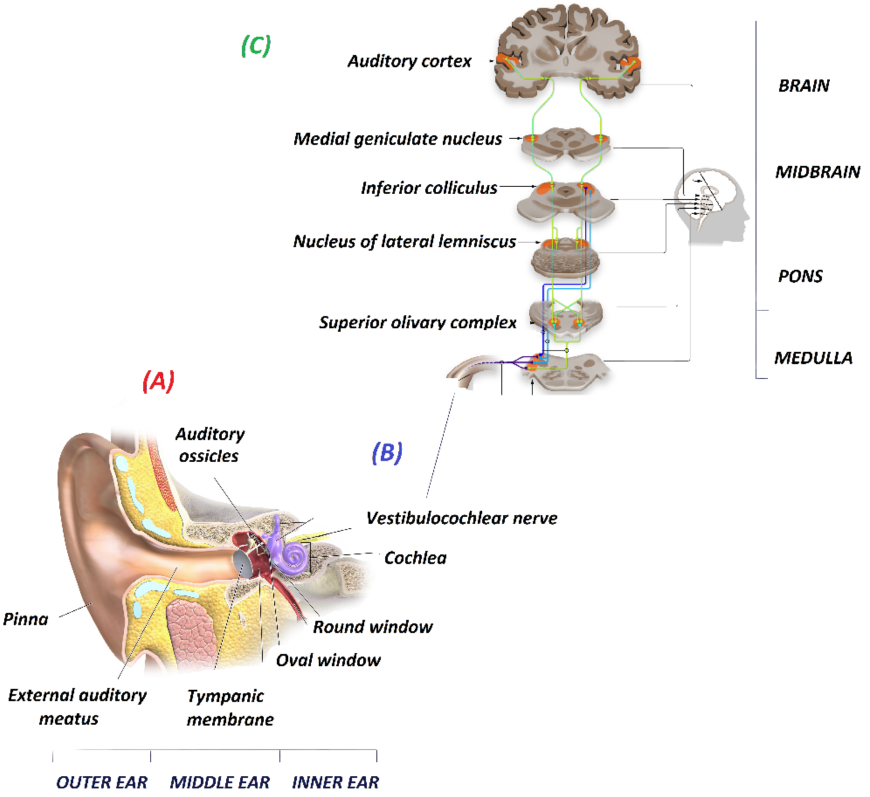


Figure 2. *Anatomical overview of the ear (A), auditory part of the vestibulocochlear nerve (B) and the central auditory nervous system (C).*

Adapted from: "Blausen_0328_EarAnatomy" by B. Blaus, 2014, DOI:10.15347/wjm/2014.010. Licensed under CC BY 3.0 (image of ear), and from: "Human Auditory Pathway" by E. Cooper, 2016, https://osf.io/u2gxc/. Licensed under CC BY 4.0, (Image of brain).

There are two types of sensory cells, outer and inner hair cells. The hair cells connect to spiral ganglion neurons, which form the auditory part of the vestibulocochlear nerve (VIIIth cranial nerve). *Afferent* nerve fibres, i.e. neurons that conduct nerve impulses to the CANS, innervate mainly the inner hair cells (95%), and to some extent, the outer hair cells (5%) (Gelfand, 2009). A smaller population of *efferent* neurons (outwards leading nerve fibres) also innervate the cochlea – predominantly the outer hair cells – relaying information from the Superior Olivary Complex to the cochlea. The efferent auditory pathways enable fine-tuning of the cochlear response to sounds, known as the cochlear amplifier (Ashmore et al., 2010).

In the CANS, information from the auditory nerve is first received by neurons in the cochlear nuclei. Thereafter, signals continue through various pathways along different processing stations in the lower brainstem, midbrain, thalamus and temporal lobes. These include the inferior colliculi, superior olivary complexes, geniculate nuclei and the auditory cortex. Ascending auditory pathways reach both the ipsilateral and contralateral hemispheres of the brain (Møller, 2012). The processing of auditory stimuli that occurs within the central auditory neural system enables sound localization and lateralization, auditory discrimination, auditory pattern recognition, temporal processing and hearing in the presence of competing acoustic signals (Chermak et al., 1999)

1.3.2 HEARING MEASUREMENTS

It may be rather complex to measure or quantify hearing, which ultimately constitutes a subjective experience that cannot be measured directly – in contrast to physical attributes, such as blood pressure, or body temperature. Hearing measurements are usually divided into *behavioural* and *physiological* methods. Behavioural, also referred to as psychoacoustic, test methods involve presenting various acoustic stimuli and asking for a response of some sort. Thus, behavioural tests rely on active participation from the patients (Gelfand, 2009). Physiological methods on the other hand, register how the ear or brain responds to acoustic stimuli. Based on the results, assumptions can be made about how and if someone hears, but not with absolute certainty.

A further method of assessing hearing is by using self-report measures. Standardized hearing questionnaires are usually concerned with the perceived ability to hear in pre-specified situations. Since self-report measures reflect the subjective experience of the person with hearing loss, several non-auditory factors may influence the outcome, for instance the physical and social environment, and personal factors like expectations and personality (Hickson & Scarinci, 2007).

Each of the methodological categories described above have pitfalls and limitations, and which measure has the highest validity or reliability depends on the testing context. Combing the results of several tests likely produces a more accurate and complete picture.

Behavioural measures

Pure-tone audiometry

Pure-tone audiometry is a psychoacoustic measurement of peripheral hearing function, which is gold standard when testing hearing. The test involves determining *hearing thresholds*, i.e. the lowest audible levels, for pure tones of various frequencies. Hearing thresholds are measured in dB Hearing Level (HL), a dB scale where reference zero has been set to reflect average hearing thresholds in a healthy reference population. The procedure involves presenting tonal stimuli, generated by an audiometer and transferred to the ear via transducers, to a patient seated in a soundproofed test booth. The patient indicates whether the tone was heard by pressing a response button, and the results are plotted in an audiogram. The validity and reliability of pure-tone audiometry relies on a number of factors, including the ambient noise levels in the test environment; calibration of the equipment; the instructions given to the patient; the physiological and cognitive fitness of the patient, etc. To minimize sources of error, and improve comparability, international standards have been developed (International Organization for Standardization [ISO], 2010).

Conventionally, pure-tone audiometry is conducted by a skilled operator (usually an audiologist) who monitors the patient throughout testing, ensuring compliance with the method. However, automated pure-tone audiometry is also used in a number of settings, having been available since the late 1940s (Békésy, 1947). Margolis and Morgan (2008) proposed that the automation of pure-tone audiometry might increase the number of hearing impaired patients that can be served and reallocate time for audiologist that can be used for other more demanding clinical tasks. Automated pure-tone audiometry is currently used as part of telehealth (Swanepoel et al., 2010) and when screening for hearing loss (e.g. in population-based studies). Screening audiometry entails testing hearing thresholds with a simplified method that leads to an outcome of pass or refer. The pass criterion for pure-tone audiometry is usually set at 20 dB HL.

Pure tone audiometry is, by far, the most common method to measure hearing. However, an important limitation of the test is that it measures hearing thresholds, i.e. sounds that are barely audible, whereas the most important applications of hearing are suprathreshold, e.g. speech perception and music listening. Accordingly, pure-tone audiometry does not directly assess some of the most important auditory functions. For this reason, other tests are necessary when evaluating the communicative capacity of the auditory system. Additionally, pure-tone audiometry only assesses peripheral hearing function, while speech comprehension relies on neural and central auditory processing abilities as well.

Speech audiometry

Speech audiometry is an umbrella term for a wide range of psychoacoustic tests that use speech signals as stimuli. Speech audiometry provides information about the ability of the auditory system to comprehend complex auditory information. Speech signals are acoustically intricate and temporally dynamic, and the process of speech perception is complex – involving both the peripheral and the central auditory pathways. Additionally, understanding speech relies on more than just auditory function, such as linguistic and cognitive abilities (Gordon-Salant & Fitzgibbons, 1993). Speech tests may be performed using syllables, words or sentences, with or without simultaneous noise. Depending on the specific stimuli and tasks, these tests may be useful in distinguishing between peripheral and central lesions of hearing impairment. Some common tests include the speech reception threshold (SRT), which measures the lowest level at which speech is audible, and speech (or word) recognition in quiet or noise (Gelfand, 2009). Furthermore, tests using degraded speech signals or dichotic listening tasks are used to assess central auditory processing abilities.

The speech intelligibility index (SII), initially known as the articulation index, is a mathematical algorithm by which predictions can be made of the intelligibility of a speech material, since the SII correlates highly with actual speech performance (ANSI, 1997). The SII takes both the audibility of the speech signal (affected by the patient’s hearing thresholds) and the importance of different frequency bands (tied to specific sets of speech materials) into account. (Magnusson, 1996a) developed an SII based algorithm for the Swedish PB (phonemically balanced) lists, which are used routinely in clinical evaluations of hearing loss in Sweden. To account for the effects of cochlear dysfunction Magnusson included a desensitization factor – introduced by Pavlovic (1987) – in the algorithm, in order to improve predictions for persons with sensorineural hearing loss. Additionally, an age factor was added to account for decreased speech performance due to age related factors (SII_{DA}). In clinical practice, when a measured speech recognition is less than predicted by the SII_{DA}, neural or cognitive pathology may be suspected.

Physiological measures

Physiological measures of hearing function and related properties offer a means of objectively assessing auditory ability. These are particularly useful in patients unable to participate in behavioural testing, e.g. in small children, or persons with dementia, or to corroborate uncertain findings. Furthermore, physiological tests provide information about the integrity of bodily structures and functions pertinent to hearing, which aids in the diagnosis of hearing impairments (Hall & Swanepoel, 2009). There is a wealth of different recording parameters that may be used with physiological methods, many of which may be specific to the manufacturers. Therefore, it has been difficult to generate normative materials that apply in general terms (Hall, 2000).

Otacoustic Emissions

Registration and evaluation of otoacoustic emissions (OAEs) are used to assess the functional ability of the cochlea, and more specifically the integrity of the outer hair cells. OAEs are minute sounds produced by the motion of the hair cells within the cochlea in response to sound, which can be recorded with a probe microphone inserted in the ear canal. OAEs were first described in human ears in the 1970s by Kemp (1980), and has since been developed into a test used for hearing screening in new born babies, for monitoring the effect of ototoxic agents and for identifying specific hearing loss pathologies. It also constitutes a non-invasive method for research on cochlear function (Kemp, 2002). A healthy young cochlea displays a strong OAE response, whereas emissions are diminished or absent when outer hair cells are impaired, for instance by acoustic trauma or ageing (Torre et al., 2003; Uchida et al., 2006). Two main types of OAEs exist, evoked using different stimuli and providing slightly different information. Transient evoked OAEs (TEOAEs) are elicited using a click stimulus, whereas Distortion Product OAEs (DPOAEs) are evoked in response to two pure tones of different frequencies (f1 and f2) and levels (L1 and L2) (Hall, 2000).

Auditory-evoked Brainstem Responses

The auditory-evoked brainstem response (ABR) is another frequently used physiological measurement, which is used to identify nerve and brainstem pathologies, or to estimate hearing thresholds in subjects unable to perform behavioural hearing tests (Prosser & Arslan, 1987). It is a type of electroencephalography, where electrical activity in the brain in response to the onset of auditory stimuli is recorded through electrodes placed on the head. The recording allows for the identification of up to seven characteristic waves (Jewett waves I-VII), of which the latencies and amplitudes may be analysed and interpreted. The information obtained from ABRs can vary depending on the choice of stimuli used to evoke the respones, e.g. chirps, clicks or speech. Choice of recording parameters, such as click rate, can also influence the outcome.

ABRs have been studied extensively in humans and animals, and the results have demonstrated effects of various factors, such as sex, peripheral hearing loss and head size (Jerger & Hall, 1980; Konrad-Martin et al., 2012). In subjects with presbycusis, latencies are longer than in control groups consisting of younger subjects (Rosenhall et al., 1986).

1.3.3 HEARING LOSS

Hearing loss can be classified in a wide variety of ways, usually dependent on the extent of the hearing loss (degree or grade) or the type of hearing loss, based on site of lesion or pathology. Further characterizations may be based on whether the hearing loss is acquired or congenital, affects one ear (unilateral), both ears (bilateral) or both ears to different extent (asymmetrical), or on which frequencies are involved (audiogram configuration). Moreover, in relation to the need for rehabilitative intervention, the degree of functional impairment and the social and emotional consequences may be of interest. Unfortunately, there is no consensus on which definitions to use (Clark, 1981).

Degree of hearing loss

The degree of hearing loss is usually based on the average hearing level – measured with pure-tone audiometry – in one or both ears. As an overall measure, the average pure-tone threshold of the speech frequencies, i.e. 0.5, 1, 2 and 4 kHz (PTA4), is frequently employed. Furthermore, distinctions are sometimes made between the higher and lower frequencies, PTA3 (average of 0.5, 1 and 2 kHz) and PTA-Hi (average of 3, 4 and 6 kHz), to better reflect the wide variety of audiogram configurations that exist. The WHO defines a hearing loss as a PTA4 > 25 dB HL in the better ear (Table 1). Moreover, hearing losses exceeding 40 dB HL in adults are labelled as “disabling”. The Global Burden of Disease (GBD) Expert Hearing Group criticized the current WHO definition, for a number of reasons (Olusanya et al., 2019). Most importantly, it excludes persons with unilateral hearing loss, even though unilateral hearing loss can impact negatively in similar ways as bilateral hearing loss can. Further, the authors argue that the cut-offs for different hearing loss grades are unevenly distributed in a way not supported by any theoretical underpinning. Therefore, they proposed a new classification, which is used in the GBD studies (Murray et al., 2015). In their classification, a cut-off of ≥35 dB HL is considered disabling. Moreover, with the event of the WHO's International Classification of Functioning, Disability and Health (ICF), the level of functional impairment associated with hearing loss is viewed in the context of the social and physical environment as well as individual factors. It is now widely recognized that pure-tone averages alone are not sufficient to predict the activity limitation and participation restriction imposed by hearing loss.

Table 1. *Grades of hearing impairment according to the WHO*

Grade of impairment	PTA4 (dB HL)	Performance
0: None	≤ 25	Able to hear whispers.
1: Slight	26-40	Able to hear and repeat words spoken in normal voice at 1m.
2: Moderate	41-60	Able to hear and repeat words using raised voice at 1 m.
3: Severe	61-80	Able to hear some words when shouted into better ear.
4: Profound	> 80	Unable to hear and understand even a shouted voice

Adapted from: World Health Organization 1991. Report of the Informal Working Group On Prevention Of Deafness And Hearing Impairment Programme Planning. Geneva, 1991; PTA4=Pure-tone average across 0.5, 1, 2 and 4 kHz, dB HL: Decibel hearing level

Types of hearing loss

Depending on the site of lesion, hearing losses are typically classified as either conductive, mixed or sensorineural.

Conductive hearing losses arise as a result of malfunction in the external or middle ear, for example through pathological changes affecting the external ear canal or the tympanic membrane, sclerosis or disruption of the ossicular chain, e.g. affecting the stapes (otosclerosis). Aetiological factors causing these types of pathological changes include infection (otitis), head trauma or genetics (Rudin et al., 1983). Depending on which structure is affected, or the extent of impairment, the transmission of acoustic energy to the inner ear is partially or completely compromised, producing an attenuation of the acoustic signal of up to 60 dB. Conductive hearing losses are characterized by poor air conduction hearing, compared with hearing by bone conduction, manifesting as air-bone-gaps in the pure-tone audiogram. Conductive pathology that coincides with sensorineural pathology is called *mixed* hearing loss.

