Peripheral *and* Central Aspects *of* Age-related Hearing Loss

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Peripheral and Central Aspects of Age-Related Hearing Loss

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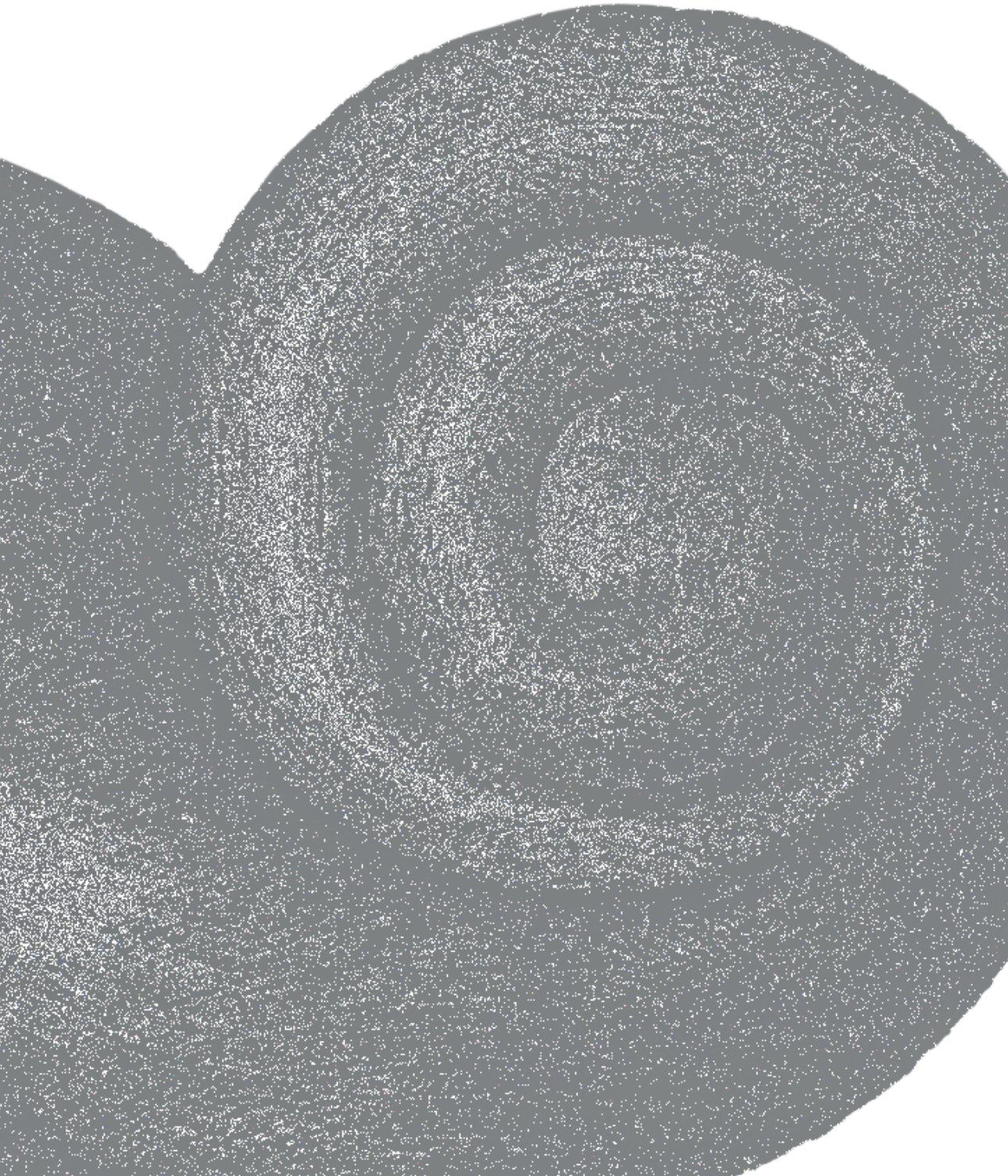

1

General introduction

PRESBYCUSIS

Presbycusis is derived from the Greek words *presbus* and *ákousis*, literally meaning old men and hearing. It refers to hearing loss associated with aging. In 1891, Hendrik Zwaardemaker, a Dutch otolaryngologist, was the first to describe high frequency hearing reduction correlated with higher age by measuring the best heard frequencies at certain ages. In 1929, Cordia Bunch, a clinical audiologist, developed the first audiometer in the United States and conducted hundreds of audiograms. By analysing them he observed that presbycusis was more severe in men than in women. From that time on a lot of research on presbycusis has been done. Several large population-based cohort studies such as Framingham[1], the Baltimore Longitudinal Study of Aging[2], the Beaver dam Study[3], the National Health and Nutrition Examination Survey[4] and the Blue Mountains Study[5] studied presbycusis. They confirmed earlier assumptions: an increase of hearing loss with higher age and average worse hearing thresholds for men than for women. A typical sloping pattern on the pure-tone audiogram is seen, as presbycusis predominantly affects the high frequencies. In general it is a progressive and irreversible sensorineural type of hearing loss. The Global Burden of Disease[6] defines the following classification for moderate hearing loss, which is often used in literature: an average hearing threshold of 35 decibels or more on 0.5, 1, 2, and 4 kilo Hertz (kHz) in the better ear. Currently, an estimated 1.27 billion people worldwide suffer from age-related hearing loss, making it the fourth leading cause of disability globally[7]. Even more, due to aging of the population prevalence numbers are expected to rise in the near future.

In literature terms as presbycusis, age-related hearing loss and age-related hearing impairment are used simultaneously and interchangeably. Often, presbycusis is used to describe hearing loss in aging adults, but in fact it is impossible to study just the effect of aging. Hearing loss or impairment in older adults comprises not just aging as a relevant factor, but actually all effects of life on our auditory system. It therefore also comprises genetic, ototoxic, environmental (*e.g.* noise-induced hearing loss) and co-morbidity associated causes which together make up for the accumulating effect on our hearing. Accordingly, in this thesis we choose to use the terms age-related hearing loss and age-related hearing impairment when we reflect on the hearing acuity of middle aged and older adults.

PERSONAL AND SOCIAL IMPACT

Age-related hearing impairment varies in age of onset and progression. It can already emerge in middle aged people and the prevalence doubles with every decade of life (Figure 1).

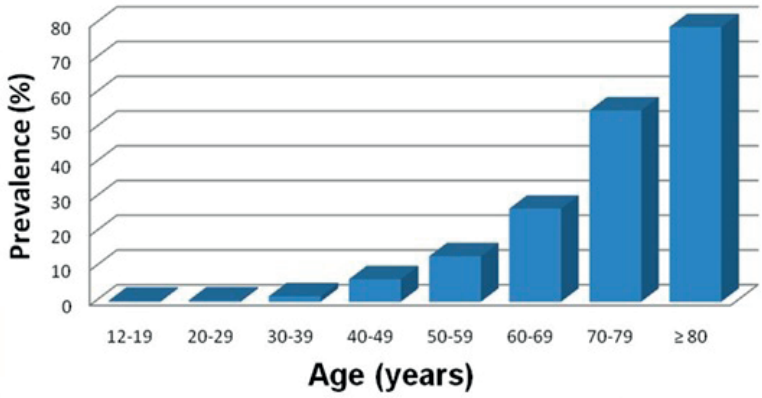

Figure 1. Prevalence of hearing loss of 7,490 individuals of the NHANES survey (United States) defined as a better ear pure-tone mean threshold of 0.5 – 4 kHz > 25 dB. Based on table from Lin et al [10].

Typically, age-related hearing impairment starts with loss of hearing sensitivity in the higher frequencies and progresses over time to the mid- and lower frequencies, which contain the speech frequencies[8]. As a result the ability to understand speech declines. This leads to communication difficulties, especially in places with competing noise such as a birthday party or work-meeting. Hearing loss can therefore have a significant impact on one's daily life: the diminishing ability to communicate can affect a person's employment opportunities and self-esteem and possibly lead to social isolation[9]. Hearing loss does not only has an influence on the relation with relatives and the surrounding community, it also affects the autonomy of a person by increasing dependence of its environment. People with age-related hearing loss are less satisfied with their life as a whole. Only 39% of the hearing impaired individuals scored a very good quality of life versus 68% in the normal hearing population[10]. It is not surprising that age-related hearing loss has been associated with a higher rate of depression[11]. Hearing loss and its burden is often underestimated while it can affect a person's social, psychic and physical well-being[12].

As a result of the high prevalence and the chronic character of age-related hearing impairment it comes with high health care costs for society. A large proportion of these costs includes those spent on prevention (*e.g.* less noise exposure) and on additional care for the above-mentioned factors such as social and physical well-being. Another amount includes the costs of hearing aids. Although hearing rehabilitation is often possible, only a small percentage (<20%) of the people who would benefit from hearing aids actually wears them[13]. For a greater part this is caused by the associated stigma[14]. Also, a lot of people who intend to wear hearing aids have trouble adapting to them which often results in non-usage. Relevant factors for non-usage among people are unawareness of their impairment, low technological commitment, low social economic status and worse health[15]. Besides motivating people to wear hearing aids, it is also

important to invest in prevention and in the early detection of hearing loss, as this will eventually lower the incidence of hearing loss and thereafter the costs for society[16].