Sensorineural hearing loss is an umbrella term for hearing losses caused by pathologies in the cochlea and/or the auditory nerve, since these types cannot be separated based on pure-tone audiometry alone. Damage of outer hair cells within the cochlea is the most frequent cause, producing a mild to moderate hearing loss. Inner hair cells may also be damaged, especially in severe hearing loss (Gelfand, 2009). Neural hearing loss (also called retrocochlear) on the other hand, arises as a result of lesions in the auditory nerve, for instance acoustic neuroma (benign tumours). Moreover, degeneration of auditory nerve fibres may also occur, either as a secondary effect of inner hair cell loss, or directly through damage in the synapses from the inner hair cells to the nerve (synaptopathy). This condition, referred to as *auditory neuropathy*, may lead to a form of hidden hearing loss, which is not detected with pure-tone audiometry or OAEs, but involves significant difficulties with speech perception and pathological ABRs (Eggermont, 2017). However, according to Hind et al. (2011), the main cause of hidden hearing losses, i.e. impaired speech recognition in spite of normal pure-tone thresholds, is likely *central auditory processing disorder* (CAPD). CAPD is a group of hearing disorders that involve deficits in the perceptual processing of auditory information in the CANS (Chermak et al., 1999).

Tinnitus

Another frequently reported hearing complaint that often accompanies hearing loss, but which may also occur alone, is tinnitus. Tinnitus is defined as the conscious expression of sound in the absence of an acoustical source (McFadden, 1982). Tinnitus can manifest as a buzzing noise, a whistling or a humming, amongst many other things. It may be perceived in one or both ears, or centrally in the head, and can be a major source of discomfort and disability. Tinnitus is a symptom, usually caused by underlying pathology or disorder anywhere in the auditory pathways. Hearing loss, whether conductive or sensorineural, is an important cause of tinnitus (Møller, 2011). Therefore, old persons are particularly at risk for developing tinnitus, with studies indicating that roughly 20-30% of older persons have tinnitus of various degree (Rosenhall & Karlsson, 1991; Shargorodsky et al., 2010). Noise exposure is a further important risk factor of tinnitus.

1.4 AGE RELATED HEARING LOSS

Age related hearing loss (ARHL), often referred to as *presbycusis,* is defined as a multifactorial, slowly progressing decline in auditory function, which occurs with advancing age (Gates & Mills, 2005). It has been described as arising through a genetically driven process where multiple intrinsic and extrinsic factors impact on the ear cumulatively over the course of a lifetime (Yamasoba et al., 2013). This degenerative development ultimately results in the damage or loss of cells essential to auditory perception. Hearing thresholds start deteriorating already in the 5th decade of life, progressing slowly up to the age of 70, and thereafter at an accelerated rate (ISO, 2017). The initial decline in hearing sensitivity affects the highest frequencies, which is why good low and mid-frequency (0.25-2 kHz) hearing in combination with poorer higher frequency (3-8 kHz) hearing characterizes ARHL in early old age.

1.4.1 HISTORY

The term presbycusis (from Greek, *presby*- meaning ‘old’, *akousis* meaning ‘hearing’) is generally credited to the Dutch scientist, Hendrik Zwaardemaker, who first used it in the late 19th century (Gacek & Schuknecht, 1969). Early work on presbycusis involved describing age related morphologic changes of the inner ear and the cochlear nuclei, through histologic studies on temporal bones and brains (Bunch, 1929; Crowe et al., 1934). It was not until the 1940s, however, that the scientific field of Audiology emerged, in response to soldiers returning from the World War II with noise injuries. Research at the time was concerned with separating noise induced hearing loss (then labelled nosocusis) from hearing loss due to pure ageing (presbycusis) and other causes (sociocusis). In addition to experimental studies in humans and animals, epidemiological methods have been employed for this purpose – in which screened (unexposed) populations may be compared to unscreened populations.

Some of the earliest epidemiological studies describing hearing as a function of age were by Corso, 1959; Glorig & Nixon, 1962; and Hinchcliffe, 1959. Since then, multiple large-scale population-based investigations of age related hearing loss and its determinants have been conducted, such as studies emanating from the Swedish *Gothenburg H70 Birth Cohort Studies* (Jonsson & Rosenhall, 1998; Jonsson et al., 1998; Pedersen et al., 1989; Rosenhall et al., 1990), which the present thesis is based upon. Furthermore, ARHL in the population has been studied in other Nordic Countries (Parving et al., 1983), in the United Kingdom (Davis, 1989), the U.S (Cruickshanks et al., 1998;

Gates et al., 1990; Moscicki et al., 1985) and Australia (Sindhusake et al., 2001). Reviewing the evidence, Rosenhall (2015) noted a reasonably high agreement between studies from various parts of the world regarding age related decline of hearing thresholds, suggesting that biological ageing is important. However, most of the studied populations were probably exposed to similar risks imposed by the environment, such as noise exposure.

Some smaller epidemiological studies of geographically or socially isolated populations have been conducted, aiming to unravel how ageing alone effects hearing ability, i.e. in the absence of noise exposure. Rosen et al. (1962), for example, studied a remote, isolated population in Sudan and found significantly better hearing compared to an age matched reference group from the US, indicating that environment does play an important part in presbycusis. Van Lier (1967), on the other hand, found that a group of nuns that had lived sheltered from noise and other exposures most of their lives had no better hearing than a control group matched for age and sex, in fact the nuns were even found to hear slightly worse. Although the findings from such studies are interesting, they may be confounded by factors such as genetics or diet. Additionally, the small sample sizes and other methodological issues may also limit the possibilities of drawing any firm conclusions.

1.4.2 PATHOPHYSIOLOGY

Age related changes of structures and functions occur in all parts of the auditory pathways, from the auditory periphery to the auditory cortex.

Peripheral changes

Peripherally, the most significant changes take place in the Organ of Corti within the cochlea, or in the spiral ganglion neurons, which relay auditory information from the hair cells to the central auditory nervous system, *CANS* (Bao & Ohlemiller, 2010). Schuknecht and colleagues conducted several histological studies on human temporal bones, to determine the pathologies involved in ARHL (Gacek & Schuknecht, 1969; Ramadan & Schuknecht, 1989; Schuknecht, 1964; Schuknecht, 1955). Based on microscopic findings that were linked to audiometric data, several subtypes of cochlear pathology were proposed and later revised to three predominant categories (Schuknecht & Gacek, 1993):

- *Sensory presbycusis* entails atrophy mainly in the outer hair cells in the organ of Corti, producing a high frequency hearing loss. This type accounts for 5% of ARHLs.
- *Neural presbycusis* is classified as the presence of damage in the spiral ganglion neurons while the Organ of Corti is relatively preserved. This type is relatively rare and leads to particular difficulties with speech perception.
- *Metabolic, or Strial,* is the most commonly seen cochlear pathology in presbycusis, observed in 1/6 of subjects. It involves atrophy in the Stria Vascularis*,* which produces and maintains the ionic composition of endolymph, vital to the function of the cochlea. Significant pathology in the Stria Vascularis leads to hearing loss of all frequencies.

The remainder of the studied objects were classified as *cochlear conductive*, *mixed* (a combination of pathologies), or *indeterminate*. More recent studies performed in mice have revealed that damage in the synapses to the auditory nerve is present in presbycusis (synaptopathy), and have corroborated the important role of Stria Vascularis atrophy in presbycusis, triggered by for example oxidative stress and microvascular factors (Ohlemiller, 2004). In reality, these distinct pathologies overlap and the clinical manifestations of presbycusis do not fit the categories perfectly.

Central changes

Difficulties in understanding speech is a typical feature of presbycusis, due the increases in hearing thresholds and diminished frequency resolution caused by outer hair cell loss. However, some persons exhibit *great* difficulties with speech comprehension in advancing age, beyond what is expected based on peripheral hearing abilities, a phenomenon labelled as central presbycusis (Gates, 2012; Stach et al., 1990). A task force within the American Speech Language Hearing Association (Humes et al., 2012), defined central presbycusis as "*age-related change in the auditory portions of the central nervous system, negatively impacting auditory perception, speech-communication performance, or both*". The presence of central auditory processing disorder (CAPD) is usually assessed by presenting speech tasks along with simultaneous competing messages, or using degraded speech stimuli, e.g. dichotic speech tests or gap detection tests (Sardone et al., 2019). Older listeners perform worse than younger listeners on CAPD tests, matched in terms of peripheral hearing loss and cognition (Frisina & Frisina, 1997; van Rooij & Plomp, 1990), and the prevalence of CAPD among old persons has been reported to be around 14% (Quaranta et al., 2014). Further, longitudinal studies have demonstrated that central auditory processing abilities deteriorate at a faster rate than peripheral hearing (Häggström et al., 2018). According to Humes et al. (2012) , untangling the contributions of peripheral hearing loss, central auditory processing disorder and cognitive deficits respectively, to poor speech performance in old age is complex. In fact, deafferentation caused by peripheral hearing loss has been shown to lead to alterations in the brain, including reduced volume of the grey matter in the auditory cortex and in the total brain volume (Rigters et al., 2017). Moreover, the deciphering and interpretation of impoverished speech signals (due to hearing loss) requires increased allocation of cognitive resources (Pichora-Fuller et al., 1995). Humes (1996) described three hypotheses to diminished understanding of speech in old listeners. First, changes in the auditory periphery reduce the magnitude of the neural response, decrease temporal, and frequency resolution, which lessens the ability to discriminate between phonemes. Second, changes in central auditory pathways may affect the deciphering of the signal. Third, reduced cognitive capacity may affect the possibility to understand speech. A schematic overview is shown in Figure 3.

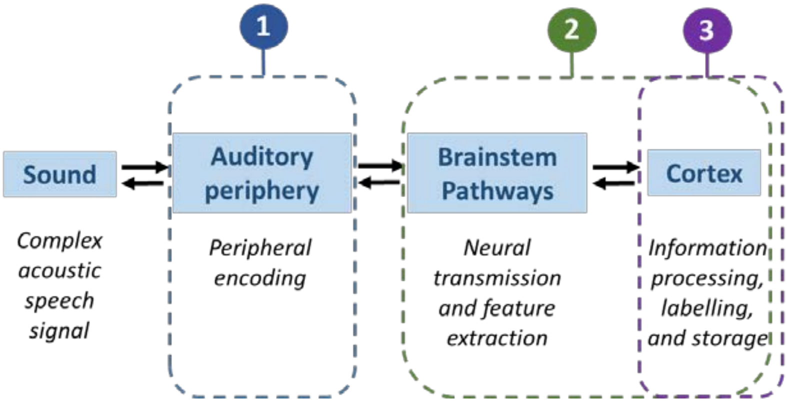


Figure 3. *Three possible underlying mechanisms explaining impaired speech understanding in older listeners. Model (1) emphasizes the importance of damage in the peripheral auditory pathways, while model (2) emphasizes degradation in the central auditory pathways. Model (3) focuses on the role of cognitive function. From Humes (1996), adapted by author.*

1.4.3 PREVALENCE

Worldwide, the number of persons affected by ARHL is estimated to be in the region of 280 million (United Nations, 2019). The prevalence and incidence of ARHL has been investigated in numerous studies, mostly from high-income countries. A key challenge, when evaluating prevalence is the relatively wide range of methodologies, definitions and classifications that have been applied in epidemiological studies to date (Cruickshanks et al., 2010). For instance, studies varied in terms of what age range was considered and whether hearing loss was self-reported or measured psychoacoustically. Pure-tone audiometry is the most commonly employed outcome measure, but studies have varied in a number of respects: e.g. using manual or automated method for determining thresholds; reporting pure-tone averages across three or four frequencies (PTA3 or PTA4); the level of hearing loss in dB HL; reporting hearing loss per individual or per ear. Taken together, these factors further complicate comparison between studies.

Summary of prevalence studies

Many studies used the criterion advocated by the WHO, i.e. a PTA4 > 25 dB HL in the better hearing ear. By this definition, a prevalence of 33% was reported for Australian adults (aged 50+ years, n=2940) in the Blue Mountains Study (Gopinath et al., 2009). In the same population, the 5-year incidence of ARHL was found to be 18% (Gopinath et al., 2010a). Using data from the 1999-2004 cycles of the National Health and Nutrition Examination Survey (NHANES), Agrawal et al. (2008) reported a prevalence of 31% among 60-69 year old Americans (n=952), a figure which rose to 49% if also including those with unilateral hearing loss. From later cycles of the same survey (2004-2010), Goman & Lin (2016) reported a prevalence of 27% in 60-69 year-olds, 55% in 70-79 year-olds and 81% in those aged ≥ 80 years. For the same age ranges and applying the same hearing loss criteria, von Gablenz et al. (2020) found a prevalence of 14% (60-69 years), 32% (70-79 years) and 59% (80+ years) in a German population (n=3105). In a large Chinese cohort (n=6984) 59% were found to have hearing loss (age range: ≥60 years). Furthermore, in the Rotterdam Study (Homans et al., 2017), disabling hearing loss (i.e. PTA4 ≥ 35 dB HL in the better ear) was found to affect 32% of the older Dutch population (n= 4743, age range: ≥ 65 years). Moreover, data regarding the prevalence of self-assessed hearing loss is available in several studies. For instance, using national census data, (Rosenhall et al., 1999) found a prevalence of ~30% of the older Swedish population (age range: 65-84), while the equivalent figure in the British population aged 75 years or above was reported at 40% (Davis et al., 2007). Moreover, in a Finish population (n=850, age: 54-66 years), 37% reported hearing difficulties (Hannula et al., 2011).

Trends in prevalence

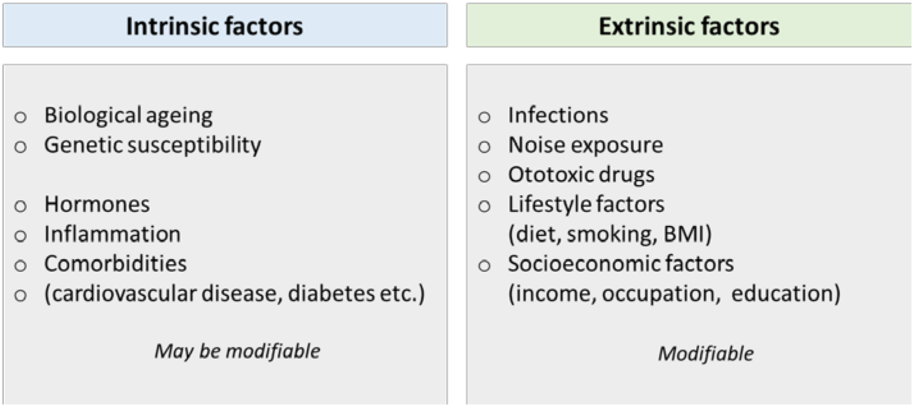
Studies investigating secular trends in ARHL are relatively rare. A recent report (Engdahl, Strand, et al., 2020) from the Trøndelag Health Study (HUNT) in Norway found that a cohort of 28 339 Norwegians had better hearing thresholds than a comparable cohort born 20 years earlier, and that the largest discrepancy (10 dB) affected men aged 60-70 years. Similarly, Hoffman et al. (2010) analysed data from the NHANES study, reporting that more recently born Americans hear better compared to those born 40 years earlier. Furthermore, indications of better hearing in earlier born cohorts were found by Zhan et al. (2010), when comparing data from four birth cohorts of the Beaver Dam Study and the Epidemiology of hearing Loss Study. In the same population, Paulsen et al. (2020) reported a decrease in the incidence of hearing loss in younger generations. Moreover, using data from the Gothenburg H70 Birth Cohort Studies, Göthberg et al. (2020) found that more recently born 85-year-old men, but not women, heard better than an earlier born cohort. On the other hand, Rosenhall et al. (2013) found no significant changes when comparing birth cohorts of Swedish 75-year olds from the same study.