NORMAL HEARING AND THE PATHOPHYSIOLOGY OF AGE-RELATED HEARING LOSS

The cochlea is a spiral shaped tube in the petrous part of the temporal bone of the skull. It contains three compartments along the spiral shape. The two lateral compartments, the scala vestibuli and scala tympani, are filled with perilymph. The central compartment, the scala media, is filled with endolymph and contains the stria vascularis and the basilar membrane with the organ of Corti. The stria vascularis is the main vascular supply of the cochlea and produces the endolymph. The basilar membrane and organ of Corti are the receptor organs for our hearing. When sound reaches the inner ear it is transmitted as pressure waves in the perilymph. This will in turn cause displacement of the basilar membrane.

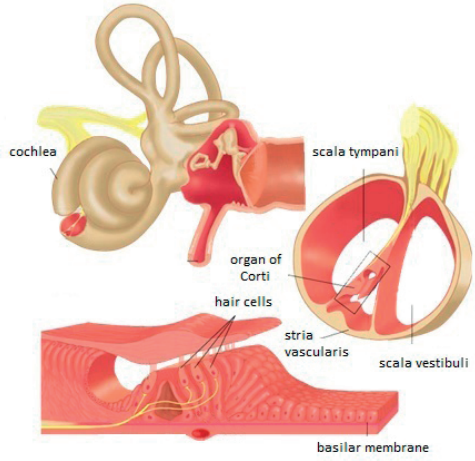

Figure 2. Anatomy of the cochlea (adjusted from audiologieboek.nl).

The basilar membrane has a different width and impedance along its length: it is more narrow and stiff at the base and more wide and floppy at the apex. In this way high frequencies are encoded at the base and low frequencies at the apex of the cochlea. This spatial arrangement is often referred to as tonotopy. The hearing range for humans is 20 to 20,000 Hz. If the basilar membrane moves, the organ of Corti is activated. The receptor cells in the organ, the hair cells, respond. Hereafter neurotransmitters make sure the signal is proceeded via the vestibulocochlear nerve via the higher auditory system to the auditory cortex in the brain. The auditory cortex lies in the temporal lobe of the brain.

The higher auditory system consists of afferent and efferent connections. The afferent connections function as the microphones of our hearing, while the efferent connections function as a feedback system from the brain to the cochlea. They play a role in the perception of and adaptation to sound. This top-down process from central to peripheral is still poorly understood.

A landmark study on the pathophysiology of age-related hearing loss was done by Schuknecht in 1974. He assigned histopathologic findings in the cochlea to audiometric patterns[17]. A high frequency loss on the pure-tone audiogram and loss of hair cells in the Organ of Corti, was defined as *"sensory hearing loss".* Several other typical pure-tone audiogram outcomes and histopathologic findings in the cochlea were determined and classified into groups. Although various researchers question this classification, it continues to be used as a framework on age-related hearing loss nowadays. After Schuknecht's study far more research has been done, but it appears no single pathological finding can account for the clinical variance seen in age-related hearing loss[18]. He was the first to show age-related hearing loss is a multifactorial problem of the cochlea and thereby a very heterogeneous disorder.

MULTIFACTORIAL DISEASE

Besides cochlear aging, it seems other factors take part in the underlying pathophysiology of age-related hearing loss[19]. These factors can be divided into demographic factors such as gender and social economic status, medical conditions such as cardiovascular risk factors, diabetes mellitus, obesity and cognition, lifestyle related factors such as noise exposure, smoking and alcohol, and genetic susceptibility. Consensus on these factors has not yet been reached, but strong associations between male gender, noise exposure, cigarette smoking, and diabetes mellitus exist. Although this is not consistently across all studies. Moreover, it is very difficult to point out the exact share of genetic variation because it is hard to separate genetics from environmental influences[20]. Clearly, besides a heterogeneous disorder, age-related hearing impairment is also a multifactorial disease.

CENTRAL AUDITORY SYSTEM AND THE BRAIN

As referred above, age-related hearing loss was initially thought to derive from aging of the cochlea and external effects on the cochlea. Nowadays, an increasing number of studies focus on changes further up in the central auditory and cerebral system. Processing of sound is not limited to the cochlea. The integrity of neuronal networks is thought to impact on auditory functioning. Even more, it is also said that changes in the health of our brain are related in some way to the pathophysiology of hearing loss. Brain health is an emerging concept that

encompasses function and plasticity of the brain during the life course. Differences here could explain why some older adults have more trouble in processing sound than others in spite of similar hearing thresholds.

Our brain consists of grey and white matter. Grey matter contains the brain's neuronal cell bodies and is the central processing unit while white matter contains mostly myelinated axons and acts as communication device between the grey matter. Commonly used techniques to study the morphology of grey and white matter are standard magnetic resonance imaging (MRI) and a specific MRI technique called diffusion tensor imaging (DTI). MRI is used to study the volume of grey and white matter and DTI is used to study the quality of the white matter microstructure by determining the diffusion of the water molecules within.

There have been a few studies performed on the relation between age-related hearing loss and grey or white matter (brain morphology). Recent studies have found evidence for reduced cortical volumes and worse organized white matter microstructure in both auditory and non-auditory regions in relation to hearing impairment. However, the results are not uniform, sample size were small (N maximum = 47) and possible causal directions remain unclear.

HYPOTHESES ON THE RELATION BETWEEN HEARING LOSS AND BRAIN HEALTH

In a relation between age-related hearing loss and altered brain morphology or brain health, in theory, there are three possible hypotheses on the causality of hearing loss and morphological brain changes.

The first hypothesis posits the idea that age-related hearing loss affects the brain by diminished sensory input which can lead to reorganization of the brain due to plasticity, or atrophy. This hypothesis is called the *"sensory-deprivation hypothesis*". In animal studies tonotopic reorganization of the auditory cortex was seen following hearing loss[21]. Although volumetric changes with MRI were not studied, this evidence could plea for the sensory deprivation hypothesis since hearing loss affects the brain. Altered grey and white matter was also found in prelingually deaf people[22]. This, however, did not concern gradual hearing loss as in age-related hearing loss.

The second hypothesis posits that brain alterations result in hearing loss and is therefore called the "*central-component hypothesis*". Although there is limited evidence for this hypothesis, in theory brain alterations could affect the hearing system in a way that it leads to hearing impairment. Multiple efferent connections from brain to the peripheral hearing system exist,

providing a feedback system. In addition, sensory deprivation related to brain changes was found in other age-related sensory transformation processes such as macular degeneration or constant pain[23, 24], implying as possible evidence for this hypothesis.

The third hypothesis posits a causal mutual factor, other than age, to cause both age-related hearing loss as brain alterations. This could possibly be an underlying pathological factor such as a cardiovascular disease, but also cognition. This hypothesis is called the "*common-cause hypothesis*".

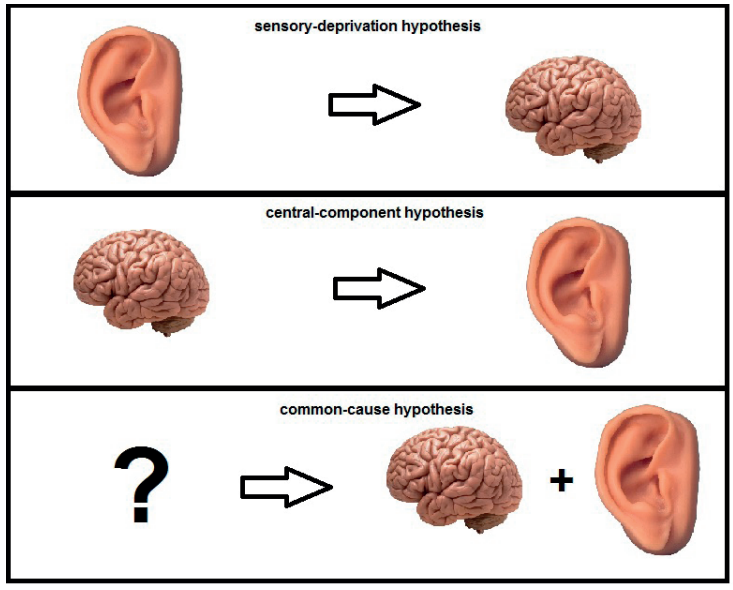

Figure 3. Schematic presentation of the three hypotheses on age-related hearing loss and brain health.

For the "*central-component hypothesis*" and the "*common-cause hypothesis*" we would expect brain alterations throughout the brain instead of local effects in the auditory regions. Moreover, we would expect that wearing hearing aids does not influence the effect found in the brain. While if the "*sensory-deprivation hypothesis*" would be accurate, it would be expected to find explicit changes in the temporal lobe when compared to other brain regions because auditory processing is predominantly located here.

POPULATION-BASED RESEARCH

The results and conclusions of this thesis are based on data from the Rotterdam Study, a population-based cohort study[25]. This type of study aims to answer questions on population

level rather than on the individual level or in a clinical population. This kind of research is an important tool if one wants to study a common disease like age-related hearing impairment with multiple phenotypes and possible multifactorial causes. To detect small effects or inferences a large population is needed.

The Rotterdam Study is an ongoing, prospective, population-based cohort study comprising the inhabitants of Ommoord, a Rotterdam district. The study targets to investigate the health in the aging population. Research focuses on cardiovascular, neurological, endocrine, respiratory, locomotor, dermatological, ophthalmic and otolaryngological diseases. The study started in 1990 with 7,983 participants aged 55 years and older who lived in Ommoord at that time. At present, four cohorts have started and the study contains almost 15,000 participants. Inclusion now starts at the age of 45 years. The overall response rate for participation to the Rotterdam Study is 72%.

At enrolment participants are interviewed at home and undergo an extensive set of examinations in the research centre. These examinations are repeated every 3 – 4 years at follow-up. Furthermore, there is close contact with the general practitioners to remain informed on new diagnoses.

From 2011, hearing assessment was implemented. Pure-tone audiometry and a simplified speech-in-noise test were conducted to test both pure-tone thresholds as speech perception in noise. Furthermore, questionnaires on *e.g.* hearing aid use were held. For this thesis, we used the data collected from 2005 until 2016.

SCOPE AND OUTLINE OF THE THESIS

The main objective of this thesis is to contribute to a better understanding of age-related hearing loss and its possible association with a central brain component. After exploring the inquiries within this topic, we are in particular interested in the following questions;

1. Which determinants, other than age, can be identified to cause different hearing loss among older adults?
2. Is there an association between age-related hearing loss and brain health (that cannot be contributed to aging itself)?

To explore if specific patient related and environmental factors cause differences in hearing loss among older adults we conducted two studies. First, the pure-tone thresholds of 3,315 participants were analysed cross-sectionally to discover which factors influence the onset of

age-related hearing loss (**Chapter 2**). Then, a longitudinal study is presented in which we study the influence of those patient and environmental related determinants on the progression of hearing loss over time (**Chapter 3**).

In the second part of the thesis we study the relation between age-related hearing loss and brain morphology, namely grey and white matter volume, and white matter tract organization, in >2,500 participants (**Chapter 4 and Chapter 5**). Furthermore, we carefully explore a possible causal direction by testing the *"sensory deprivation"* hypothesis in a study among hearing aid users and non-users (**Chapter 6**).

Finally, we reflect on all of our findings in the general discussion (**Chapter 7**).

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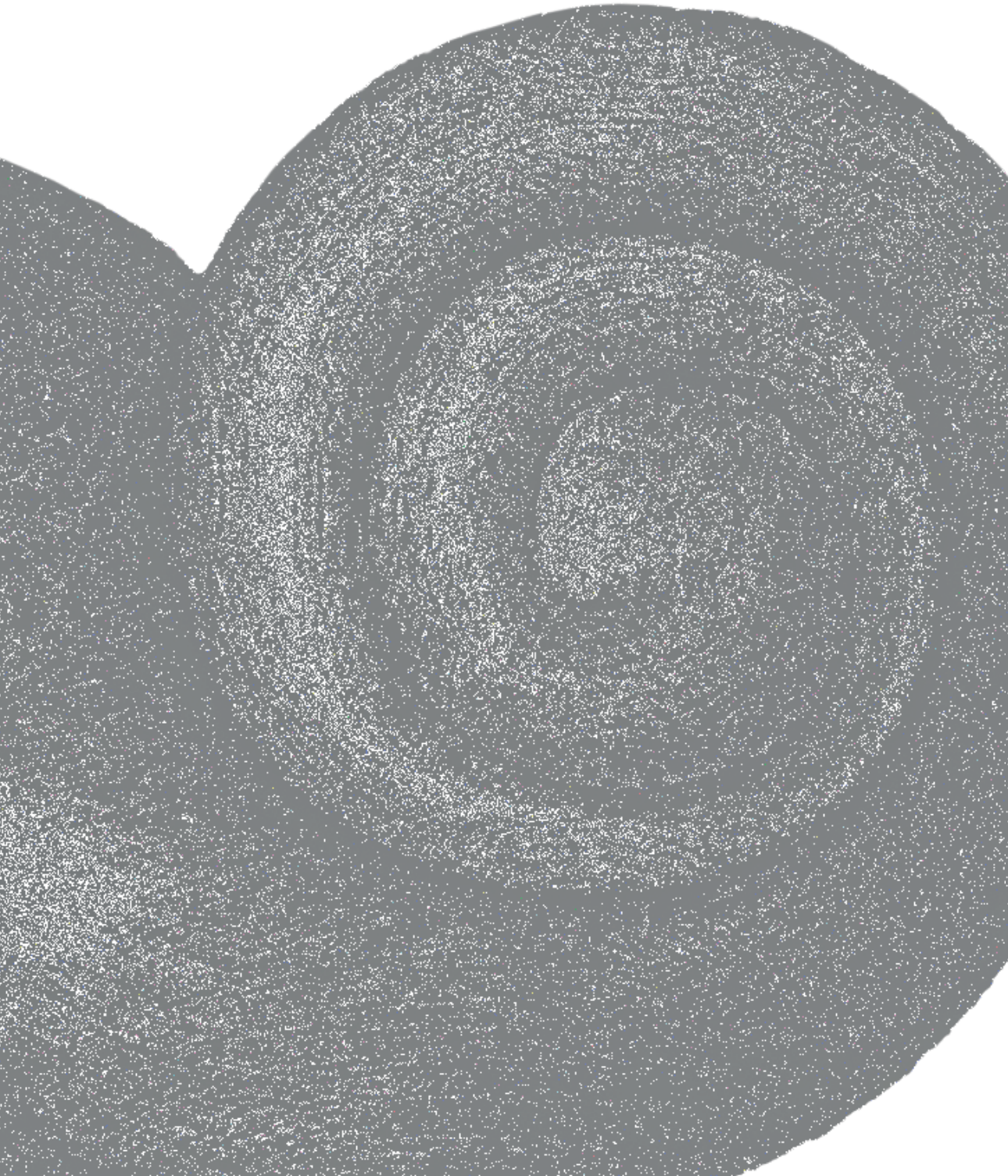

2

Contributing determinants to hearing loss in elderly men and women: results from the population-based Rotterdam Study

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ABSTRACT

To contribute to a better understanding of the etiology of age-related hearing loss, we carried out a cross-sectional study of 3,315 participants (aged 52–99 years) in the Rotterdam Study, to analyse both low- and high frequency hearing loss in men and women. Hearing thresholds were obtained with pure-tone audiometry, and other detailed information on a large number of possible determinants was collected. Hearing loss was associated with age, education, systolic blood pressure, diabetes mellitus, body mass index, smoking and alcohol consumption (inverse correlation). Remarkably, different associations were found for low- and high frequency loss, as well as between men and women, suggesting that different mechanisms are involved in the etiology of age-related hearing loss.

INTRODUCTION

Age-related hearing loss is highly prevalent[1] and contributes substantially to the global burden of disease[2]. Age-related hearing loss is a disease with a complex etiology[1]. Schuknecht and Gacek[3] described several audiological threshold patterns belonging to different pathological types, possibly with several etiologies and determinants. Since multiple determinants may interact in age-related hearing loss, it is essential to identify the individual and independent contribution of each of the determinants. To date, several cross-sectional cohort studies have identified multiple contributing determinants to age-related hearing loss such as hypertension[4-6], diabetes mellitus[5], body mass index (BMI)[7], smoking[7-9], an inverse correlation of alcohol consumption[7-9], occupational noise[7, 10], education[10], and race[5, 10]. Although consensus has been established about the associations with age, sex and occupational noise, less consistent results were found for determinants related to systemic diseases and lifestyle factors. Methodological differences or insufficiencies in study design and data quality may be the reason for inconsistent results. Firstly, some studies rely on self-reported hearing loss instead of audiometric measurements. Secondly, many studies approach hearing loss as a categorical instead of a continuous variable introducing loss of statistical power. Thirdly, most studies do not distinguish between low- and high frequency hearing loss. Fourthly, some studies describe or select a specific cohort, rather than the general elderly population at large. And lastly, in some cases of research only one or two determinants are examined while determinants will have a potential to influence one another and should thus be studied simultaneously. With this study we aimed to contribute to a better understanding of age-related hearing loss alongside the existing literature by studying the effects of known lifestyle factors and cardiovascular factors, on both low- and high frequency hearing loss, among healthy aging men and women within a large study cohort.

MATERIALS AND METHODS

Study Design and Subjects

This cross-sectional study was embedded in the Rotterdam Study[11], an open-ended prospective cohort study, which focuses on factors associated with healthy aging. We included participants from cohorts RS-I-1, RS-II-3, and RS-III-2, who underwent pure-tone audiometry between 2011 and 2013. We excluded subjects with an air-bone gap of 15 decibels (dB) or more in the best hearing ear to eliminate conductive hearing loss, leaving 3,315 participants. The Rotterdam Study was approved by the medical ethics committee according to the Population Screening Act: Rotterdam Study, executed by the Ministry of Health, Welfare and Sports of the Netherlands. A written informed consent was obtained from all participants.

Pure-Tone Audiometry

Pure-tone thresholds (air conduction: 0.25, 0.5, 1, 2, 4, and 8 kHz; bone conduction: 0.5 and 4 kHz) were measured in dB HL by pure-tone audiometry performed by a trained person according to the ISO standard 8253-1[12]. All measurements were performed in a soundproof booth. A computer-based clinical audiometry system (Decos Technology Group, version 210.2.6 with AudioNigma interface) and TDH-39 headphones were used. Outcome variables were the overall hearing loss (mean threshold of all measured frequencies), low frequency hearing loss (mean thresholds at 0.25, 0.5, and 1 kHz), and high frequency hearing loss (mean thresholds at 2, 4, and 8 kHz). We calculated the mean for the best hearing ear (i.e. lowest mean thresholds of all measured frequencies), to exclude the confounding effects of asymmetrical hearing loss and focus on bilateral hearing loss. If both ears were equal, we alternately chose right and left.