1.4.4 RISK FACTORS

In addition to individual cochlear ageing, described in a previous subchapter, several intrinsic and extrinsic factors that increase the risk for ARHL have been identified in epidemiological studies. These may be non-modifiable or modifiable in part or completely (see Figure 4 for an overview).

Non-modifiable factors include age, sex, and race. Age has consistently and strongly been linked to an increased risk for hearing loss (Agrawal et al., 2008; Corso, 1959; Cruickshanks et al., 1998; Davis, 1989; Gates et al., 1990; Glorig & Davis, 1961; Gopinath et al., 2009; Nash et al., 2011; Pedersen et al., 1989; Wiley et al., 2008). Male sex has also rather consistently been shown to be associated with poorer hearing (Corso, 1959; Homans et al., 2017; International Organization for Standardization, 2017; Robinson, 1988), at least in the higher frequencies, often attributed to higher exposure to occupational noise and other risk factors. On the other hand, women have been found to have poorer hearing in the lower frequencies, referred to as the gender reversal effect (Jerger et al., 1993). Furthermore, biological sex differences most likely also play a part in explaining hearing differences between men and women (Nolan, 2020). The risk associated with race has mostly been reported in American populations, where non-Hispanic black persons have been shown to have a reduced risk of hearing loss compared with white persons (Agrawal et al., 2009; Helzner et al., 2005). Additionally, genetics is almost certainly an important factor, for instance, ARHL has been shown to aggregate within families (Gates et al., 1999), and several genes have been identified as potential candidates affecting the development of ARHL, such as the GRM7 (Newman et al., 2012).

Comorbidities is yet another group of risk factors known to affect the risk for ARHL. These may or may not be modifiable. Cardiovascular factors have been shown to increase the risk for ARHL in several studies, including hypertension (Rigters et al., 2016) and coronary artery disease (Wattamwar et al., 2018). Diabetes is another condition that has been associated with higher risk for ARHL in several studies (Bae et al., 2020; Helzner & Contrera, 2016).



Intrinsic factors

- Biological ageing
- Genetic susceptibility

- Hormones
- Inflammation
- Comorbidities
- (cardiovascular disease, diabetes etc.)

May be modifiable

Extrinsic factors

- Infections
- Noise exposure
- Ototoxic drugs
- Lifestyle factors
  (diet, smoking, BMI)
- Socioeconomic factors
  (income, occupation, education)

Modifiable

Figure 4. *Model over risk factors for ARHL according to whether they are modifiable or not. The potentially modifiable risk factors listed in the left column may be targets for intervention in the future.*

Many environmental factors affect the risk for ARHL, including for example noise exposure, ototoxic drugs, tobacco use, alcohol consumption and life-style factors.

Noise exposure is perhaps the most extensively studied variable, and although there is strong evidence for the harmful effect of noise exposure on hearing, it is unclear how noise exposure affects the development of ARHL. Noise exposure has been associated with increased risk for ARHL in several studies (Dobie, 1994; Rosenhall et al., 1990). Additionally, some evidence suggests interactions between noise induced hearing loss and ARHL, suggesting that cochlear vulnerability may lead to an accelerated rate of ageing (Fernandez et al., 2015; Kujawa & Liberman, 2009). This is somewhat contradicted by the fact that the progression of hearing loss was equal among noise exposed and unexposed participants in a longitudinal study (Hederstierna & Rosenhall, 2016). Similarly, Cruickshanks, Nondahl, et al. (2010) found no significant difference in the incidence of ARHL between noise exposed and unexposed.

Smoking has been demonstrated to increase the risk for ARHL, while moderate alcohol consumption may have a protective effect (Dawes et al., 2014; Gopinath et al., 2010b). Moreover, dietary habits may have an effect on ARHL. In one study (Rosenhall et al., 2015), high intake of fish was associated with better hearing, whereas high intake of low molecular carbohydrates (“junk food”) was linked to poorer hearing. Socioeconomic factors, like income, education or occupation, are also important determinants of ARHL. Having a lower income or shorter education increases the risk for hearing loss (Frank R. Lin et al., 2011), and several occupations are associated with higher prevalence of ARHL (Cruickshanks et al., 2010). There may be significant interactions between many of these factors, which makes it difficult to untangle the unique contributions to ARHL specifically.

1.4.5 CONSEQUENCES

ARHL mainly leads to problems in following conversations, which impacts in several aspects of daily life, including maintaining social relationships (Pichora-Fuller et al., 2015). Viewed through the lens of the International classification of functioning, disability and health (ICF), a biopsychosocial health model, ARHL can be described as limiting a number of activities and restricting participation in social engagements (Hickson & Scarinci, 2007). For ARHL, activities that are limited include speech perception (especially in adverse listening conditions), listening to TV and radio, and the localization or detection of sound sources and alarms (i.e. hearing an approaching car in traffic or hearing the doorbell). At a social level, ARHL may lead to withdrawal from involvement in community life and interpersonal interactions (Laplante-Lévesque et al., 2010). Consequently, ARHL impacts negatively on the quality of life of those affected (Dalton et al., 2003), as well as their significant others.

The Global Burden of Disease (GBD) studies estimate the impact of a vast number of health conditions on global and regional public health. To describe the impact of a specific condition, a measure known as DALY (Disability adjusted life years) is used, which takes both mortality and morbidity into account. In 2019 (Vos et al., 2020), ARHL ranked among the ten leading causes of DALYs, and was found to be among six health conditions that are the main drivers of global increase in disease burden. More specifically, research has shown that ARHL is associated with diminished physical, mental and cognitive health. For instance, several studies have linked ARHL to an increased risk for falls (Lin & Ferrucci, 2012; Viljanen et al., 2009), which is a major determinant of health and independency in old age. Furthermore, in a nationwide study of 60-69 year old American women, ARHL was found to increase the odds of social isolation (Mick et al., 2014). ARHL was also shown to be cross-sectionally and longitudinally associated with depression in some studies (Brewster et al., 2018; Saito et al., 2010).

1.4.6 REHABILITATION

ARHL is chronic in nature, but negative effects can be prevented or managed through rehabilitation. Hearing aids have a demonstrated beneficial effect on the level of disability (Mulrow et al., 1992; Parving & Philip, 1991), and quality of life of older persons. Hearing aids may also offer additional advantages. For instance, some studies have shown that hearing aid use may improve cognitive functions (Acar et al., 2011; Amieva et al., 2015), or improve functioning and health outcomes in persons with dementia (Allen et al., 2003). Further, hearing aid use has been linked to improved balance (Rumalla et al., 2014) and reduced symptoms of depression and anxiety (Mulrow et al., 1992). Furthermore, due to the impact of ARHL in social and emotional domains, individual and group based counselling is warranted (Kricos, 2006). Teaching of communication strategies, educational interventions and psychosocial adjustment counselling can help old persons to accept and adapt to hearing loss, as well as overcoming factors preventing the successful use of hearing aids.

In spite of the high prevalence of ARHL, the prevalence of hearing aid use is comparatively low (Davis et al., 2007; Popelka et al., 1998). Many social and physical barriers to hearing aid adoption in old persons exist. For example, the stigma (perceived or real) associated with hearing loss can lead to denial, avoidance and other maladaptive coping strategies, affecting help seeking behaviour and motivation. The combination of old age and hearing loss has been described as a dual stigma (Wallhagen, 2010). Further, physical disabilities that are common in old age, such as loss of vision, manual dexterity and arthritis may also affect hearing aid adoption (Kricos, 2006). Rosenhall and Karlsson Espmark (2003) found that 6% of participants accepted an offer of hearing rehabilitation when directly asked as part of a population-based study, suggesting that actively offering older persons help may improve the rate of hearing aid adoption. In the same vein, Davis et al. (2007) found a positive effect on hearing aid adoption when offering hearing screening to adults in the UK.

1.5 COGNITION

Cognition refers to a system of mental processes relating to the acquisition, storage and retrieval of information. Cognitive performance is often divided into conceptual domains that may be viewed as hierarchically structured, e.g. attention, memory, executive function, language, visuospatial ability and abstract thinking. Sensory and perceptual operations (bottom-up processes) are regarded as being more basic, while executive function and logical thinking may be more complex, requiring coordination of several cognitive abilities (top-down processes). However, there is an overlap between domains, and there are inconsistencies in the literature in how these are labelled (Harvey, 2019). It is also common to distinguish between crystallized and fluid cognition, where the former refers to abilities learned over the course of a lifetime and the latter refers to the ability to solve problems in novel situations, without referring to pre-existing knowledge (Horn, 1982). Cognitive abilities are often assessed using a battery of tests that may include both verbal and non-verbal tasks. Additionally, global cognitive function can be determined with screening instruments, such as the Mini-Mental State Examination (Folstein et al., 1975).

Table 2. *Overview of neurocognitive domains.*

Domain	**Subdomain**
Language	Object naming, word finding, fluency, grammar and syntax, receptive language
Social cognition	Recognition of emotions and non-verbal cues
Executive function	Decision making, problem solving, inhibition, working memory, processing speed
Complex attention	Selective attention, divided attention, sustained attention (concentration)
Memory	Free recall, cued recall, recognition memory, semantic long-term memory (storage and retention)
Perceptual-motor function	Visual perception, visuoconstructional reasoning (drawing, copying), perceptuomotor coordination

From: Sachdev et al. (2014). Classifying neurocognitive disorders: the DSM-5 approach. Nature Reviews Neurology, 10, 634.

1.5.1 AGE RELATED COGNITIVE DECLINE

With advancing age, old persons often develop deficits in several cognitive domains, such as reasoning, attention, mental speed and memory, but it is unclear to what extent these changes are caused by normal ageing versus disease (Peters, 2006). Ageing of the brain leads to gradual deterioration of anatomical structures, which in turn impacts on mental functions and behaviours. For example, longitudinal studies using MRI (magnetic resonance imaging) have provided evidence that general brain volume decreases with age, and that grey and white matter atrophy affects various brain regions differently (Resnick et al., 2003). These changes have been found to correlate with cognitive decline. Moreover, age-related decline in cognitive function is often caused by dementias. Dementia is a group of progressive neurodegenerative brain disorders that involve decline of intellectual, mental and physical function, which leads to disability and death (National Collaborating Centre for Mental Health, 2007). The majority of dementias are caused by Alzheimer’s disease (AD) or cerebrovascular causes, or mixed pathologies. Additionally, some individuals have problems with cognitive functions that are not severe enough to classify as dementia, but that still deviate significantly from the average, referred to as *mild cognitive impairment (MCI)* (Petersen et al., 1999). MCI may be a preclinical stage to dementia, and may be amnestic, i.e. involving memory deficit, or non-amnestic.

1.5.2 ARHL AND COGNITION

Hearing and cognition in old age are related in several ways. As described previously, cognitive factors are important to speech perception in adverse listening conditions. The increased need for cognitive resources when attempting to understand speech in the presence of competing noise, is referred to as listening effort, which has been studied with pupillometry and behavioural tests (Gagné et al., 2017). Further, Wild et al. (2012) were able to demonstrate the increasing importance of attention when subjects listened to degraded speech, by using functional MRI. Working memory, i.e. the ability to temporarily store and process information required to carry out a complex cognitive task, is another well-studied factor in speech comprehension (Rönnberg et al., 2019).

Moreover, peripheral and central ARHL are now recognized risk factors for dementia and mild cognitive impairment (Gates et al., 2002; Lin et al., 2013; Livingston et al., 2020; Peters et al., 1988; Uhlmann et al., 1986). It is not established whether treating hearing loss can reduce the effects of ARHL on cognitive decline, but some studies suggest that it may be the case (Amieva et al., 2015; Dawes et al., 2015). Randomized controlled trials could address this research questions, but would be difficult to perform for ethical reasons.

Several review articles describing the possible mechanisms underpinning the association between ARHL and cognitive impairment have been published in recent years (Fulton et al., 2015; Jayakody et al., 2018; Uchida et al., 2019). (Baltes & Lindenberger, 1997; Lindenberger & Baltes, 1995) provided strong evidence of the link between sensory and intellectual abilities in older subjects and formed three hypotheses. First, due to changes in the "physiological architecture" there may be common causes of age related sensory and cognitive decline, e.g. microvascular deficiencies, inflammation or atrophy due to oxidative stress. Second, degradation of sensory input may increase the cognitive load, which over time may deplete cognitive resources resulting in accelerated decline. Third, the reduction of afferent input to the CANS may "starve" neurons leading to atrophy or changes in the structure and function in the cortex (sensory deprivation). Sensory deprivation may also indirectly occur as a result of social isolation, which may be referred to as the *Cascade theory* (Dawes et al., 2015). Figure 5 shows an overview of the possible mechanistic pathways linking ARHL and cognitive decline.

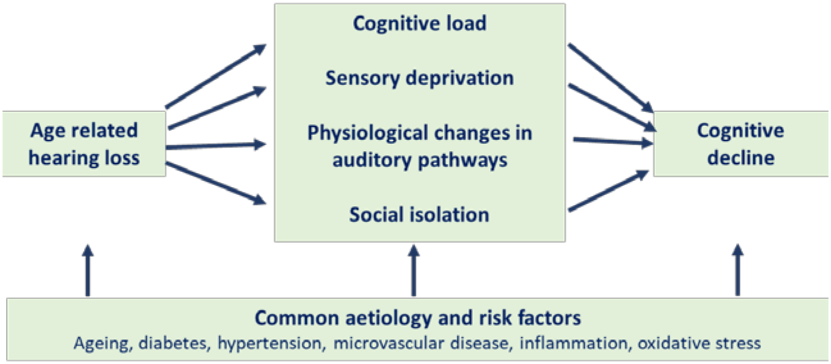


Figure 5. *Model of the potential mechanisms of ARHL as a cause of cognitive decline. Source: Fortunato et al. (2016), modified by author*

Moreover, there is certainly a possibility of concurrent hearing loss decreasing the performance on verbally loaded tasks, thus biasing the assessment of cognitive abilities. In support of this notion, Dupuis et al., 2015 found that scores on the Montreal Cognitive Assessment (MoCA) improved in persons with hearing loss once verbally loaded tasks were omitted. A further aspect of interest is that instructions for tests are given verbally in many instances, which may put persons with hearing loss at a disadvantage. However, Uhlmann et al. (1989) failed to demonstrate any significant difference in scores when the MMSE was administered both verbally and in written to persons with hearing loss, indicating that any bias probably is not an important factor. Regardless of whether hearing loss leads to over-diagnosis of cognitive impairment or not, it does not fully explain the increased risk for cognitive decline in persons with hearing loss (Shen et al., 2016).

1.6 SUMMARY AND RATIONALE

In summary, due to the demographic changes that are occurring in populations across the world, the number and proportion of old persons will continue to increase in the forthcoming years. In light of these changes, there is a necessity for epidemiological research, which can help in identifying factors that can promote successful ageing. ARHL is a prevalent condition that is associated with poorer health outcomes, physically, socially and emotionally. Additionally, in recent years, a growing body of evidence has demonstrated that ARHL is a potentially modifiable risk factor for cognitive decline. As such, ARHL – especially untreated – has implications for the prospects of healthy ageing, and therefore constitutes an important area of research.