Determinants

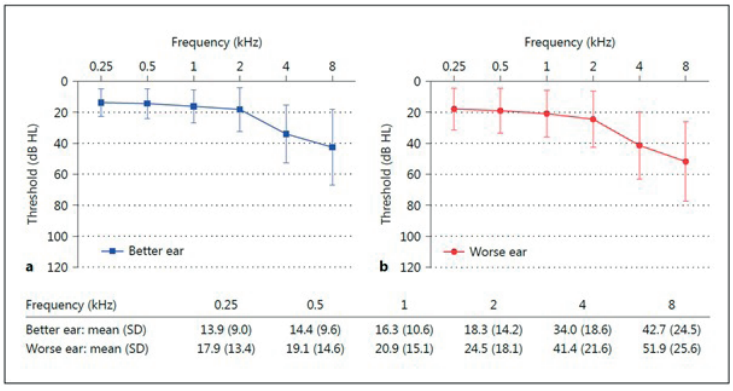
Several lifestyle and cardiovascular factors were investigated as possible determinants for age-related hearing loss. Age, sex, educational level, smoking status and alcohol consumption were determined at enrolment in the study through a questionnaire that was administered by a researcher at a home visit. Both smoking status and alcohol consumption were reassessed every 5 years at follow-up visits in the cohort study. Smoking status was categorized as never, former, or current smoker. Alcohol consumption was categorized as non-consumer, light-consumer (1 unit per day for women and 1–2 units per day for men), or above-average consumer (more than 1 unit per day for women and more than 1–2 units per day for men)[13]. Educational level was categorized as completed primary level, secondary level, or higher education. As well as audiometry, a set of examinations was done. Blood pressure was measured and the BMI was calculated. The cholesterol level was measured in serum, and the cholesterol ratio (the quotient of the total and high-density lipoprotein cholesterol) was calculated. Diabetic status was either confirmed at the home interview, tested by measuring glucose (fasting 7 mmol/l or more, nonfasting 11 mmol/l or more), or registered when a participant was prescribed diabetic medication.

Statistics

Data was checked for outliers and quadratic terms, which appeared not to be present. Missing data on covariates in 211 subjects (6.7%) were entered via multiple imputation. Missing values were present for educational level (1.5%), blood pressure (1.1%), diabetes mellitus (1.4%), cholesterol ratio (2.9%), BMI (1.2%), smoking (0.9%), and alcohol consumption (0.5%). Allowing for a 5% risk of type I error, significance was set at $p < 0.05$. A linear regression analysis was performed to assess the contribution of all determinants simultaneously. Data analysis was done using IBM SPSS Statistics version 21.

RESULTS

Characteristics of the study population are summarized in table 1. Male participants had more hearing loss at high frequencies, while women had more hearing loss at low frequencies. Mean hearing thresholds for worse and better ears are shown in figure 1. A classic sloping audiogram can be seen.



Frequency (kHz)	0.25	0.5	1	2	4	8
Better ear: mean (SD)	13.9 (9.0)	14.4 (9.6)	16.3 (10.6)	18.3 (14.2)	34.0 (18.6)	42.7 (24.5)
Worse ear: mean (SD)	17.9 (13.4)	19.1 (14.6)	20.9 (15.1)	24.5 (18.1)	41.4 (21.6)	51.9 (25.6)

Figure 1. Mean thresholds and standard deviations per frequency shown in pure-tone audiogram and table. a. better hearing ear, b. worse hearing ear.

Table 1. Characteristics of the study population (N = 3,135). Values are means (and standard deviation) for continuous variables or numbers (and percentage) for categorical variables.

Characteristics	Value for men	Value for women
Sample size, N	1,376 (43.9%)	1,759 (56.1%)
Age, years	65.5 (±7.4)	65.6 (±7.8)
Low frequency hearing loss, dB HL	13.2 (±7.9)	15.0 (±9.1)
High frequency hearing loss, dB HL	34.7 (±17.3)	28.5 (±15.8)
Educational level		
Secondary	659 (48.7%)	845 (48.7%)
Higher	456 (33.7%)	321 (18.5%)
Systolic blood pressure, mmHg	141.4 (±20.4)	139.3 (±21.5)
Diastolic blood pressure, mmHg	84.5 (±11.0)	82.4 (±11.2)
Diabetes mellitus, yes	182 (13.4%)	155 (8.9%)
Cholesterol ratio	4.3 (±1.3)	3.7 (±1.1)
BMI	27.7 (±3.8)	27.5 (±4.8)
Smoking		
Former	826 (60.4%)	830 (47.7%)
Current	188 (13.8%)	247 (14.2%)
Alcohol consumption		
Light consumer	1,145 (83.5%)	1,242 (71.1%)
Above-average	102 (7.4%)	207 (11.8%)

Alcohol consumption calculated in average grams a day. Light consumption for women is 0–10 g a day, for men 0–20 g a day. Above-average consumption for women is more than 10 g a day, for men more than 20 g a day[13].

Results of the multivariable linear analyses are shown in table 2. In men, low frequency hearing loss was significantly associated with age (0.44 dB loss per year of age) and systolic blood pressure (0.03 dB loss per increase in 1 mm Hg of blood pressure). High frequency hearing loss in men was significantly associated with age (1.34 dB loss per year of age), lower educational level and being a current smoker.

Table 2. Multivariable model for low- and high frequency hearing loss in men and women.
Effect sizes (β) are shown (and 95% confidence interval).

	Low frequency hearing loss		**High frequency hearing loss**	
	Men β (95% CI)	Women β (95% CI)	Men β (95% CI)	Women β (95% CI)
Determinants				
Age				
Per year ↑	**0.44 (0.38;0.50)***	**0.56 (0.50;0.61)***	**1.34 (1.22;1.46)***	**1.25 (1.17;1.34)***
Educational level				
Secondary vs. higher	0.67 (-0.19;1.54)	0.45 (-0.58;1.48)	0.88 (-0.85;2.60)	0.42 (-1.23;2.06)
Primary vs. higher	1.00 (-0.13;2.12)	**1.87 (0.75;2.99)***	**3.87 (1.62;6.12)***	1.52 (-0.27;3.31)
Systolic blood pressure				
Per mmHg	**0.03 (0.00;0.06)***	-0.02 (-0.04;0.01)	0.03 (-0.03;0.09)	-0.04 (-0.09;0.00)
Diastolic blood pressure				
Per mmHg	-0.03 (-0.08;0.03)	0.01 (-0.04;0.06)	-0.03 (-0.14;0.08)	0.03 (-0.05;0.11)
Diabetes mellitus				
Yes vs. no	0.48 (-0.68;1.64)	0.87 (-0.45;2.20)	0.12 (-2.13;2.38)	**2.21 (0.08;4.34)**
BMI				
Per point ↑	0.10 (-0.01;0.20)	**0.09 (0.00;0.17)**	0.06 (-0.15;0.27)	**0.18 (0.05;0.31)***
Cholesterol ratio				
Per unit ↑	0.04 (-0.26;0.33)	-0.12 (-0.45;0.22)	0.32 (-0.27;0.91	0.08 (-0.46;0.63)
Smoking				
Former vs. never	-0.15 (-1.04;0.74)	0.22 (-0.60;1.04)	1.57 (-0.19;3.32)	0.61 (-0.72;1.93)
Current vs. never	0.98 (-0.29;2.25)	**1.69 (0.50;2.88)***	**3.01 (0.51;5.52)**	**2.49 (0.60;4.38)***
Alcohol consumption				
Light vs. never	0.22 (-1.09;1.53)	-1.51 (-2.52;-0.50)	1.85 (-0.76;4.45)	-0.59 (-2.20;1.02)
Above-average vs. never	0.57 (-1.29;2.42)	**-2.02 (-3.46;-0.58)***	1.10 (-2.58;4.77)	-0.08 (2.37;2.22)

Data in bold are significant findings for $p < 0.05$, with * for $P < 0.01$. Alcohol consumption was calculated in average grams a day. Light consumption for women is 0-10 g a day, for men 0-20 g a day. Above-average consumption for women is more than 10 g a day, for men more than 20 g a day[13].

In women, low frequency hearing loss was significantly associated with age (0.56 dB loss per year), lower educational level, BMI (0.09 dB loss per increase in 1 BMI point) and being a current smoker. Alcohol consumption was significantly associated with less low frequency hearing loss (1.51 dB better hearing for light consumers, 2.02 dB better hearing for above-average consumers) when compared to non-consumers. High frequency hearing loss in women was significantly associated with age (1.25 dB loss per year), diabetes mellitus, BMI (0.18 dB loss per increase in 1 BMI point), and being a current smoker.