Although several epidemiological studies on ARHL exist, robust data from well-characterized populations in Europe are relatively scarce. Especially if one considers investigations that use standardized hearing test methods. Although self-report measures and pure-tone audiometry are important methods, they are limited in their ability to provide a comprehensive characterization of ARHL. Additionally, there is no recent epidemiological study on ARHL from Sweden specifically. Given the fact that socioeconomic and environmental determinants of population health vary over time, population-based data need to be renewed continuously. Accurate and current prevalence figures of ARHL in the general population are vital for appropriate planning and commissioning of hearing health care services. Finally, an increased understanding of the link between ARHL and cognitive function may serve to prevent poor health outcomes in old age, and encourage better coordination of geriatric health care services.

Each of the papers presented in this thesis strives to address specific knowledge gaps that are outlined in the reprinted publications and manuscripts.

2 AIMS

The overall aim of the present thesis was to investigate, explore and describe various aspects of hearing function in early old age – including its association with cognitive function – by analysing data from a contemporary age-homogenous birth cohort of 70-year old men and women, representative of the City of Gothenburg, Sweden. The specific aims for each of the papers were as follows:

Paper I

- To describe the distribution of hearing thresholds, and estimate the prevalence and severity of ARHL,
- to investigate secular trends in hearing acuity and hearing loss prevalence, by comparing with earlier born cohorts from the H70 Studies.

Paper II

- To characterize auditory function, based on an audiological test battery comprising both behavioural and physiological measures,
- to estimate the prevalence of specific ear and hearing related pathologies in ARHL.

Paper III

- To assess the agreement between automated and conventional manual pure-tone audiometry in “younger old” and “older old” persons,
- to investigate whether the agreement is affected by age group, level of hearing loss and cognitive status.

Paper IV

- To describe the association between hearing and cognitive function in early old age,
- to compare the association of subjective and objective hearing measures with cognitive function,
- to explore the effect of hearing on different cognitive domains and tasks,
- to assess the impact of tinnitus and hearing aid use on cognitive function.

3 METHODS

3.1 THE H70 BIRTH COHORT STUDIES

Data for all four papers included in the present thesis comes from the Gothenburg H70 Birth Cohort Studies (The H70 Study for short), an ongoing prospective population-based health investigation of the older population in Gothenburg City, with a current population of 578,000 inhabitants (November 2019). The study was first initiated in 1971, aiming to survey health and its sociodemographic determinants in old age (Steen & Djurfeldt, 1993). In the H70 Studies, age-homogenous birth cohorts that are representative of the city of Gothenburg are examined with cross-sectional and longitudinal methods (see Figure 6) covering multiple aspects of health. All participants are aged 70 at baseline, with follow-ups being performed at regular intervals. The present thesis is primarily based on data from the most recent birth cohort of 70-year olds, born in 1944, which also includes an extended audiological investigation performed in a subsample.

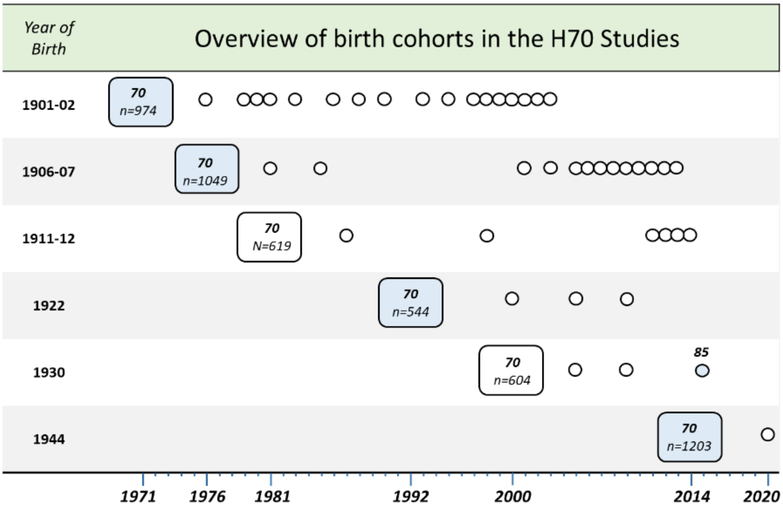


Figure 6. *Overview of all birth cohorts within the Gothenburg H70 Birth Cohort Studies. The Y-axis shows birth year of each cohort, and the x-axis shows the test year. The circles represent points in time at which longitudinal follow-ups were done. The present thesis includes cross-sectional data from the cohorts highlighted in blue.*

3.1.1 MAIN INVESTIGATION

A detailed account of the methods used in the 1944 cohort is available elsewhere (Rydberg Sterner et al., 2018) and summarized here. The study was conducted in the years 2014-16. All residents of Gothenburg, including the adjacent municipalities of Ale, Kungsbacka, Kungälv, Lerum and Mölndal, that were aged 70 (at the time of invitation) and born on specific dates (ending in 0, 2, 5 or 8) were eligible for the study (n=1839). Potential participants were identified through information from the Swedish Tax Agency. To be included, participants were required to have sufficient Swedish language proficiency and health/fitness to participate in tests. Those that fitted these criteria and could be traced constituted the effective sample, n=1667. Potential participants received an invitation by letter and a subsequent telephone call. Reminders were sent up to three times. The invitation was accepted by 1203 (52% women, response rate 72%) persons. The most common given reasons for non-participation included illness (30%) or attending regular health check-ups (26%). These were not mutually exclusive. Nearly half did not state any reason.

The study was conducted over the course of a full day in the neuropsychiatric outpatients department in Wallinsgatan, Mölndal, or during a domiciliary visit if required. The study protocol included:

- Blood samples, measures of weight and length
- Interviews, e.g. about general health, functional ability, family history and social factors
- Physical examinations, such as blood pressure and ECG
- Psychiatric examination
- Clinical and psychometric cognitive examination
- Hearing test (automated pure-tone audiometry and wide band tympanometry)
- Self-rating questionnaires

The tests and interviews were mostly conducted by trained research nurses. Physiotherapists, medical doctors, psychiatrists and other professional categories conducted some of the tests. Additionally, a number of extended studies were performed in subsamples of varying sizes, e.g. dietary examination, brain imaging (CT, MRI), cerebrospinal fluid sampling and audiological examination (the procedure of which is described on the next page). These were conducted under separate ethical applications.

3.1.2 EXTENDED AUDIOLOGICAL EXAMINATION

The selection of participants to be included in the subsample was also based on birth dates. In order to obtain a smaller but still representative sample, participants born on dates ending with two or eight were selected. Participants born in months from July-December were not included in the study, since the data collection was stopped earlier due to time constraints. Selected participants (n=305) were briefly informed about the study during the basic hearing examination of the main investigation. Shortly after, they received more comprehensive information and a consent form through the post, followed by a telephone call. Those that accepted (n=251) were booked in for an appointment in the Audiological research facility at the University of Gothenburg, which lasted for 1.5-2 hours. Transportation was offered if needed. Reasons for declining participation (n=31) included for example, “too good hearing”, “tired of being tested”, “already has a hearing aid, “too poorly”. The remainder of non-responders could not be booked in, or did not show up to the appointment.

The test protocol included:

- Brief medical interview
- Otoscopy
- Pure-tone audiometry (Clinical)
- Speech in noise recognition
- Tympanometry
- Distortion Product OAE
- Auditory-evoked Brainstem Responses

The tests were conducted by audiologists in soundproof conditions adhering to international standards (ISO, 2010) in terms of calibration, ambient noise levels and methodology. Participants who were diagnosed with either hearing loss or ear pathology requiring medical attention were offered referral to an Audiology department for a hearing aid consultation, or to an Ear Nose and Throat Physician.

3.2 SUMMARY OF PAPERS

3.2.1 STUDY DESIGN

Table 3 outlines the design of the four papers of the present thesis. **Paper I** was a cross-sectional cohort comparison study, in which hearing acuity (measured with air conduction pure-tone audiometry) and hearing loss prevalence was determined and compared to earlier born birth cohorts that had been sampled in similar ways (see under ‘study samples’). **Paper II** was a descriptive study of the subsample of the birth cohort (1944) that had performed an extended audiological evaluation, in which the prevalence of specific subtypes and pathologies of ARHL was determined. Furthermore, factors explaining poor speech-in-noise performance were explored. **Paper III** was a method validation study, in which results obtained with conventional clinical pure-tone audiometry were compared to automated pure-tone audiometry, in subsamples of 70 year-olds (born in 1944) and 85-year olds (born in 1930). Finally, **Paper IV** was a cross-sectional analysis of the association between hearing and cognition in participants of the birth cohort (1944) without dementia.

3.2.2 STUDY SAMPLES

All samples examined in the present thesis were drawn from the Gothenburg H70 Cohort Studies. Table 4 presents sample sizes and gender distributions for each of the papers, as well as the birth cohorts from which the samples were derived.

In **paper I**, the sample included participants from the 1944 cohort who had performed automated pure-tone audiometry as part of the main investigation (n=1135, 53% women). The non-response (n=68) was explained in part by the fact that pure-tone testing was not included in the domiciliary visit (n=46). Further reasons included lack of time or the participant being too tired. To address the study aim, hearing was compared to earlier born cohorts of the H70 studies, born in 1901-02, 1906-07 and 1922 respectively. The two earliest born cohorts were merged in the statistical analysis. Further details about the sampling and test methods used in these cohorts are available in the reprinted publication, or in the original publications by Jonsson et al. (1998). Demographic and health characteristics of the 1944 birth cohort were presented in the publication by Rydberg Sterner et al. (2018). Briefly, 98% were community dwelling and mostly retired. Some ~20% still worked (paid labour), predominantly part time. Selected demographic variables of the cohort are presented in table 5, and compared with census data for the population in Gothenburg of the same age.

Table 3. *Overview of the study design and main outcomes for each paper.*

Paper	Design	Outcomes measures	Group variables
I	Cross-sectional cohort comparison study	Pure-tone audiometry *(automated)*	*Birth cohort* *Gender*
II	Cross-sectional study, descriptive	Pure-tone audiometry *(conventional, manual)* DPOAE ABR Tympanometry	*Gender*
		Speech recognition in noise	*Gender* *Audiogram Configuration* *ABR, Interpeak latency*
III	Method validation study	*Automated* and *manual* pure-tone audiometry	*Age Group* *Hearing level* *MMSE*
IV	Cross-sectional birth cohort study	Cognitive test battery	*Pure-tone audiometry* *Speech recognition in noise* *Self-reported hearing* *Tinnitus* *Hearing aid use*

DPOAE=Distortion product otoacoustic emissions; ABR=Auditory-evoked brainstem response; MMSE=Mini-Mental State Examination

In **paper II**, the sample consisted of those who had responded to the substudy (as explained in the previous chapter), i.e. 251 persons (52% women). The representativeness of the subsample was tested by comparing the distribution of various health and demographic variables in the subsample to that of the remaining birth cohort (n=952). Participants had a slightly higher rate of ear surgery history (women), poorer self-assessed hearing (men) and higher level of physical activity (men).

In **paper III**, the sample consisted of participants from the 1944 cohort (aged 70), and the 1930 cohort (aged 85), who had valid results from both automated pure-tone audiometry (main investigation) and conventional manual pure-tone audiometry (substudy). Additionally, ears that were found to have significant air-bone-gaps due to collapsing ear canals (determined within the substudies) were excluded. The final sample consisted of 238 participants aged 70, and 114 participants aged 85. There were some significant differences found in comparison with the birth cohorts that the samples were drawn from. Both samples (70, 85) were somewhat more educated. Additionally, the 85-year old sample had a higher proportion of men, better self-assessed general health and better global cognitive function (assessed with the Mini Mental State Examination). These differences were slight, but statistically significant.

In **paper IV**, the sample was again drawn from the 1944 cohort, this time both from the main investigation and the substudy. Most study variables (pure-tone audiometry, self-reported hearing loss, tinnitus, hearing aid use, cognitive examination) were available in the whole sample, but speech recognition in noise was only perfromed in the subsample. Persons with dementia (n=23) were excluded, as was participants who had missing results on any of the hearing or cognitive tests. The final sample consisted of 1105 persons, of which 247 persons had performed speech testing. There were generally no significant differences between the subsample (n=247) and the remainder of the sample (n=858), however the subsample had a higher educational attainment.

Table 4. *Overview of samples used in papers I-IV.*

Paper	Age*	Birth Year	n	% female	% of cohort
I	70	1944	1135	53	94
	70	1922	226	72	42
	70	1906-07	297	58	28
	70	1901-02	376	52	39
II	70	1944	251	55	21
III	70	1944	238	55	20
	85	1930	114	49	23
IV	70	1944	1105	52	92

Table 5. *Sociodemographic characteristics of the 1944 birth cohort (n=1203) in comparison with the population in Gothenburg of the same age, based on census data from 2014.*

		1944 Cohort	**Gothenburg**[a]
Gender	Man	46%	48%
	Woman	54%	52%
Marital status	With Partner	71%	n/a
	Other[b]	29%	n/a
Education	≤9 years	17%	20%
	>9 years	83%	80%
	University degree[c]	*29%*	*17%*[d]
Country of birth	Sweden	85%	81%
	Other	15%[e]	19%

[a]Figures compiled by author based on publically available census data from Göteborgs stad or Statistics Sweden (SCB); [b]including widowed, divorced and single; [c]Part of the >9 years category; [d]including the census data categories of “at least 3 years undergraduate studies” and “doctoral studies”; [e]Most in this category were from other Nordic countries followed by Europe

3.2.3 STUDY VARIABLES

As part of the main investigation, a basic hearing evaluation and a detailed cognitive examination were performed. Furthermore, self-reported and measured data regarding demographic, social and health characteristics were collected. As part of the extended audiological examination performed in a subsample, a battery of physiological and psychoacoustic audiological tests were conducted. The specific procedures and how the variables are used in each paper are described here:

Main investigation

Pure-tone audiometry - automated

Automated computerized pure-tone audiometry was conducted in a quiet office, administered by research nurses that were trained by audiologists. Otoscopy was performed with a hand-held otoscope. Nurses made a note if wax was present, but no wax removal was performed. Only air conduction thresholds were obtained at the following eight discrete test frequencies: 0.25, 0.5, 1, 2, 3, 4, 6, and 8 kHz in the measurement range of 0-90 dB HL.

An Entomed SA 202IV audiometer was used in conjunction with Sennheiser HDA200 headphones. The participants were seated facing away from the audiometer and were instructed to press a button each time they heard a tone, no matter how faint. The automatic test started once the nurse had placed the headphones and pressed a start button on the audiometer. The procedure always began in the right ear at 1 kHz with a familiarization procedure, to ensure compliance with the method. If not satisfactory the test was halted and the participant was re-instructed once. The method of determining the pure-tone threshold was similar to the modified Houston-Westlake procedure (Carhart & Jerger, 1959), combining descending and ascending series of stimuli (referred to as a bracketing technique), with the threshold accepted if two correct responses were obtained during an ascending sequence.

The equipment was calibrated prior to the commencement of data collection and regularly throughout the study period (2014-16). Sound level measurements were performed in the test environment on a number of occasions and were found not to exceed permitted values (ISO, 2010).

The results from automated pure-tone audiometry were used to describe hearing function in the 1944 cohort in **paper I** and **paper IV**. Additionally, the validity of this test was tested in **paper III**. In **paper I**, the pure-tone average across 0.5,1,2 and 4 kHz (PTA4) in the better ear was used to describe the prevalence and degree of hearing loss. The better ear was defined as the ear with the lowest (in dB HL) average threshold of all tested frequencies. The pure-tone averages across 0.5, 1 and 2 kHz as well as across 4 and 8 kHz were used to separate hearing ability in the mid frequencies vs. the high frequencies in the linear trend analysis of **paper I**.