DISCUSSION

Since age-related hearing loss is a growing problem in our increasing elderly population, it is important to gain a better understanding about its exact etiology. Obviously, age-related hearing loss is the cumulative effect of aging on hearing; however, multifactorial determinants are likely to contribute to the large variance observed in hearing loss among people of the same age. In this study, we found a large number of determinants to be associated with age-related hearing loss including: age, smoking habits, consumption of alcohol, BMI, systolic blood pressure, diabetes mellitus, and educational level. Interestingly, these associations substantially differed between low- and high frequency hearing loss, and also between men and women. The largest effect on age-related hearing loss was found in age, as expected. For every decennium increase in age, hearing thresholds increase around 5 and 13 dB for low- and high frequency hearing loss, respectively, in both men and women. Furthermore, we found a substantial effect of smoking in both low- and high frequency hearing loss in women and in high frequency hearing loss in men. Associations with smoking were found in other studies[8, 9], but those studies did not stratify on gender, nor did they differentiate between high- and low frequency hearing loss[7]. Hypothetically, smoking can cause alterations in the cochlear blood flow, thereby leading to different effects on the base and apex of the cochlea. However, such alterations are hard to investigate because of the cochlea's location[14]. The consistent associations found for high frequency loss suggest that at least the basal part of the cochlea is involved. The contrary seems true for the effect of alcohol consumption, as associations are only found with low frequency loss, suggesting an influence upon the apical part of the cochlea. Dawes et al.[8] also found an inverse effect of alcohol on hearing loss suggesting alcohol has a protective function on hearing due to complex cardiovascular pathways[15]. Concerning other cardiovascular risk factors, we found an effect of systolic blood pressure in low frequency hearing loss in men, an effect of BMI in low- and high frequency hearing loss in women and an effect of diabetes mellitus in high frequency hearing loss in men. The more pronounced effects of determinants upon low frequency hearing loss in women serve as support for the hypothesis of a cardiovascular disease related cause. However, we did not find significant associations with all cardiovascular determinants in our model as possibly our determinants were not sufficiently accurate to detect a vascular origin of hearing loss. The strength of this study includes the fact that we measured pure-tone thresholds for individual frequencies, treating the mean threshold as a continuous variable as opposed to using self-reported hearing loss estimations as categorical variables, thus permitting for greater power in analysis in our study design. Race was not considered as a variable since the cohort represented almost 100% Caucasians. A limitation of this study is the lack of information on noise exposure, as this was not included in the questionnaire for participants. Noise exposure is an obvious determinant as it causes direct mechanical damage to the cochlea[16]. The only implication about noise exposure as a possible determinate in this study is in considering the association between educational level and the amount of noise exposure. We

found a significant association between lower educational attainment and hearing loss, while in other studies there was controversy on this issue[5, 10, 17]. Indirectly, we could assume people with a higher education to be less exposed to occupational noise and, if exposed, they might be more inclined to use hearing protection. Previous studies that did take noise exposure into account, still found an independent effect of smoking and alcohol on hearing loss[7, 8].

The results of the current study confirm that age-related hearing loss is highly prevalent and influenced by many factors. Extending the knowledge about these contributing factors is essential for the prevention and future treatment of age-related hearing loss. This can be achieved by comprehensive population-based studies, taking into account relevant environmental and medical aspects.

CONCLUSION

In conclusion, hearing loss was associated with age, education, systolic blood pressure, diabetes mellitus, BMI, smoking, and alcohol consumption (inverse correlation). Results were different for low- and high frequency loss among men and women, suggesting that different mechanisms are involved in the etiology of age-related hearing loss. Overall, a healthy lifestyle, *e.g.* without smoking or being overweight, may contribute to less hearing loss at an older age.

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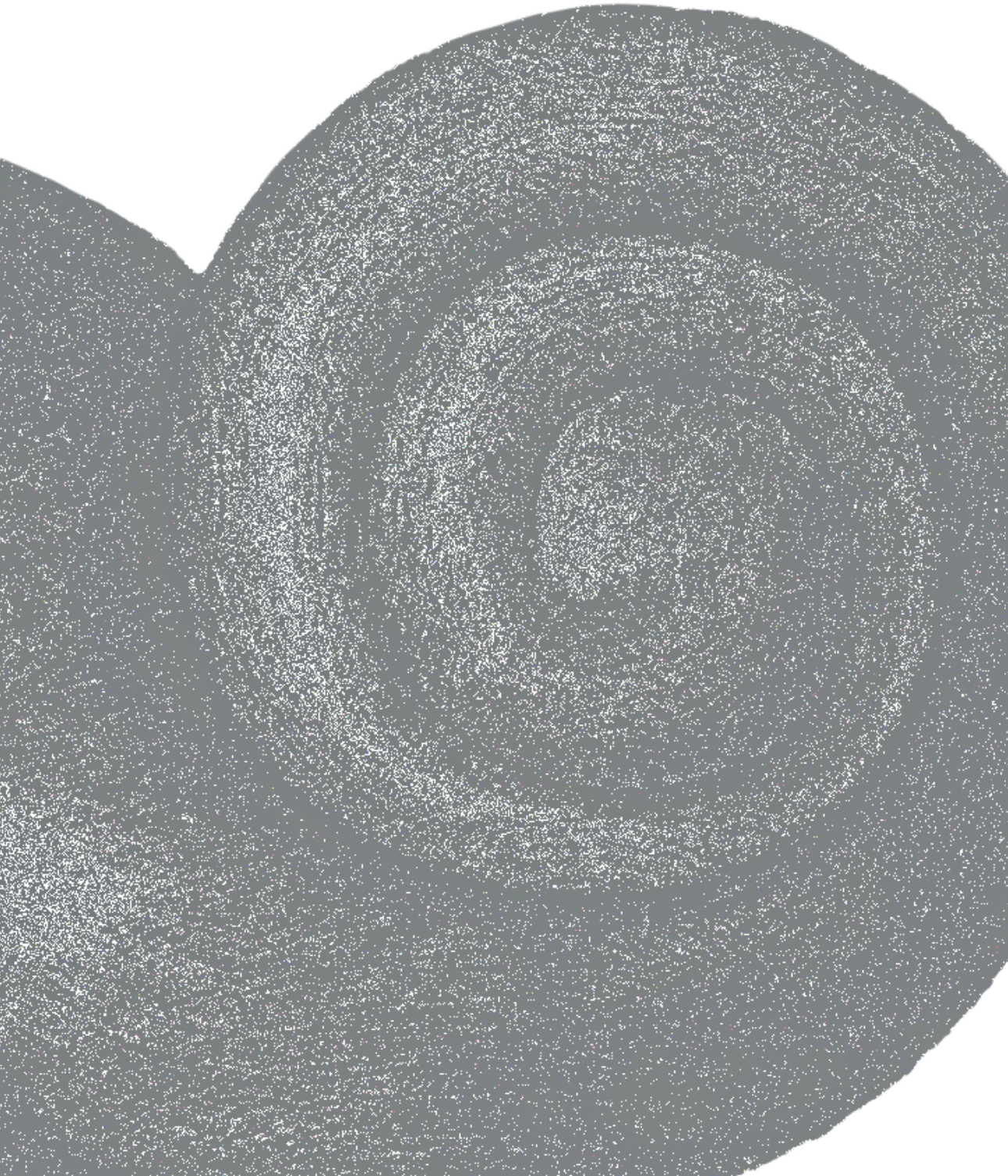

3

Progression of hearing loss in the aging population: repeated auditory measurements in the Rotterdam Study

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ABSTRACT

We quantified changes in the auditory acuity of 675 aging adults (mean age 71.1 years, 52.0% female, mean follow-up 4.4 years ± 0.2) of an ongoing cohort study with a pure-tone audiogram and a speech-in-noise test. Generalized estimating equation models were used to study the association between hearing loss and the progression with age, sex, education, cognition, BMI, blood pressure, having type 2 diabetes mellitus, cholesterol ratio, smoking and alcohol consumption. The mean progression of hearing loss was 0.29 and 1.35 dB per year (low- and high frequencies). Progression of hearing loss was associated with baseline hearing thresholds. Besides, the presence of type 2 diabetes, smoking, age, sex and time were associated with worse hearing at baseline, but there was no statistical evidence that the tested determinants were associated with progression of hearing loss. This finding indicates that the 4-year progression of hearing loss in older adults in this study is not influenced by the measured determinants. More research with multiple follow-up rounds is desired.

INTRODUCTION

Age-related hearing loss affects over a billion people worldwide[1], and its prevalence keeps rising due to aging of the population[2]. As the fourth leading cause of years lived with disability in developed countries[1], hearing loss has a major impact on daily life and is associated with high health care costs.

The nature of hearing loss in older adults is progressive[3]. From approximately the fifth decade onwards, hearing thresholds and speech understanding in noise gradually decline. Multiple determinants are thought to influence the onset and severity of hearing loss in older adults, namely demographic factors such as age, sex and social economic status[4], medical factors such as cardiovascular disease, cognition, diabetes mellitus, cholesterol level and obesity[5-9], lifestyle-related factors such as noise exposure, smoking and an inverse correlation for alcohol consumption[4, 10-12] and genetic susceptibility[13]. The rate of the progression of hearing loss varies widely among people of the same age[14]. The decline of pure-tone thresholds over time has been found associated with several factors such as age, being male or female, blood pressure, obesity, having diabetes, cognitive impairment and manual occupation[15-18]. When reviewed critically, some studies that claim to address associations on progression, in fact addressed the incidence of hearing loss[19]. In general, previous studies lack the combination of (1) a representative aging population with a wide range of hearing (instead of a group of hearing-impaired compared to a group of normal-hearing participants), where (2) auditory acuity (thresholds and speech perception) as well as the possible determinants were measured and (3) sufficient statistical methods were used. Knowing who are at risk of more rapid deterioration of hearing acuity could influence counseling, rehabilitation and possible treatment of the underlying condition. The purpose of this study is to identify if and to what extent the progression of hearing loss in older adults over time is associated with potentially relevant determinants.

MATERIALS AND METHODS

Study Population

This study is embedded in the Rotterdam Study, an ongoing population-based prospective cohort study designed to investigate the health of aging people[20]. The population consists of inhabitants aged 55 years and above of the Ommoord district in the city of Rotterdam, the Netherlands. In 2011, hearing assessment was implemented in the study protocol, and participants are invited for reassessment approximately every 4 years. In 2015 the first group of participants was invited for their second hearing assessment. For the current study, we included participants with two hearing assessments (N = 722 from 5,762). Those who had been reassessed within less than 3 years (N = 18) and those with conductive hearing loss on the best hearing ear (N = 29) were excluded. This resulted in a total number of 675 participants. Included

participants did not significantly differ in age, sex and mean hearing loss from participants with one hearing assessment. The Rotterdam Study has been approved by the Medical Ethics Committee of the Erasmus University Medical Center and by the Ministry of Health, Welfare and Sport of the Netherlands, implementing the Population Screening Act: Rotterdam Study. All participants provided written informed consent to participate in the study and to have their information obtained from treating physicians.

Hearing Assessment

Participants were tested by a single qualified professional in a soundproof booth at the research center. TDH-39 headphones and a clinical audiometer (Decos audiology workstation, version 210.2.6 with AudioNigma interface) were used. A pure-tone audiogram and speech-in-noise test were performed. First, pure-tone thresholds were measured according to the ISO-standard 8253-1[21]. Air conduction (0.25, 0.50, 1, 2, 4 and 8 kHz) and bone conduction (0.5 and 4 kHz, due to limited time) were measured for both ears. Masking was done according to the method of Hood[22]. Bone conduction thresholds at 4 kHz were +10 dB adjusted afterwards[23]. The best hearing ear was determined by calculating the mean threshold over all frequencies. If hearing was equal between both ears, alternately the right or left was chosen. On the best hearing ear, we calculated low- (mean of 0.25, 0.50 and 1 kHz), speech- (mean of 0.50, 1, 2 and 4 kHz), and high (mean of 2, 4 and 8 kHz) frequency hearing thresholds to determine the low-, speech-, and high frequency hearing loss. To eliminate clinically relevant conductive hearing loss, test results of participants with an air-bone gap of 15 dB or more were excluded from the analyses. Subsequently, a simplified speech-in-noise test was done to quantify the speech recognition ability in noise. We performed the digits-in-noise (DIN) test on the best-hearing ear[24]. Participants repeated digit triplets in an automated adaptive procedure, while the signal-to-noise ratio was changed according to the correctness of the answer. This resulted in a speech reception threshold which represents a speech-in-noise ratio for 50% correctly repeated triplets. A higher threshold means a worse ability of understanding speech in noise. After a preliminary evaluation of our hearing data, suprathreshold noise levels were changed from 55 dB at baseline to 65 dB during follow-up. To avoid confounding with the peripheral hearing level, we additionally adjusted for the high frequency hearing thresholds in the subsequent analysis concerning the DIN test. Progression of hearing loss was defined as devaluation of hearing thresholds from baseline to reassessment.

Determinants

Information on the potentially relevant determinants was acquired through a home interview, physical examination and blood sampling at baseline. Educational level was classified as having completed primary, secondary or higher schooling. Cognition was defined as the score on the Mini-Mental State Examination (MMSE). Body mass index (BMI) was calculated through weight and length. Systolic blood pressure was measured twice on the right brachial artery with the

participant in a sitting position and in between a resting period of 5 minutes. The mean of the two values was used. Cases of type 2 diabetes were identified from general practitioners' records. If we could not retrieve this information, diabetes mellitus was considered present if the glucose measurement was abnormal or if the participant used antidiabetic drugs. Abnormal glucose measurement was defined as fasting glucose 7 mmol/L or more, or (if unavailable) as nonfasting glucose 11 mmol/L or more. Cholesterol ratio was calculated as the quotient of serum total cholesterol and high-density cholesterol. Smoking was classified as never, former or current. Alcohol consumption was categorized as non-consumer, light consumer (1 unit of alcohol per day for women and 1–2 units of alcohol per day for men) or above-average consumer (more than 1 unit of alcohol per day for women and more than 2 units of alcohol per day for men)[25].

Statistics

To examine the characteristics of the study population, we calculated mean and standard deviation or percentage for all demographics. In the first analysis we calculated the association between baseline thresholds and the progression of hearing loss using a linear regression model, accounting for the different participant demographics. In a second analysis we used generalized estimating equations, to assess the effect of the different determinants on the progression of hearing loss[25]. Population-average progression was defined as the main effect of time. To study the differences in progression of hearing loss between subgroups of the population, we allowed for interactions between time and all the determinants. Separate generalized estimating equation models were used for each of the hearing outcomes: the low-, speech-, and high frequency hearing thresholds and the outcome of the DIN test; the speech reception threshold (SRT). To account for the correlation between measurements coming from the same subject, we assumed an exchangeable correlation structure. We started by specifying an elaborate model including the main effects of all the determinants as well as higher-order terms such as interactions of baseline determinants with time and a quadratic effect of age. The higher-order terms were then tested using multivariate Wald tests. A p value of 0.05 or less was considered significant. All higher-order terms were not found to be significantly different from zero and thus were dropped from the final models. The models including the higher-order terms are shown in Table 1 of the supplementary material (see www.karger.com/doi/10.1159/000492203 for all online suppl. material). Missing data were assumed to be missing completely at random. Analyses were performed using R 3.4.1[26] and package geepack 1.2-1[27-29].

RESULTS

Characteristics of the Study Population

A total of 650 complete cases were analysed. The mean (SD, range) age at baseline was 71.1 (4.1, 66-87) years, and 52% were females. The mean (range) follow-up was 4.4 (3.3–5.1) years. All relevant characteristics of the study population are displayed in Table 1.

Table 1. Characteristics of the study population at baseline (N = 650).

Characteristics	
Age, years	71.1 (±4.1)
Sex, female	338 (52.0%)
Educational level	
Primary	154 (23.7%)
Secondary	344 (52.9%)
Higher	152 (23.4%)
MMSE score (median, IQR)	28 (27;29)
Body mass index	27.6 (±3.7)
Systolic blood pressure, mmHg	150 (±20.6)
Diabetes mellitus, yes	78 (12.0%)
Cholesterol ratio	3.74 (±1.10)
Smoking	
Never	217 (33.4%)
Former	380 (58.4%)
Current	53 (8.2%)
Alcohol consumption	
Never	89 (13.7%)
Light consumer	457 (70.3%)
Above-average	104 (16.0%)

Unless stated differently values are means (and standard deviation) for continuous variables or numbers (and percentage) for categorical variables. IQR, interquartile range; MMSE, Mini-Mental State Examination.

Progression of Hearing Loss

The difference in hearing thresholds was large (95% confidence interval at baseline for the mean threshold of lower frequencies 6.7 with 36.7 dB, of higher frequencies 18.3 with 68.3 dB). Pure-tone thresholds at baseline were worse for higher than for lower frequencies, and thresholds worsened with each age category (Figure 1).

The prevalence of age-related hearing impairment according to the WHO (pure-tone audiogram 0.5, 1, 2 and 4 kHz > 25 dB loss at best-hearing ear) at baseline was 48.5%. The prevalence rose with each age category (respectively 38.8% for subjects aged 66–69 years, 53.1% for 70–79 years and 81.8% for 80–87 years). At the follow-up, this was 61.4% (53.6, 65.5 and 84.8%). Figure 2 shows the mean threshold at baseline in relation to the mean threshold at follow-up,

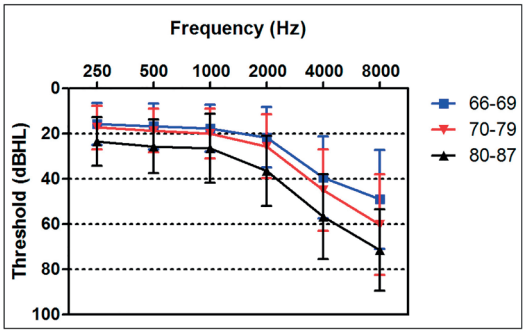

Figure 1. Mean pure-tone thresholds of the study population at baseline. Thresholds are shown for three categories. HL, hearing level.

again displayed for the three age categories. All participants left and above of the drawn line showed progression of hearing loss. An increase in hearing thresholds – progressive hearing loss – was present for 512 participants (78.8%).

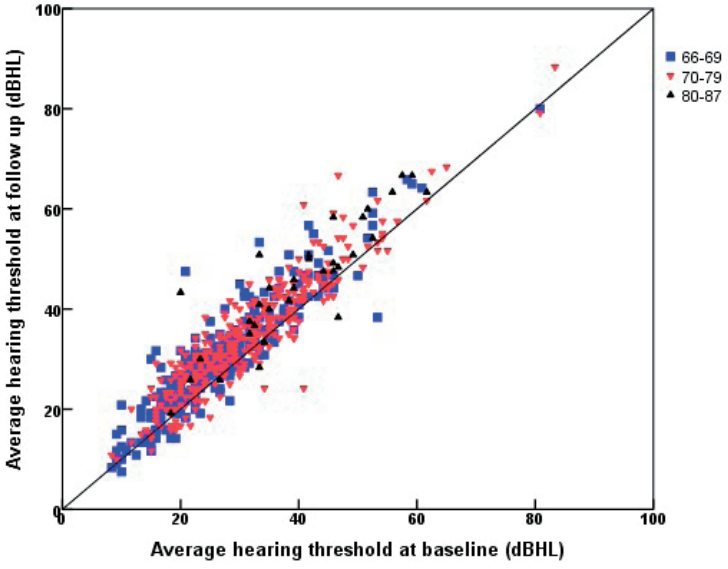

Figure 2. Mean hearing threshold at baseline and follow-up. Mean pure-tone threshold for 0.5, 1, 2 and 4 kHz at baseline in relation to the mean threshold at follow-up shown for the three age categories. Every participant left of the line suffers decline of hearing during follow-up. HL, hearing level.