Hearing questionnaire

A questionnaire about perceived hearing problems, tinnitus, hearing aid use, history of ear surgery, family history, and history of seeking healthcare for ear or hearing problems, was administered as an interview by the research nurses.

Self-assessed hearing problems were assessed with eight items, first developed for the H70 Birth Cohort Study (1971-72) and having remained unchanged ever since. The first item concerns perceived general hearing ability, phrased as “How is your hearing”. The response scale consist of three categories: “*Fine, no problems*”, “*Slight problems*” or “*Significant problems*”. The remaining seven items concern the ability to hear conversations with one talker, conversations in group, hearing birds, hearing in traffic, hearing music, hearing TV and telephone and localization of sounds.

The presence and severity of tinnitus was assessed with the following question: “Do you have tinnitus (buzzing in the ear)?”. The response scale included “No, do not have tinnitus”, “Yes, not at all bothersome”, “Yes, slightly bothersome”, “Yes, moderately bothersome”, and “Yes, severely bothersome”. Hearing aid use was assessed with two items: “Do you own a hearing aid?”, and “Do you use a hearing aid”. This was done to be able to identify those who do not use their hearing aids in spite of having them.

In **paper IV**, item one from the hearing questionnaire was used to represent self-reported hearing loss. Furthermore, all the “Yes” categories were collapsed to represent presence of tinnitus, and hearing aid use was based on the second question as described above.

Cognitive examinations

Cognitive function was assessed in two steps. First, a clinical examination was conducted by psychiatric and research nurses, as well as psychiatrists and medical doctors. The clinical examination contained a number of tests widely used in the diagnosis of dementia and mild cognitive impairment, for example tests of word fluency (animals), orientation, selective attention, understanding proverbs, and memory. Second, a more detailed psychometric cognitive examination was carried out by research nurses that were trained by a psychologist. This examination comprised an interview about cognitive abilities and habits. Additionally, a cognitive test battery was administered, based on the *Dureman & Sälde* (1959) psychometric test battery. For the purpose of the present thesis, the following tests were used:

The ***Mini-Mental State examination*** (Folstein et al., 1975) was used to represent global cognitive status in **paper III**. It is a test of orientation, attention, memory, language and visuospatial skills, with a maximum score of 30. The cut-off score indicating possible dementia varies depending on level of education. From <23 for those with only basic education, to <27 for those with college level education.

In **paper IV**, cognitive function was assessed with selected tasks from the neuropsychiatric/cognitive examinations performed within the H70 Study. These tasks corresponded to specific cognitive domains highlighted in bold in the bullet list below. Additionally, an index of ***global cognitive function*** was created by averaging the z transformed raw scores of each domain, if at least four domains had valid data.

- ***Episodic memory*** (storage and retention) was assessed with two tasks, one verbal and one non-verbal. The former consisted of a task that involved delayed recall of 12 objects. This test is part of the Alzheimer's Disease Assessment Scale-Cognitive, ADAS-COG (Rosen et al., 1984). The latter involved delayed recall of five images, known as the Thurstone's Picture Memory test (Thurstone, 1938)

- ***Working memory*** was assessed with a supra span memory task (Bus II), in which the participant repeats a list of items of clothing directly after hearing it.

- ***Verbal fluency*** was assessed with Controlled Oral Word Association Test—FAS (Benton et al., 1994). To test

  phonemic fluency participants had to orally generate as many words as possible beginning with /F/ or /A/ in 60 seconds, and ***semantic fluency*** was tested by determining how many words of a semantic category (animals) that could be named in 60 seconds.

- ***Mental Speed*** was tested with a task of figure identification (Psif), in which participants had to identify which image out of five was repeated (Dureman & Sälde, 1959).

- ***Logical reasoning*** was tested with a figure logic task (SRB2), in which participants were required to identify which image out of five differed from the rest.

- ***Visuospatial ability*** was tested with a building block task (Kohs Block Test), where participants had to produce a block design according to a visual instruction (Wechsler, 1991)

Extended audiological investigation

Pure-tone audiometry – conventional

Conventional manual pure-tone audiometry was conducted in a soundproofed test environment, administered by audiologists. Otoscopy was performed with a hand-held otoscope. In the case of occluding wax (n=2) the participant was referred for wax removal and rebooked at a later point in time. Air conduction thresholds were obtained at the following eight discrete test frequencies: 0.25, 0.5, 1, 2, 3, 4, 6, and 8 kHz, and bone conduction at 0.5, 1, 2, 3, and 4 kHz. The measurement range for air conduction spanned from -10 to 110 dB HL and for bone conduction from -10 to 70 dB HL (40 dB HL at 500 Hz).

An Equinox AC440 audiometer was used in conjunction with Telephonics TDH-39 headphones with standard cushions, and a Radioear B71. The participants were seated inside a test booth and were instructed to press a button each time they heard a tone, no matter how faint. The test started in the better hearing ear at 1 kHz, or in the right ear if the participant could not tell which one was better. The 1 kHz threshold was retested in the first ear and adjusted if deviating by more than 10 dB from the first occasion. The procedure was conducted according to the ISO-standard 8253:1 (ISO, 2010), and the threshold was defined as 3 out of 5 correct responses during an ascending sequence. Air and bone conduction masking was applied according to Swedish standardized methodology (Almqvist, 2004).

The results were used in **paper II** to describe peripheral hearing function and to distinguish between conductive and sensorineural hearing loss (table 6 and 8). It was also used as reference in the validation of automated pure-tone audiometry in **paper III**.

Tympanometry

Tympanometry was performed using a handheld clinical Interacoustics Titan Middle Ear Analyzer. The tympanic peak pressure (TPP), the static admittance (SA) and the ear canal volume (ECV) were recorded and used to classify the tympanograms according to criteria supplied by the manufacturer: Type A (TPP: -150 to +50 daPa); Type As (Type A with a low SA, <0.3 mmho); Type Ad (Type A with a high SA, >0.7 mmho); Type C (TPP <150); Type B (Flat curve, no recordable peak in SA).

The results were used in **paper II** for support in identifying middle ear pathology (in conjunction with other tests).

Speech in noise recognition (SPRIN)

Speech Recognition in Noise (Magnusson, 1995) performed according to clinical standards (Almqvist, 2004), was conducted using the same equipment as described above. A recording of phonemically balanced lists consisting of 50 monosyllabic words - read by a male speaker - were presented to one ear at the time, again starting with the better ear. The presentation level was set to 35 dB above the estimated speech recognition threshold, based on the PTA3 (0.5, 1, 2 kHz), but adjusted if the participant experienced discomfort or struggled to hear. An unmodulated speech-weighted noise was presented simultaneously at a fixed SNR of +4 dB. Further, a wide band masking noise was applied in the contralateral ear when indicated. The results were expressed as the percentage of correctly identified words, referred to as the Word Recognition Score in noise (WRS-N) in **paper II** and the SPRIN Score in **paper IV**. In the event of participants not being able to identify any of the first 10 words, a score of zero was given. In these cases, the SPRIN test was performed in quiet (without the noise). Furthermore, for each ear, a predicted SPRIN score was calculated with an SII based algorithm described earlier (Magnusson, 1996a). SPRIN scores that were >16 points worse than the predicted score were classified as poor speech performance.

SPRIN was used in **paper II** to represent ability to perceive speech in noise, and to identify possible auditory neural pathology (Criteria available in Table 7 and 8). It was also used in **paper IV** as one of the three different hearing measures that were associated with cognitive function.

Distortion Product Otoacoustic Emissions (DPOAE)

DPOAEs were measured with an Otodynamics Echoport ILO292-II and the ILO version 6 Software installed on a PC laptop. The equipment was calibrated in accordance with the manufacturer manual. Responses were elicited using a 70/70 dB SPL stimulus with a fixed frequency ratio of 1.22 at six discrete test frequencies: 1, 1.5, 2, 3, 4 and 6 kHz. The noise level and the amplitude in dB SPL were recorded and the emissions were classified as present if reaching a SNR of 6 dB. Additionally, if the amplitude of a present emission was lower than a normative value based on criteria described by Vinck et al. (1996), an outcome of *present but abnormal* was given. In **paper II**, DPOAEs that were classified as ‘absent’ or ‘present but abnormal’ outcomes were considered to represent cochlear dysfunction (Table 7).

Auditory-evoked brainstem responses (ABR)

ABR was recorded with an Interacoustics Eclipse (EP25) with EAR insert earphones, with the participant seated comfortable in a chair. To evoke the responses, clicks of 80 dBnHL were used (alternating polarity, 22.1 clicks per second). The latency of Jewett waves I, III and V were recorded with standard electrodes placed on the ipsilateral mastoids and forehead. The signal was filtered with a 0.1–3 kHz band pass filter. All responses were interpreted by the same person, for consistency. In order to identify abnormal ABR results, an age and sex specific reference material was created based on the ABR results of participants with pure-tone thresholds within normal limits and a pure-tone threshold at 4 kHz of ≤ 50 dB HL, and with no self-reported hearing difficulties. Individual values that were longer than two standard deviations from the means were considered abnormal (table 7).

Table 6. *Criteria used for classifying audiogram configurations/shapes in **paper II**, as described by Hederstierna et al. (2007).*

Audiogram configuration	**Criteria**
Gradually falling	Average threshold of 0.5 and 1 kHz is ≥15 dB better than the average of 4, 6, and 8 kHz
Sharply falling	Average threshold of 0.5 and 1 kHz is ≥30 dB better than the average of 4, 6, and 8 kHz
Flat	Thresholds across the frequencies 0.25–8 kHz differ ≤15 dB from each other.
Miscellaneous[a]	Audiogram configurations that do not meet any of the above criteria.

[a]category includes 'rising' configuration that was not present in any of the ears in paper II.

Table 7. *Criteria used for pathological outcomes in **paper II***

Outcome	**Criteria**
Poor speech performance	A SPRIN score that is > 16 points poorer than the score predicted by the $SII_{DA.}$
Cochlear dysfunction	DPOAE absent (<6 dB SNR) or present with abnormally low amplitude. Values collected from Vinck et al. (1996).
Auditory neural dysfunction	ABR interpeak latency (IPL) of waves I-V ≥ 4.8 ms for men, ≥ 4,6 ms for women, or an interaural latency difference of the IPLs ≥ 0.4 ms.
Abnormal tympanogram	Type B tympanogram: no recordable peak in Static Admittance.

SPRIN: Speech Recognition in Noise; SIIDA: Speech Intelligibility Index with desenzitation and age factors added; DPOA: Distortion Product Otoacoustic Emissions; ABR: Auditory-evoked Brainstem Response; ms: milliseconds.

Table 8. *Criteria used to classify subtypes of ARHL according to pathology in* ***paper II***

Type of ARHL	Criteria
Conductive/mixed	Presence of air-bone-gaps of at least 15 dB at 3 consecutive frequencies, and/or of at least 20 dB at any individual frequency, in combination with either otoscopy, tympanometry or patient history that supported a middle ear pathology. (Labelled *mixed* if present simultaneously as SNHL)
Sensorineural	Hearing loss (PTA4>25 dB HL) with no air-bone gaps present according to above criteria (or false air-bone gaps, in the presence of normal tympanometry, such as with collapsing ear canals)
Cochlear profile [a]	SNHL with normal ABR results
Neural profile	SNHL with abnormal ABR results combined with poor speech in noise performance according to criteria describe in table 7.
Indeterminate	SNHL of a severe degree or worse, preventing a distinction to be made between cochlear and neural pathology.

SNHL: Sensorineural Hearing Loss

[a] Category includes SNHL with abnormal speech in noise performance but normal ABR findings, which may be caused by central auditory dysfunction (not classified here).

3.2.4 DATA ANALYSIS

For all papers, statistical analyses were conducted using IBM SPSS for Windows version 25.0. Additionally, in **paper I** (linear trend analysis), **paper II** (test of representativity) and **paper III** (ordinal regression analysis and tests of representativity), a local software was used: GIDSS (Geriatric Department's Interactive Database and Statistical System). Furthermore, in **paper IV** the R studio version 1.2 was used to produce scatter plots. The significance level was set to $p<.05$ for all analyses and missing data were always excluded listwise.

In **paper I**, pure tone thresholds were presented as medians and percentiles, since these were measured in 5 dB-steps in fixed intervals. Additionally, floor effects applied in the lower frequencies of the sample. To improve the sensitivity of detecting differences in hearing acuity, medians and percentiles were interpolated. This was performed in the same manner as previously done in the H70 Studies (Jonsson & Rosenhall, 1998; Jonsson et al., 1998) and described in detail by (Hoffman et al., 2010). To assess significant differences in prevalence and degrees of hearing loss, pairwise z-tests were conducted. Since the pure-tone averages ($\text{PTA}_{0.5,\ 1,\ 2}$ kHz and $\text{PTA}_{4,\ 8\ \text{kHz}}$) were normally distributed, they were used as dependent variables (outcomes) in the linear regression analyses. As independent variables, cohort (three categories) and gender (binary) were used. Additionally a test for interaction between cohort and gender was included in the models. The distribution of thresholds in each cohort were also compared pairwise with the Mann Whitney U test.

In **paper II**, descriptive data from all tests were presented as means and standard deviations. All variables were sufficiently normally distributed to warrant parametric statistical analysis, especially considering that the number of observations was high. However, slight ceiling effects were found for speech recognition in noise in female participants, and floor effects were found for PTA4 in both genders. To test for differences between men and women, Students t-tests were used for numeric variables and Z-tests for proportions. To test whether the subsample studied in **paper II** was representative, responders were compared with non-responders in a range of variables (health, demographics, hearing questionnaire etc.), using logistic regressions with responder/non-responder as the outcome variable.

Multiple linear regression analysis was conducted to investigate factors associated with poor speech performance. It was hypothesized that early ageing of the auditory nerve could be one such factor, as well as audiogram configuration and gender (based on prior experience and knowledge). As the dependent variable, we used the deviation of the measured SPRIN score from the predicted score (using the SII based algorithm). An advantage of this is that it is already corrected for peripheral hearing loss, which otherwise is a known factor that reduces speech in noise performance. As main explanatory variable, we used the interpeak latency of ABR waves I-V (IPL I-V) as an indicator for neural integrity. Additionally gender (binary) and audiogram configuration (four categories) were entered simultaneously in the model.

In **paper III**, the agreement between automated and conventional manual pure-tone audiometry was assessed by analysing means and standard deviations of the differences and the percentage of thresholds that corresponded within 0, 5, 10, 15 or >15 dB. The thresholds correspondence was also used to create an ordinal scale with five scale steps, ranging from perfect agreement (no difference between automated and manual thresholds) to poor agreement (automated threshold deviates by >15 dB compared with manual threshold).

The difference was defined as the pure-tone threshold obtained with automated audiometry in a specific ear and at a specific test frequency (e.g. left ear, 500 Hz) minus the equivalent threshold obtained with conventional manual audiometry. These differences were presented descriptively, and the limits of agreement for PTA4s were determined through Bland-Altman analysis. Based on reported test-retest variability data (Dobie, 1983), a difference of >10 dB at an individual frequency, or >7.5 dB for the PTA4, was considered clinically meaningful.