The mean decline of hearing loss was 0.29 dB per year in the low frequencies and 1.35 dB per year in the high frequencies. The progression was significantly associated with the baseline thresholds. For the lower frequencies an effect estimate of –0.07 dB per 4 years of follow-up (*p* value 0.010) was found and for the higher frequencies an effect estimate of –0.06 dB per 4

years of follow-up (*p* value 0.002), after correcting for age, sex and the other determinants. In other words, for approximately every 16 dB elevation of the baseline threshold, 1 dB less progression in the follow-up period was expected.

Determinants

Using the full model specification, none of the interaction terms with time was found statistically significant at the 0.05 significance level. That is, there was no statistical evidence to support a difference in progression of hearing loss by the determinants investigated in this study. The interaction terms were therefore dropped from the final generalized estimating equation models. Table 2 displays the results of the final models for the low-, speech-, and high frequency thresholds, as well as for the SRT. The initial, full models can be found in the online supplementary material. Worse hearing thresholds in the low frequencies were associated with time, aging, being of female sex and being a current smoker. Increase in BMI and having type 2 diabetes were border significant. Worse hearing thresholds in the speech- and high frequencies were associated with time, aging, being of male sex, having type 2 diabetes mellitus and being a current smoker. Worse hearing on the SRT was inversely associated with time. Thus, speech reception seemed to improve over time. Furthermore, the SRT was associated with age, being of female sex and having type 2 diabetes. The implications of our outcomes are visualized in Figure 3 by means of progression lines for high frequency hearing loss over time for different groups of participants. Smokers with diabetes mellitus had initial higher pure-tone losses at baseline (both males and females), but the progression of hearing loss in both groups was equal. The progression of hearing loss was also equal for males and females.

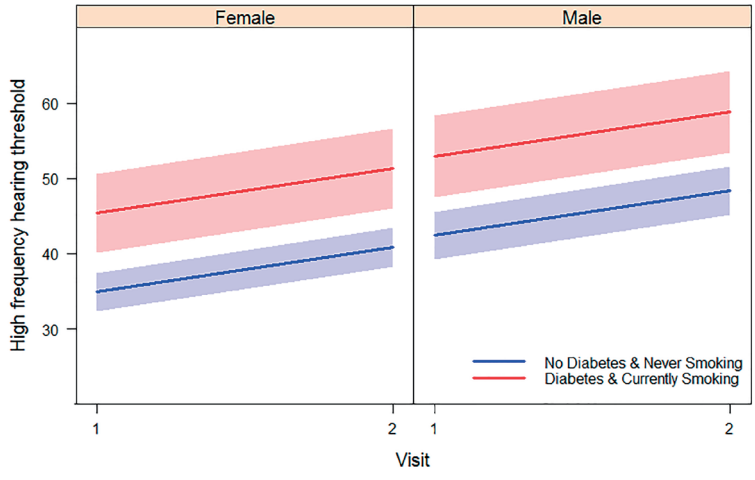

Figure 3. Progression of high frequency hearing loss over time for different categories of participants. HL, hearing level. The progression lines and 95% confidence intervals shown are for a participant with median outcomes (70 years, secondary educational level, MMSE score 28, BMI 27, systolic blood pressure 149 mmHg, average consumer, cholesterol ratio 3.63). Only sex, presence of diabetes and smoking status differed.

Table 2. Effect estimates from the final generalized estimating equation models for hearing acuity.

	Low	***p***	**Speech**	***p***	**High**	***p***	**SRT**	***p***
Intercept	-25.08 (-46.23;-3.93)	0.020	-42.26 (-68.28;16.23)	0.001	-65.74 (-100.14;-31.34)	0.000	-11.73 (-17.01;-6.45)	0.000
Time (follow-up, years)	**1.29 (0.86;1.72)**	**0.000**	**3.18 (2.80;3.55)**	**0.000**	**5.96 (5.46;6.46)**	**0.000**	**-2.93 (-3.23;-2.62)**	**0.000**
Age (per year)	**0.51 (0.32;0.70)**	**0.000**	**0.76 (0.53;0.98)**	**0.000**	**1.20 (0.92;1.48)**	**0.000**	**0.06 (0.00;0.11)**	**0.040**
Sex	**-2.04 (-3.60;-0.49)**	**0.010**	**2.18 (0.30;4.05)**	**0.023**	**7.53 (5.00;10.08)**	**0.000**	**-0.42 (-0.78;-0.06)**	**0.022**
Education: secondary	1.18 (0.54;2.89)	0.179	1.79 (-0.28;3.85)	0.091	2.15 (-0.60;4.90)	0.126	0.00 (-0.41;0.40)	0.983
Education: primary	1.81 (-0.36;3.98)	0.101	2.44 (-0.01;4.89)	0.051	2.86 (-0.40;6.13)	0.086	0.35 (-0.17;0.87)	0.183
MMSE	-0.05 (-0.50;0.41)	0.841	0.17 (-0.38;0.72)	0.537	0.34 (-0.42;1.10)	0.377	-0.07 (-0.17;0.04)	0.216
BMI	0.20 (-0.03;0.42)	0.083	0.11 (-0.15;0.37)	0.395	0.03 (-0.29;0.35)	0.850	0.02 (-0.04;0.07)	0.602
Systolic blood pressure	0.03 (-0.01;0.06)	0.141	0.03 (-0.01;0.07)	0.141	0.003 (-0.03;0.08)	0.362	0.00 (-0.01;0.01)	0.392
Diabetes mellitus	2.47 (-0.10;5.04)	0.060	**4.04 (0.97;7.12)**	**0.001**	**5.53 (1.83;9.23)**	**0.003**	**0.68 (0.04;1.31)**	**0.036**
Cholesterol ratio	-0.31 (-1.01;0.39)	0.379	-0.07 (-0.89;0.76)	0.875	0.12 (-0.92;1.16)	0.822	-0.04 (-0.19;0.11)	0.603
Smoking: former	0.58 (-1.03;2.19)	0.478	0.58 (-1.36;2.53)	0.557	1.06 (-1.51;3.62)	0.420	-0.24 (-0.81;0.41)	0.233
Smoking: current	**3.45 (0.74;6.15)**	**0.012**	**3.35 (0.21;6.48)**	**0.036**	**4.96 (0.79;9.13)**	**0.002**	-0.20 (-0.73;0.27)	0.523
Alcohol: light consumer	-0.87 (-2.89;1.16)	0.400	-1.25 (-3.52;1.01)	0.278	-0.22 (-3.22;2.78)	0.888	-0.23 (-0.73;0.27)	0.371
Alc: above-average	-0.78 (-3.41;1.85)	0.561	-0.84 (-3.79;2.11)	0.576	-0.77 (-4.68;3.13)	0.698	-0.31 (-0.14;0.17)	0.333

The reference group for each variable is female, finished higher education, no diabetes, never smoker, no alcohol consumption. Results are expressed as effect estimates (and 95% confidence intervals); those given in bold are significant. The SRT analysis was also corrected for the high frequency hearing threshold. Low, low frequency threshold mean (0.25, 0.50 and 1 kHz); Speech, speech frequency threshold mean (0.50, 1, 2 and 4 kHz); High, high frequency threshold mean (2, 4 and 8 kHz); SRT, Speech reception threshold; MMSE, Mini-Mental State Examination; BMI, body mass index; Alc, alcohol.

DISCUSSION

This study showed that the progression of hearing loss over a short time was not affected by age, sex, educational level, cognition, BMI, systolic blood pressure, presence of type 2 diabetes mellitus, cholesterol ratio, smoking and alcohol consumption. On the other hand, higher initial hearing thresholds had a decelerating effect on the progression rate. A baseline difference of approximately 16 dB resulted in 1 dB less progression over the 4 years of follow-up, which effect is substantial in view of the average 1.35 dB decline of hearing loss per year. Previous studies have reported inconsistent effects of the initial hearing level on the rate of progression. In line with our results, poorer baseline thresholds for the higher frequencies (4–8 kHz) were found to be associated with less progression in hearing loss[30]. In that same study no effect of lower frequencies (0.25–1 kHz) was found. A similar result was also found in a study in which the progression of hearing loss was defined as a deterioration of >5 dB on 0.5–4 kHz[31]. In contrast, worse hearing thresholds were associated with a faster decline in another large cohort-based study[18]. The follow-up period in that study was longer (12 years), which could explain different findings. However, the authors presented only the results of the univariate analysis between progression and baseline thresholds, while we presented ours after correcting for age and sex. Because their study population included far younger participants than ours (24.0–83.7 years), the found effect might also have been a consequence of a different etiology of hearing loss, for example a genetic cause. In our second analysis, the generalized estimating equation models, none of the determinants had an effect on the progression of hearing loss according to the *p* value chosen to test statistical significance, other than the elapse of time itself. Remarkably, the time effect found on the SRT was inverse. Time seemed to have an inhibitory effect on speech perception loss. This can be ascribed to having adjusted the DIN test after a first cross-sectional evaluation of our hearing data[24]. To reduce the confounding effect with pure-tone thresholds, suprathreshold noise levels were adjusted from 55 dB at baseline to 65 dB during follow-up. Implying to reduce the confounding effect with pure-tone thresholds. Age had no significant effect on the progression of hearing loss. This is surprising, as the ISO standard[21] uses a model with a consistently increasing progression of hearing loss with age, which is in line with several studies that show accelerated progression with higher age[17, 18]. These studies were able to use linear mixed models because they had multiple audiometric measurements. Because in the present study only two audiometric measurements per participant were available, our analysis was restricted to generalized estimating equations rather than mixed-effect models. Still, the time span between the two measurements may have been too short to identify a significant difference in progression. Furthermore, due to interpretation purposes and the endogenous nature of some of the exposures only the baseline values of the determinants were used as exposure variables. Another difference with the studies of Kiely et al. and Linssen et al. is that our study population was older and thus more prone to a higher prevalence of age-related hearing loss. In older adults, not only the effect of aging itself, but also a ceiling