To test the influence of various factors on the agreement, a multiple ordinal regression analysis was performed. The ordinal scale of agreement described above was used as the dependent variable. As independent variables, age group (binary, 70 vs. 85), MMSE score (continuous variable) and PTA4 (continuous variable) were used.

In **paper IV**, multivariate multiple linear regression analyses were conducted to describe the association between hearing and cognition. As dependent variables, global cognitive function and domain-specific cognitive functions were used. Three models were created for each dependent variable, using either the PTA4 in the better ear, the SPRIN score in the better ear, or self-assessed hearing ability (three categories: no problems, mild problems, significant problems). Each model was adjusted for gender (binary), educational attainment (continuous variable, number of years of completed education), hypertension (binary), cardiovascular disease (binary), tinnitus (binary) and hearing aid use (binary).

Standardized regression coefficients were reported to enable comparison between the independent variables. The cognitive tasks were also divided in verbal and non-verbal tasks, to be able to judge whether any association between hearing and cognition was driven mainly by language aspects.

Table 9.

Paper	Dependent variables	Independent variables
I	▪ Hearing acuity in the mid frequencies, $\text{PTA}_{0.5,\ 1,\ 2\ \text{kHz}}$, and high frequencies, $\text{PTA}_{4,\ 8\ \text{kHz}}$. (*continuous*)	o Birth cohort (*3 categories*) o Gender (*binary*)
II	▪ Speech-in-noise recognition, relative to predicted score. (*continuous*)	o AN function (*continuous*) o Gender (*binary*) o Audiogram configuration (*4 categories*)
III	▪ Agreement of automated and manual pure-tone audiometry (*5 categories*)	o Age group (*binary*) o MMSE Score (*continuous*) o PTA4 (*continuous*)
IV	▪ Global cognitive score ▪ Working memory ▪ Semantic fluency ▪ Phonemic fluency ▪ Episodic memory (visual/ verbal) ▪ Logical reasoning ▪ Mental speed ▪ Visuospatial ability (*all continuous*)	o PTA4 (*continuous*) o SPRIN score (*continuous*) o Self-assessed hearing (*3 categories*) o Gender (*binary*) o Education (*continuous*) o Hypertension and CVD (*binary*) o Tinnitus (*binary*) o Hearing aid use (*binary*)

PTA: Average Pure-tone Threshold, AN: Auditory nerve, MMSE: Mini-Mental State Examination; PTA4: Average of Pure-tone thresholds at 0.5-4 kHz; SPRIN: Speech Recognition in Noise, CVD: Cardiovascular Disease.

3.3 ETHICAL CONSIDERATIONS

Research ethics involves the evaluation of risks and benefits, applicable to all aspects of the research process, including designing a project, formulating research questions, securing funding, selecting participants, publishing results and disseminating knowledge to the public. The possibility for participants to give free and informed consent is of particular relevance, as well as privacy and confidentiality issues. Epidemiological research specifically involves conducting detailed health surveys of the general population, aiming to establish the prevalence, distribution and determinants of various health conditions. Thus, an advantage of participating in epidemiological research is getting a comprehensive health examination free of charge. However, the outcome of the tests may involve revealing previously undetected health conditions, or the presence of risk factors or biomarkers of serious disease. It is therefore of ethical significance to offer participants information on how to interpret the findings of each of the tests, and advice on when and how to seek further medical care (Coughlin, 2006).

Ethical approvals for the studies included in this PhD Project were sought and granted in two separate applications. The basic audiological examination was covered by the ethical approval for the main H70-investigation, registration no: 869-13. For the hearing investigation specifically, some specific actions were taken to ensure ethical acceptability for the participants. For example, a written instruction on how to read and interpret the audiogram was provided. Participants who had questions about their results or hearing in general that could not be satisfactorily answered by the research nurses, were offered to discuss these with an audiologist (the author of this thesis). Participants in need of medical evaluation were advised to contact their GP.

Ethical approval for the extended audiological examination was granted under registration no: 976-13. As described earlier, those who were selected for the substudy received information and invitation through the post, and were thereafter contacted and briefed about the study via telephone. Particular care was taken to give potential participants sufficient time to understand the potential risks and benefits, and the right to decline or withdraw from the study. If accepting to participate, the signed and dated consent forms were brought along to the test occasion, at which point further opportunities to ask questions were offered. Photocopies of the consent form and test results were handed out. Any participant who needed referral to Ear Nose and Throat specialist services or Audiology Services were offered this. Those who needed hearing aids were offered appointments at Hörselverksamheten, Västra Götalandsregionen.

4 RESULTS

This chapter presents an overview of the principle findings from papers I-IV. Further details are available in the reprinted publications and manuscripts. Table 10 presents the results of selected self-reported hearing and ear related items, distributed as part of the somatic interview in the main investigation.

Table 10. *Percentage of the cohort (n=1203) that reported various ear and hearing related history and symptoms. Missing data was less than <3% for all items, apart from for 'self-reported hearing' where 7% of the data was missing.*

Questionnaire item	M	F	All
Family history of hearing loss, tinnitus or vertigo	29%	32%	31%
Ear disease (current)	19%	17%	18%
History of ear surgery	3%	1%	2%
Tinnitus – Any	33%	27%	30%
Not bothersome	*13%*	*9%*	*11%*
Somewhat bothersome	*15%*	*12%*	*13%*
Moderately bothersome	*3%*	*4%*	*4%*
Severely bothersome	*2%*	*2%*	*2%*
Self-reported hearing loss - Any	53%	49%	52%
Mild	40%	38%	36%
Significant	13%	6%	9%
Hearing aid use	11%	9%	10%

M: Male, F: Female

4.1 PAPER I

Air conduction pure-tone audiometry was performed in 1135 participants as part of the main investigation. The distribution of the pure-tone thresholds are presented in Figure 7 (below). There was a clear tendency of left ears being worse than right ears. Moreover, thresholds were worse in men than in women in the 3-8 kHz region.

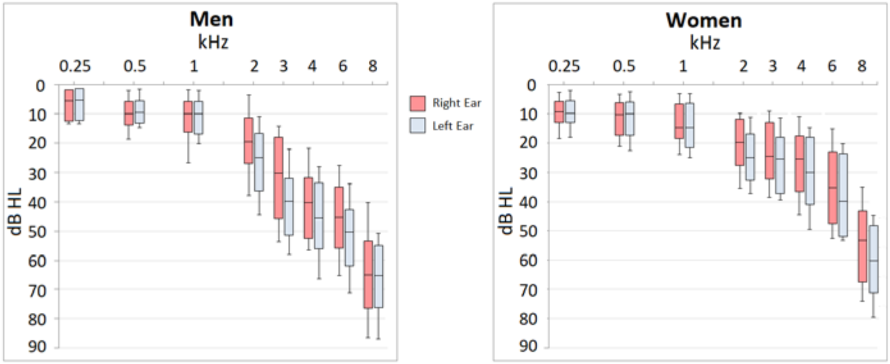


Figure 7. *Distribution of pure-tone thresholds among 70-year-old men (n=535) and women (n=600), split by ear. The whiskers represent the 10th and 90th percentiles. All percentiles were interpolated.*

The overall prevalence of hearing loss, defined as a PTA4<25 dB HL in the better ear, was estimated at 25% (95% CI: 23-28). For men this figure was 28% (95% CI: 26–30) and for women it was 22% (95% CI: 20–24). The prevalence of hearing loss was significantly better in the 1944 cohort compared to both earlier born cohorts ($p<.01$, pairwise Z-tests) for men as well as women, see Figure 8.

Figure 9 shows the differences in median pure-tone thresholds between the birth cohorts included in the comparison. These differences were significant, as tested with linear trend analysis (further details are available in the reprinted publication). Moreover, there was a significant interaction effect between cohort and gender, as well as cohort and education, suggesting that the improved hearing sensitivity was larger in men and participants with lower educational level. The latter finding was not included in the published article.

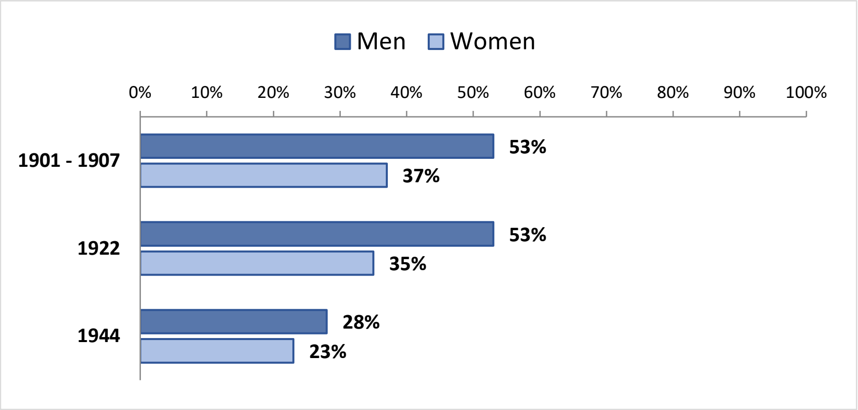


Figure 8. *Prevalence of hearing loss, defined as a PTA4 >25 dB HL in the better hearing ear in four birth cohorts of 70-year olds, born >40 years apart. (The two earliest born cohorts were merged for the purpose of this study).*

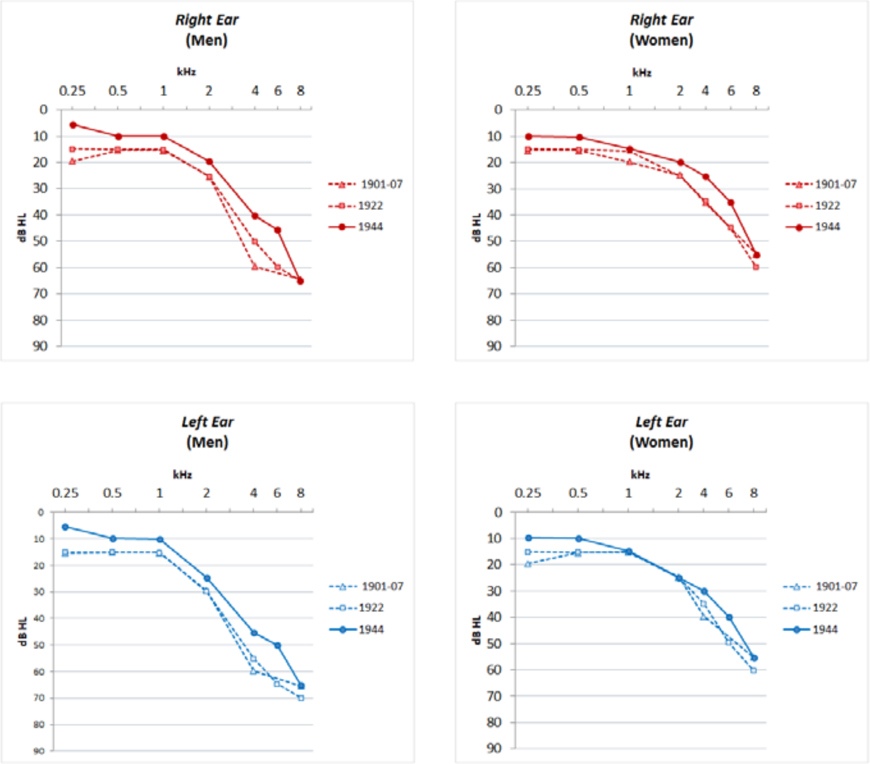


Figure 9. *Median pure-tone thresholds in four birth cohorts of 70-year-olds born more than 40 years apart (the two earliest cohorts were merged). The medians were interpolated.*

4.2 PAPER II

This study aimed to characterize ARHL based on a more comprehensive audiological test battery including both psychoacoustic and physiological measures. Descriptive statistics of all the tests are available in the reprinted publication. Hearing loss in either ear exceeding 25 dB HL (based on PTA4) was found in 51% of the sample (53% in men, 46% in women), of which approximately half were unilateral losses. Sensorineural hearing loss of cochlear origin was by far the most common pathology (Figure 10). Two percent of the sample were diagnosed with possible neural pathology, with poor speech in noise recognition and prolongation of the ABR interpeak latency of wave I-V. Two percent had conductive hearing loss in addition to cochlear (mixed).

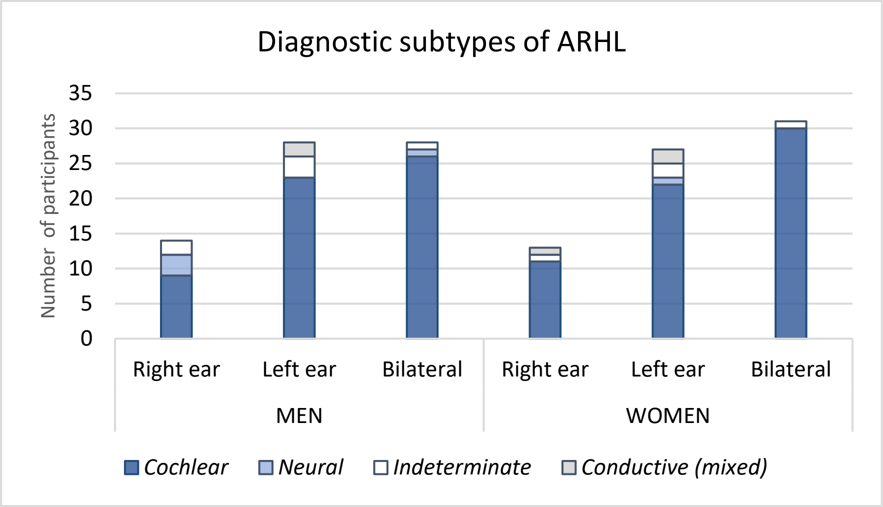


Figure 10. *Distribution of hearing loss by type of pathology and gender.*

Based on DPOAE findings, cochlear dysfunction was present in the vast majority of ears, even ears without elevated hearing thresholds (see Figure 11). The number of abnormal DPOAE results by test frequency and gender is available in the reprinted manuscript, showing that cochlear dysfunction increases with frequency, peaking at 99% for men at 6 kHz. Men had a higher rate of cochlear dysfunction at 3-6 kHz, whereas women had a slightly higher rate at 1.5 kHz.

Among men, 25-29% of participants had a speech in noise recognition score that was worse than predicted by the SII based algorithm. The corresponding figure among women was 12-13%. In the regression analysis, gender, audiogram configuration and ABR interpeak latency of wave I-V were identified as predictive factors of poor speech-in-noise performance, in the right ear only (Table 9).

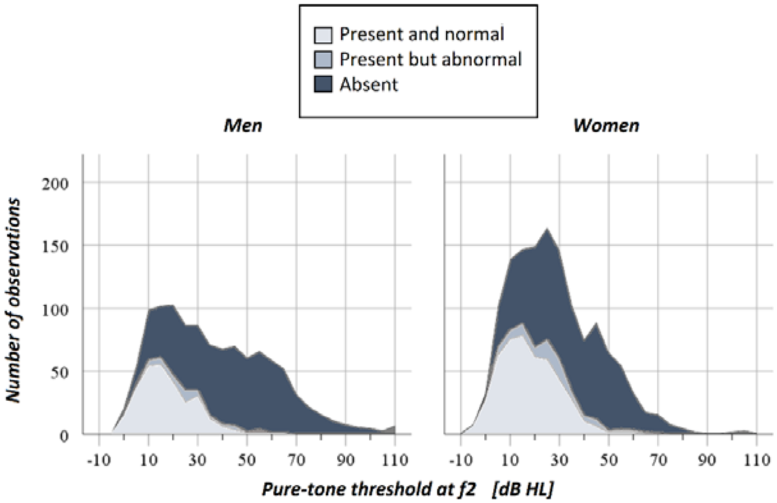


Figure 11. *Distribution of pure-tone thresholds depending on whether DPOAEs were present, present but abnormal or absent at the specific test frequency.*

Table 9. *Factors associated with speech recognition in noise in the right ear. Longer ABR latency and having a sharply sloping audiogram was associated with poorer performance, whereas being female was associated with better performance.*

Predictor	**Adjusted β[a]**	***p* value**	**R^2**
ABR, Interpeak latency of I-V	0.13	.042	0.13
Female gender	-0.15	.027	
Audiogram configuration	0.24	< .001	

Dependent variable: Deviation from predicted Word Recognition Score (SNR +4 dB). [a]Adjusted for other variables in the table.

The results for **paper III** and **paper IV** have been somewhat compressed since they contain unpublished data. For full details, please refer to the reprinted manuscripts.

4.3 PAPER III

In this paper, the agreement between air conduction pure-tone thresholds obtained with automated method (main investigation) and conventional manual method (extended investigation) was analysed. All analyses are based on individual differences, i.e. no group comparisons were made. There were no significant differences between left and right ears, why averages of these are reported. Further, men and women did not differ in terms of agreement. Taking both age groups and all frequencies into account, the mean difference between the methods was -0.7 dB (SD=8.8 dB). The agreement varied depending on test frequency. In the younger subjects, the agreement was poorer in the higher frequencies (4-8 kHz), whereas no such effect was seen in the older subjects. The proportion of measured thresholds that corresponded within +/- 10 dB, +/- 15 dB or >15 dB are seen in Figure 12.

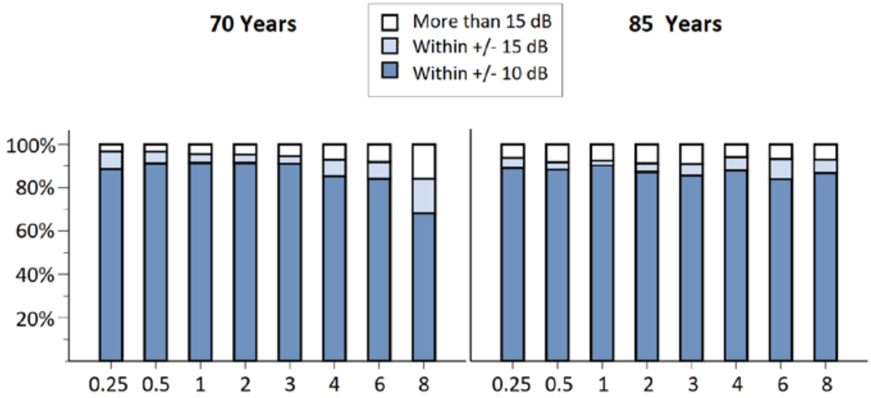


Figure 12. *Threshold correspondence within 10, 15 or >15 dB of the equivalent manually obtained pure-tone threshold.*

No significant associations were observed in the ordinal linear regression analysis, neither for age group, level of hearing, nor global cognitive function (MMSE score). However, the Bland-Altman analysis revealed larger variation in results in participants with mild hearing losses (70-year old subjects only).

4.4 PAPER IV

In **paper IV**, hearing function assessed with three different measures was cross-sectionally associated with cognitive function. A reasonably strong correlation (r=-0.6, p<.001) was found between the PTA4 and the SPRIN score in the better ear.

Poorer hearing was associated with poorer global and domain-specific cognitive function, adjusted for educational level, gender, cardiovascular factors, tinnitus and hearing aid use. However, this result only applied when considering measured hearing (pure-tone audiometry and SPRIN), and not self-assessed hearing (Table 11). Moreover, both pure-tone audiometry and SPRIN were associated with most cognitive domains, regardless of if assessed with verbally loaded or non-verbally loaded tasks, with SPRIN showing stronger effects. Self-reported hearing was weakly associated with two of the cognitive domains.

Additionally, hearing aid use was associated with better global cognitive function, whereas having tinnitus was weakly associated with better global cognitive function.

Table 11. *Linear regressions results for global cognitive function on three different measures of hearing. The hearing measure were included in three separate models adjusted for factors listed below the table. The R^2 values refer to the entire model.*

Independent variable	**β**	**(95% CI)**	**Adjusted R^2**
PTA4, better ear	-0.18	(0.22, -0.12)	0.193
SPRIN, better ear	0.34	(0.23, 0.44)	0.222
Self-reported hearing loss			
Mild, vs. none	-0.01	(-0.07, 0.01)	0.172
Significant, vs. none	-0.05	(-0.13, 0.03)	

Dependent variable: Global cognitive score*,* Adjusted for gender, educational level, hypertension, cardiovascular disease, tinnitus and hearing aid use

5 DISCUSSION

The first chapter of this section contains a discussion of the main results in relation to the overall aims of the thesis, as well as the specific aims of each paper. The second chapter provides a methodological discussion including strengths and limitations. The third chapter lists the implications of the results for clinicians and policy makers.

5.1 INTERPRETATION OF THE FINDINGS

The aim of this thesis was to investigate, explore and describe hearing function in early old age. The findings of **paper I** described the distribution of hearing thresholds and prevalence of hearing loss in an unscreened population-based sample of individuals aged 70 and compared it to earlier born cohorts. The perspective on hearing function was expanded in **paper II**, which reported on the findings of a detailed audiological examination in a subsample, allowing for identification of audiological profiles and specific pathologies. In **paper III**, the validity of the automated method used for determining hearing thresholds in **paper I** was described, and further explored by including corresponding data for a sample of 85-year old subjects. Finally, in **study IV**, different hearing measures, hearing aid use and tinnitus were analysed in relation to cognitive function.

5.1.1 PREVALENCE OF HEARING LOSS

Our finding in **paper I** that bilateral ARHL affects 25% in early old age, agrees well with other contemporary studies on samples of equivalent age (Bamini Gopinath et al., 2009; von Gablenz et al., 2020) that used the same definition of hearing loss (based on the pure-tone average over speech frequencies in the better ear). In spite of the limitations of this definition, which only accepts bilateral hearing losses, we chose to use it in order to facilitate comparison with other studies, as advocated by Roth et al. (2011). Further, the prevalence doubled to nearly 50% when also considering unilateral hearing losses, as was done in **paper II** (estimated based on the subsample). Additionally, in **paper IV** an overall prevalence of 46% was found for self-reported hearing problems (Table 2 in the reprinted manuscript), which actually corresponds better to the prevalence found when including unilateral hearing losses. The quandary of which definition to use to represent hearing loss in epidemiological studies is certainly a relevant issue. Considering that a major reason for estimating the prevalence of health conditions is to assess the need for rehabilitation, and the contribution to disease burden, it may be argued that the definition should be sensitive to individuals who indeed experience disability. Interestingly, in **paper IV** we found that the distribution of PTA4s among participants who reported experiencing mild or significant hearing problems overlapped considerably, i.e. there were participants with no or mild degree of hearing loss as indicated by pure-tone findings that still experienced problems. Overall, these findings highlight the complexity of describing the magnitude of hearing problems in the population using just one measure. By complementing the results of **paper I** with more detailed hearing data (**paper II**), the results of the present thesis can hopefully stimulate further discussions on how to best assess ARHL in population-based investigations.

5.1.2 TRENDS IN HEARING

As reported in **paper I**, the prevalence of ARHL was lower in the studied birth cohort (born in 1944) in comparison with earlier born cohorts from the H70 study. Since the largest improvements were observed in men and at 4-6 kHz, reductions in noise-exposure seems a plausible explanation. The fact that 4 kHz is particularly affected in noise induced hearing loss is well described in the literature (Le et al., 2017). However, the differences observed in **paper I** did affect other frequencies as well. Therefore, several other potential reasons must be considered, such as improvements in general health and nutrition. In fact, a shift in dietary pattern has been observed in the present birth cohort (1944) in comparison with earlier born cohorts (Samuelsson et al., 2019), indicating an increased intake of healthier foods, such as fish, fruits and vegetables and nuts and seeds. Engdahl et al (2020) recently observed a similar improvement in hearing among recent generations of the Norwegian population, where 70-year old subjects showed the largest increase in hearing acuity (around 10 dB). Additionally, in a new preliminary report (Engdahl et al., 2020), these improvements in hearing status were demonstrated to be driven mainly by higher educational attainment and reductions in noise exposure, as well as fewer recurrent ear infections, and lower prevalence of smoking among later born participants. At the time of publication of **paper I** of the present thesis, corresponding variables were unavailable for inclusion in the trend analysis. However, subsequent analyses (unpublished) showed an interaction effect between cohort and education, suggesting that the difference in hearing acuity between earlier and later born cohorts in the H70 study was significantly higher among participants with lower educational attainment. This may indirectly support the hypothesis that reduced occupational noise exposure explained the trend of better hearing, as observed in **paper I**.

Participants with lower educational level are likely to be over-represented among those with occupational noise exposure (through work in industry). Self-reported noise exposure was unfortunately not included in the hearing questionnaire in the recent cycle of the H70 study, however data regarding occupations and other sociodemographic factors are, and will be interesting to examine in future studies. Additionally, in **paper II**, the results indicated that the prevalence of conductive hearing loss was lower compared with earlier born cohorts, in agreement with the findings of Engdahl and colleagues. Only 2% (five ears) had confirmed conductive hearing loss in our study (**paper II**), which may be compared to ~6% in 70-year olds born in 1901-1922 (Rosenhall et al., 2011).

5.1.3 SUBTYPES OF ARHL

In **paper II**, we demonstrated that sensorineural hearing loss with a cochlear profile was the dominating pathology in the sample, but that 1 in 5 had poor speech performance in relation to their predicted scores, as calculated with an SII based approach. Through linear regression analysis, audiogram configuration, gender and ABR latency were indicated as factors explaining this finding. However, only a fraction (13%) of the variance in speech-in-noise performance was explained by these factors. Cognitive ability is likely a further factor, as demonstrated previously (van Rooij & Plomp, 1990) and supported by the fairly strong association found between cognitive ability and SPRIN score in **paper IV** of this thesis. Still, a rather significant amount of variance could not be explained by any of the aforementioned factors. CAPD is another potential reason for poor speech-in-noise performance in old age (Frisina & Frisina, 1997), but it is unclear to what extent this would be an important factor in our study since the SPRIN tests, which uses monosyllabic words and an unmodulated noise, is more of a peripheral test. One interesting finding in **paper II** was that male subjects were more likely to have poor speech-in-noise performance, even when taking peripheral hearing loss and audiogram configuration into account in the regression analysis (On average, men had worse hearing and more sloping audiograms, which increased the likelihood of poor speech recognition). We did not investigate this further in our study, but it is of interest to speculate why men might have poorer ability to perceive speech in noise. Some factors that could be of interest is that men likely are more noise exposed. Noise injuries have been shown to lead to alterations in the CANS, which may lead to hidden hearing loss, and may be involved the generation of tinnitus and hyperacusis (Eggermont, 2017). Another possibility is gender differences in cognitive function. For instance, in a meta-analysis (Hyde & Linn, 1988), men were shown to have poorer verbal ability than women.

5.1.4 HEARING MEASURES

In this thesis, hearing function was assessed with a variety of different methods, which provides an opportunity to reflect on the possibilities and limitations of these. One of the aims of **paper II** was to explore whether using both physiological and psychoacoustic measures could illuminate ARHL beyond what is possible when only including pure-tone audiometry, typically reported in epidemiological research. Although the description of auditory function based on physiological measures, such as DPOAE and ABR, in this population-based sample provides a valuable reference material for clinicians, we did not find support for general use of these measures in population-based studies. The use of DPOAE testing in population-based studies to screen for hearing loss is a tempting prospect, as it would save time and enable mass screening of large populations. However, such application of DPOAE testing is not supported by the findings of **paper II**, owing to the fact that there was considerable overlap in distribution of hearing thresholds in participants with and without pathologic DPOAEs. However, as a method of estimating cochlear dysfunction in experimental or clinical research it should be of great significance.

In **paper II**, pure-tone audiometry and speech in noise recognition were found to be the most valuable measures to characterize ARHL in population-based research. Additionally, audiogram configurations seem an important factor to include, which perhaps is an under-used one. One difficulty is certainly the wide range of configurations that occur, especially in unscreened samples. Although most of the hearing losses in our study (**paper II**) could be classified as either gradually or sharply falling (nearly 90% in men, and 65% in women), some did not fit any of the criteria. As mentioned, we found that having a sharply falling slope affected speech recognition, and in other studies, audiogram configuration has been linked to tinnitus (Demeester et al., 2007) and self-reported hearing problems (Hannula et al., 2011). The value of investigating audiogram configurations is not fully understood and therefore warrants further research.

The findings of **paper III** supports the use of automated pure-tone audiometry in old persons when screening for hearing loss. The fact that “younger old” and “older old” (70- versus 85-year-olds) showed similar levels of agreement, and that cognitive status was not identified as a significant predictor, suggests a broad application of this test. While the vast majority had results that agreed within accepted error margins of manual conventional pure-tone audiometry, a small – but not insignificant – proportion showed large deviations that would not be acceptable in a diagnostic setting. Due to the study design, it is rather difficult to ascertain whether these large deviations were caused by using an automated method specifically, or other factors. Possible alternative explanations range from data input errors, methodological issues (such as the lack of contralateral masking in the automated procedure), or a true change in hearing level between the two measurement occasions. In general, the time that passed between the automated test and the conventional test was ~1 month, but significantly longer in some cases, due to participants not being available for the suggested appointment (many travelled out of town to summerhouses etc.). Further research exploring why the method fails in some individuals is needed.

5.1.5 HEARING AND COGNITION

Our finding in **paper IV** that poorer hearing was associated with poorer cognitive function, supports the evidence of a robust link between hearing and cognition in ageing, which has been demonstrated by a range of studies to date (Alattar et al., 2020; Amieva et al., 2015; Dawes et al., 2015; Deal et al., 2015; Gurgel et al., 2014; Jayakody et al., 2018; Lin, 2011a; Lin et al., 2011b; Uhlmann et al., 1986). In our study, we were able to compare the effect on cognitive function depending on which measure was used to assess hearing ability. Contrary to several other studies (Amieva et al., 2015; Curhan et al., 2019; Zekveld et al., 2013), we did not find any significant association with the self-report hearing measure, which highlights the importance of measuring hearing psychoacoustically rather than relying on self-report measures in population-based geriatric studies, something which is frequently not done. It is possible that the self-report measure was not sensitive enough to detect an association with cognitive function at this particular age (70 years), when the cognitive health is still good for the vast majority of people. Alternatively, the particular measure that was used was inadequate (only three categories were used). However, it has previously been found to be valid in relation to pure-tone audiometry (Pedersen & Rosenhall, 1991).

It was interesting that the association between objectively measured (rather than self-reported) hearing was associated with nearly all cognitive domains, regardless of whether the task was verbally or non-verbally loaded. It may be tempting to assume that hearing and cognitive impairment are only associated due to measurement bias, since many cognitive tasks rely on hearing, but the results from **paper IV** do not support this. Rather, it seems that there is a more general relationship between hearing and cognition.

In **paper IV**, participants who used hearing aids were found to have better global cognitive function, although the effect was rather weak and only applied in some of the models. Several interpretations of this finding are possible. One is that participants using hearing aids retain good cognitive function as a direct result of using amplification, perhaps through preventing social deprivation and changes in the central auditory pathways. Alternatively, the use of hearing aids enable old people to remain socially engaged and active, which indirectly promotes good cognitive function. A further option is that persons with poor cognitive function do not benefit from amplification and therefore do not use hearing aids. It is also conceivable that social and demographic factors influence this relationship, e.g. people of lower socioeconomic status may be less likely to use hearing aids. However, the fact that we adjusted for educational attainment in all models of **paper IV** contradicts that idea. In our study, hearing aid use was assessed with a dichotomized item (yes/no). More detailed information on whether the hearing aid was used in one or both ears, hours of usage per week etc. would strengthen the analysis. Additionally, the prevalence of hearing aid use was very low at this age, which decreased the power.

Surprisingly, the presence of tinnitus (dichotomized outcome) was associated with better cognitive function in **paper IV**. This finding is rather difficult to explain, since there is evidence of tinnitus being associated with poorer cognitive function (Tegg-Quinn et al., 2016). However, most studies to date are not performed in population-based samples. The analysis on tinnitus and cognition in our study may have been more informative if tinnitus severity and other factors, such as depression and anxiety, were taken into account. Further research in this area would certainly be of interest.

5.2 METHODOLOGICAL CONSIDERATIONS

5.2.1 STUDY DESIGN

This thesis used cross-sectional methodology to study hearing function and associated factors. Cross-sectional studies provide a snapshot of a population at a specific time point. While this is the method of choice when studying prevalence, which was an aim of **paper I** and **paper II**, it is insufficient for establishing causal relationships between variables. In **paper IV**, we investigated the effect of hearing on cognitive function. We used previous knowledge to hypothesize the direction of the association, and we adjusted for confounding factors based on knowledge from previous studies. Yet, it is not possible without longitudinal data to ascertain the directionality of the association, which is a limitation of **paper IV**.

In **paper III**, we aimed to investigate the validity of automated pure-tone audiometry. However, due to the population-based design we were not able to control for other factors that may have influenced the results, such as the time between test occasions or choice of headphones. An experimental study design would have been better in this regard. On the other hand, the population-based design permitted a large sample size and the availability of data regarding other factors (such as educational level) that were interesting for the study. Moreover, the results are probably more applicable to real life situations since the sample was reasonably representative of the general older population.

The use of age-homogenous samples has both advantages and disadvantages. Most importantly, it removes age as a confounding factor that otherwise would need to be adjusted for. On the other hand, it only provides information at a specific stage in ageing, which could be a limiting factor. In **paper I**, age-homogeneity increased the comparability of the different birth cohorts, which was a strength. In **paper II** however, it could have been interesting to include a range of ages to generate data for older persons in general. In **paper IV**, using an age-homogenous sample provided a description of the well-studied association between hearing and cognition in early old age specifically, which provided new insights.

5.2.2 SAMPLING AND REPRESENTATIVENESS

The ambition was to achieve representative samples in all four papers, striving for generalizability of the results to the general population of early old age. The high response rate of the 1944 birth cohort (72%) is certainly a strength in this regard, as are all the steps taken to ensure inclusion, such as offering domiciliary visits (main investigation) or transports (extended audiological investigation). Nevertheless, some groups of people are not fully represented in the present thesis. For example, in the 1944 birth cohort, some individuals that were eligible for participation in the study were not included due to very poor health. Thus, the birth cohort is likely somewhat biased towards healthier individuals, which is a general problem in epidemiological research. Moreover, the subsample that participated in the substudy was selected at random (based on birth dates), but still may have unintentionally excluded some groups, e.g. responders were found to have higher educational level than non-responders did (**paper II**). There was also a tendency of overrepresentation of participants with perceived hearing problems, possibly because of the perceived value of getting a detailed hearing check and a hearing aid consultation.

In **paper I**, pure-tone audiometry was not included during domiciliary visits, which may have been chosen by less healthy participants. However, this accounted for a small percentage of the sample (3.8%) and therefore likely did not skew the results. Moreover, for **paper III** and **paper IV**, samples were drawn from the birth cohorts and their subsamples according to specific criteria, which once again means a step away from full representativeness. In **paper III**, the 85-year old study sample in particular differed from the original birth cohort (born in 1930) in a number of respects. Men were over-represented, as were participants with higher education and better cognitive function. In **paper IV**, participants with dementia were excluded. A dementia diagnosis was very rare in the 1944 cohort at age 70, and many of those with dementia had not completed the advanced cognitive test battery or hearing tests, therefore it was not meaningful to include these. Moreover, there may have been other health factors responsible for missing data in some participants. Some were too tired to complete hearing and/or cognitive testing, both of which involve reasonably demanding tasks.

5.2.3 CHOICE OF TESTS

In the four papers presented in this thesis, hearing was assessed with a battery of tests, which is a strength. The rationale for using automated pure-tone audiometry in the main investigation was that it could be administered by the same research nurses that conducted most other tests, and hence could more easily be included in the test protocol. Considering the number of hearing tests performed (n=1135) and the length of the study period (2014-16), it was also a way of saving on resources that could instead be used for other parts of the study that required the expertise of audiologists. For similar reasons, it is more and more common to use automated methods in population-based investigations. The fact that we were able to validate the automated method against the gold standard in a subsample further strengthened our choice. The hearing questionnaire was kept the same as in previous H70 cycles, to allow for time trend analysis. Some items were added, such as separating occurrence of tinnitus from severity of tinnitus, which was previously assessed with the same question (i.e. assuming that having tinnitus sometimes meant not being bothered). It would perhaps have been good to use a standardized international questionnaire, to be able to compare the results with other studies.

The rationale for selecting the various tests included in the extended audiological investigation was that these were widely used tests with documented validity and reliability that made it possible to distinguish between specific pathologies and audiological profiles. In addition to gold standard pure-tone audiometry, The SPRIN test was included to assess ability to hear supra-threshold stimuli, and speech signals specifically, since communication is the most important hearing function. SPRIN is routinely used in clinics in Sweden, and is well-researched (Magnusson, 1995, 1996a, 1996b; Magnusson et al., 2001). Additionally, the availability of an SII based algorithm for predicting scores was seen as a strength. DPOAE and ABR were used as physiological examinations of auditory functions. DPOAEs provide frequency specific information, which was seen as an advantage, and ABR is a highly reliable measurement which is sensitive to auditory neural function. A test of central auditory processing was also included, the Dichotic Digits Test, but is not used in any of the papers of the present thesis.

Some limitations existed with the test battery that was used. For example, the use of supra-aural TDH-39 transducers led to problems with collapsing ear canals in some individuals. Insert ear phones could have been better in that respect, but have other disadvantages. Importantly, these are not routinely used in Sweden. Another limitation is that the SPRIN test uses monosyllabic words for stimuli, whereas normal day-to-day conversations consist of sentences. Further, we used a 70/70 dB SPL stimulus to elicit DPOAEs, which has been found to sometimes produce artefacts, i.e. false emissions (Petersen et al., 2018). However, steps were taken to eliminate false positives as far as possible (further information is available in the reprinted publication, **paper II**).

For the ABR testing, the same person interpreted the results and identified the wave peaks, for consistency. However, it may also be argued that using two different raters could have increased the reliability. Furthermore, we only analysed latencies in **paper II**, whereas amplitudes could have been interesting as well.

The cognitive test battery used in **paper IV** has strengths and limitations. Using a standardized neuropsychiatric test battery has many advantages over widely used screening instruments, such as the MMSE. For example, it allows for measuring domain-specific cognitive abilities. The MMSE is known to produce ceiling effects and for not being sensitive to small variations in cognitive function (Devenney & Hodges, 2017). It has also been shown to potentially lead to biased results in persons with hearing loss, especially in verbal parts of the test (Gates et al., 1996). The global cognitive index that was created for **paper IV** was normally distributed in the sample, which strengthens the results of the linear regression analysis. On the other hand, it may be less comparable with other studies that used different cognitive test batteries.

5.3 STRENGTHS AND LIMITATIONS

In general, a major strength for this thesis is that the samples were large, well characterized, and had good response rates. Some of the strengths and limitations were already highlighted in the previous subchapter (under ‘methodological considerations’), such as the value of using both physiological and behavioural measures of hearing, as well as using a standardized neuropsychiatric test battery. Additionally, some specific strengths and limitations of each paper are summarised below:

A strength of **paper I** was that the trend in hearing was investigated over a long time period, nearly 50 years, and that the birth cohorts that were compared were sampled and tested in very similar ways. A limitation was that pure-tone audiometry was conducted with an automated method in the most recent born birth cohort, and with different headphones, in comparison with the earlier born birth cohorts. The implications of these discrepancies were discussed in the published paper. A further weakness was that we did not investigate potentially explanatory factors in the modelling, which would have been of interest.

A strength of **paper II** was that the sample was large, considering the amount of testing that was done, and was found to be representative. A further strength was that the combination of tests allowed for more specific identification of subtypes than typically reported in population-based studies. A potential limitation was the lack of information regarding central auditory processing ability.

The main strength of **paper III** was the focus on older persons specifically, which has not been done in previous studies on the validity of automated pure-tone audiometry. Another strength was the inclusion of factors that could affect the agreement, such as age group, hearing level and cognitive status. A limitation was that no test-retest data were available for automated pure-tone audiometry and that a relatively long time period passed between test occasions in some cases.

In **paper IV**, the major strength was the combination of using different types of hearing measures and a detailed cognitive test battery, which allowed for exploration of the association beyond what has been done in many previous studies. A limitation was that the independent variables of the linear regression analysis were not explored in terms of whether they were main effects, mediators or moderators. Another limitation was that the data was cross-sectional.

5.4 IMPLICATIONS

The results of papers I through IV have a number of implications for policy makers and clinical practice.

Although the prevalence of bilateral hearing loss was considerably lower in the latest born birth cohort (**paper I**), born in 1944, the projected rise in the proportion of older persons will lead to a higher number of people with ARHL in the population, and the demand for hearing rehabilitation will consequently increase. Modern hearing aids can help with a wider range of hearing losses, both in terms of degree and type, compared with the hearing aids that were available during the lives of the earlier born cohorts in paper I. Old persons today are also more likely to work (Larsen & Pedersen, 2017) and engage in other activities that require good hearing.

An important implication of the observed lower hearing loss prevalence among 70-year olds born in 1944, is that it is possible to prevent ARHL by modifying environmental risk factors. It is encouraging that work-place noise regulation may have led to an effect on public hearing health, but it is important to remember that many occupations exist where risk for hearing impairment is still imminent. For instance, preschool teachers have been demonstrated to be at increased risk for several self-reported hearing symptoms (Fredriksson et al., 2019). Exposure to lower noise levels than those regulated in work places for long periods of time has also been shown to possibly cause hidden hearing losses (Eggermont, 2017). Thus, the need for interventions that prevent hearing loss and its associated negative effects is high.

In spite of hearing aids being available free of charge in the Gothenburg region, the prevalence of hearing aid use observed in **paper IV** was low. Given the fact that poorer hearing was associated with poorer cognition and that hearing aid users had better cognitive function, there are good reasons to take actions to improve hearing aid uptake. In **paper III**, we demonstrated that automated pure-tone audiometry produces accurate assessments of hearing in the majority of “younger old” and “older old” persons. This method could relatively easily be implemented in a number of places, such as primary care units or nursing homes, which may serve to increase the availability and accessibility of hearing tests for old persons. In the long run it may also lead to a higher number of people being fitted with hearing aids.

Furthermore, given the reasonably strong association between speech-in- noise performance and cognitive function observed in **paper IV**, and the relatively large proportion of participants that performed poorly on the SPRIN test (**paper II**), it is important to reflect on how hearing rehabilitation should be devised. Hearing aid provision is the standard intervention to alleviate hearing problems, but amplifying sounds may not be sufficient to improve speech understanding, functioning and quality of life in patients with hearing loss of neural or central origin, or with worse cognitive function. Thus, it is very important that hearing rehabilitation be expanded beyond hearing aids. Provision of assistive listening devices, and teaching communication strategies, preferably in a group setting and involving communication partners, are examples of interventions that may increase the beneficial outcomes of hearing rehabilitation and minimize the negative effects of hearing loss (Kricos, 2006; Malmberg et al., 2017).

Furthermore, there is a need for higher awareness among clinicians and researchers working with geriatric patients of the powerful link between hearing and cognition in old age (observed in **paper IV**). For example, not appropriately controlling for hearing loss in studies on cognitive function may lead to erroneous results in some instances. There is also a risk of inadequate clinical cognitive assessments in persons with hearing loss unless competence in hearing issues is available. Some cognitive screening tests have been adapted to better suit persons with hearing loss, but these are not routinely used (Shen et al., 2016). Moreover, audiologists encounter old persons with cognitive problems on a daily basis, and could therefore be viewed as important gatekeepers that identify patients with mild cognitive impairment or dementia. A better coordination of healthcare services addressing hearing and cognitive impairment would probably lead to better outcomes.

6 CONCLUSIONS

Based on the results of **papers I-IV**, the following conclusions are made:

- The prevalence of bilateral ARHL is approximately 25% at age 70. If including unilateral hearing losses this figure rises to 50%,
- The prevalence of hearing loss is lower among 70-year olds born in 1944, compared to earlier born birth cohorts, and the difference is larger in men.
- Cochlear pathology is the predominant underlying cause of ARHL at age 70, while ~2 % have auditory neural pathology.
- ~20% have poor speech in noise performance, which is partly explained by having a sharply sloping audiogram configuration, having a prolonged ABR interpeak latency (I-V) and being male.
- Conductive pathology (mixed type) affects ~2 %. The occurrence conductive hearing loss has decreased compared to earlier born cohorts.
- Cochlear dysfunction, determined with DPOAEs, is common – even in ears without elevated hearing thresholds. DPOAEs are not suitable to screen for hearing loss at age 70.
- Automated pure-tone audiometry (air conduction) provides accurate assessments of hearing in the majority of ‘younger old’ and ‘older old’ persons. Cognitive function was not associated with the accuracy.
- Poorer hearing – measured with pure-tone audiometry or speech in noise recognition test - is associated with poorer global and domain-specific cognitive function.
- Self-assessed hearing is not associated with cognitive function and hearing aid use is associated with better global cognitive function.

7 FUTURE PERSPECTIVES

Given the amount of available data on hearing parameters in the 1944 birth cohort (in focus of the present thesis), there are plenty of opportunities for further studies on hearing in early old age. For instance, describing the prevalence and severity of tinnitus, determining risk factors for ARHL and investigating cross-sectional associations with other variables, such as visual loss, vertigo, depression etc. Furthermore, all studies presented in the present thesis were cross-sectional. There is currently an ongoing follow up being done of the 1944 cohort, at age 75, which includes a hearing evaluation. With the availability of longitudinal data in this cohort, many interesting prospects arise. Based on the findings of this thesis, future research should focus on:

- Pinpointing the underlying factors explaining the trends of improving hearing. A better understanding of modifiable risk factors of ARHL could further reduce the associated global burden of disease.

- Investigating trends in the incidence of ARHL and other ear and hearing related symptoms, like tinnitus and vertigo.

- Investigating whether rehabilitation outcomes in old persons could improve by taking audiological diagnostic profiles into account.

- Assessing the prevalence and nature of central auditory processing disorder in early old age.

- Further exploring the risk for cognitive decline and investigating whether it is different depending on subtype of ARHL, including audiogram configurations and specific pathology.

- Ascertaining whether hearing aids can delay the onset and progress of cognitive decline, and – if so – whether any such delay is caused by increasing the afferent input to the central nervous system or by alleviating the social effects of ARHL.

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