effect has been described: the more the loss of high frequency hearing, the less the rate of progression, possibly because a maximum loss was being reached[32, 33]. Because age-related hearing loss is thought to be a risk factor for the onset of dementia[34], we studied the risk of developing dementia using poor performance on the DIN test. Prior studies mainly focused on peripheral hearing loss (pure-tone audiometry), while we hoped with the DIN to reflect the higher auditory function. Dementia was stated as a MMSE score of 26 or lower, and we calculated the odds ratio of the onset of dementia according to a worse performance on the DIN test using a univariable logistic regression model, due to the fact that only 40 of the 559 nondemented subjects at baseline developed dementia (7.2%). We found an odds ratio for dementia according to worse performance on the DIN test of 1.05 (CI 0.99–1.12) with a *p* value of 0.065; however, this result should be looked at with care, since other baseline characteristics were not taken into account for this analysis. Some studies identified determinants that had an effect on the progression of hearing loss, such as a lower cognitive impairment, hypertension, having had a manual occupation and waist circumference[17, 18]. Still, all effects were very small and may only become apparent after a longer time. Although in the present study type 2 diabetes and smoking were not associated with the progression of hearing loss, they were associated with the onset of age-related hearing loss. We found a significant effect regardless of the correction for cardiovascular confounders. This association of type 2 diabetes[7] and smoking[10, 11, 35] with the prevalence of hearing loss in older adults was shown before. Possible hypotheses on the underlying pathogenesis of diabetes or smoking and hearing loss could be microangiopathy of the stria vascularis[36], neuropathy or mitochondrial damage[37]. For diabetes we found no significant effect in the lower frequencies and a larger effect in the higher frequencies when compared to the speech frequencies. This could indicate a vascular cause taking into account that the base of the cochlea is more vascularized than the apex and thus has a greater blood supply. The higher frequencies may therefore be more affected by microangiopathy[38]. One of the limitations of this study is that with two measurements per subject the statistical modeling options for studying the progression of hearing loss were limited (*e.g.* mixed-effects models with random slopes are not feasible). We therefore used generalized estimation equation models to fit the data best[39]. With more follow-up rounds planned, we expect to report on this in the future. Another limitation was the short follow-up time. We consider our results therefore to reflect the short-term effects of hearing loss. Also, we did not have any information on noise exposure. Although in previous research no relation between noise-induced hearing loss and the progression of hearing loss was found[40], some cross-sectional studies did find associations with the prevalence of hearing impairment. We tried to account for this by including educational level in our analysis. The strength of this study lies in the representativeness of our cohort as compared to the general population. At baseline there was a natural distribution of age and of all levels of hearing loss. Many earlier studies compared hearing-impaired and normal-hearing participants, while we studied the whole spectrum of hearing loss. Second, we structurally collected data and called in the help of a statistician for the analyses. Last, the

prevalence of age-related hearing impairment was in line with prevalence numbers of other cohort studies using the WHO criteria[4, 41, 42]. Therefore, we found more progression in the lower than in the higher frequencies. With an average age of 90 years, the study population of Wattamwar et al. was much older than ours, but it may well be that this stagnation of progression is already apparent at an earlier age, which may counteract a possible accelerated progression of hearing loss at higher ages as suggested by the ISO standard. Like age, also sex was not associated with the progression of hearing loss. This is in line with the adaptation of the new ISO standard[43], in which sex differences are much smaller than in the older version[21]. We did find that sex was associated with the onset of hearing loss. Worse hearing thresholds in the lower frequencies were associated with being female and worse hearing in the speech- and higher frequencies was associated with being male. Former cross-sectional studies found that women have better high frequency hearing and that men have better low frequency hearing[11]. This is possibly explained by the assumption that men are at higher risk of noise-induced hearing loss.

CONCLUSION

In summary, in this study we showed that although hearing loss in the aging population was associated with type 2 diabetes, smoking, age and sex, we did not find an association with the progression of hearing loss for any of these determinants. Worse baseline hearing levels were associated with a less rapid progression, which could be proof of a ceiling effect in hearing deterioration. This study indicates that the 4-year progression of hearing loss among older adults aged 66–87 years is not influenced by the measured demographic and clinical determinants. To further clarify this, more research with multiple follow-up rounds is warranted.

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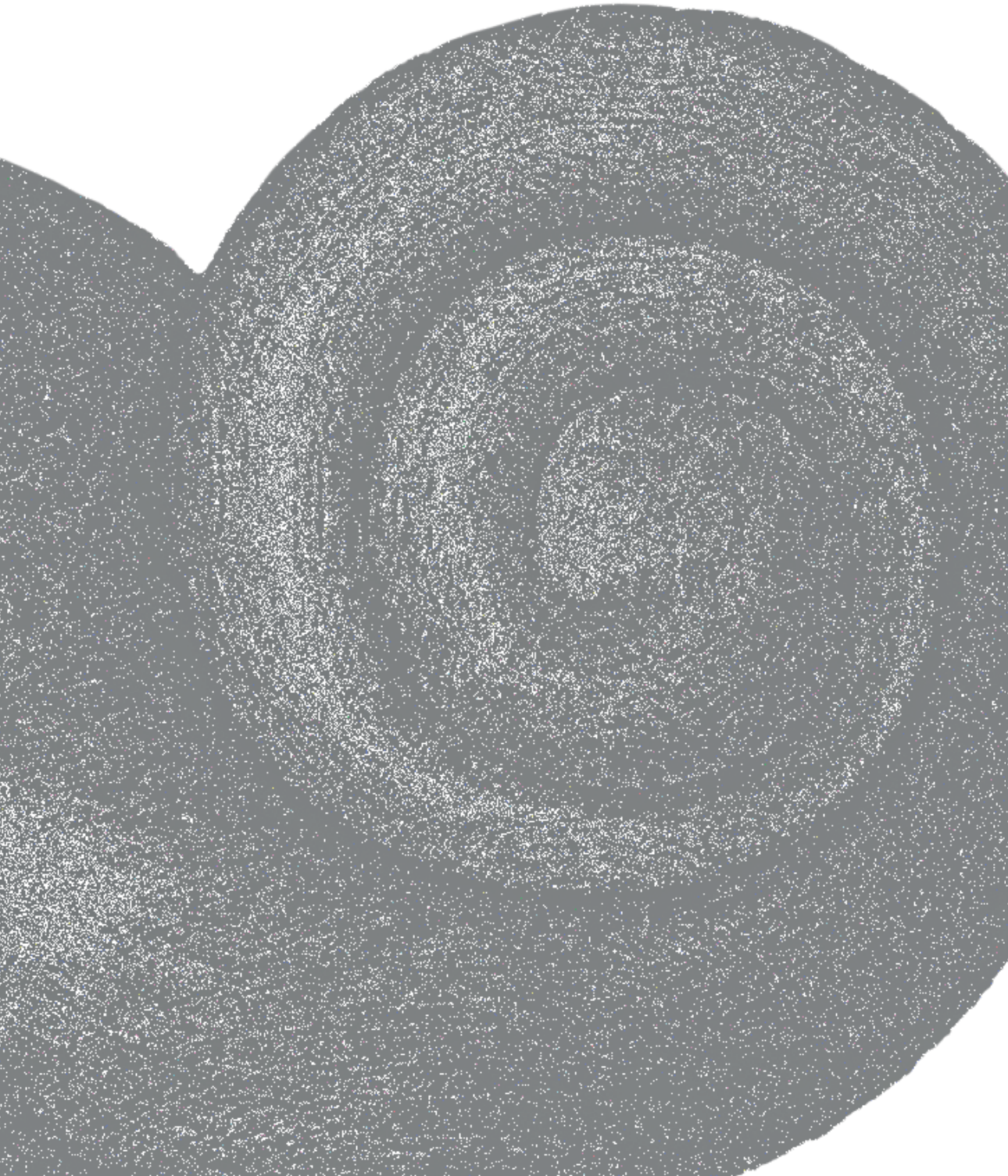

4

Hearing impairment is associated with smaller brain volume in aging

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ABSTRACT

Although recent studies show that age-related hearing impairment is associated with cerebral changes, data from a population perspective are still lacking. Therefore, we studied the relation between hearing impairment and brain volume in a large cohort of older adults. From the population-based Rotterdam Study, 2,908 participants (mean age 65 years, 56% female) underwent a pure-tone audiogram to quantify hearing impairment. By performing MR imaging of the brain we quantified global and regional brain tissue volumes (total brain volume, grey matter volume, white matter volume, and lobe-specific volumes). We used multiple linear regression models, adjusting for age, sex, head size, time between hearing test and MR imaging, and relevant cognitive and cardiovascular covariates. Furthermore, we performed voxel-based morphometry to explore sub-regional differences. We found that a higher pure-tone threshold was associated with a smaller total brain volume (difference in standardized brain volume per decibel increase in hearing threshold in the age-sex adjusted model: −0.003 (95% confidence interval −0.004; −0.001). Specifically, white matter volume was associated. Both associations were more pronounced in the lower frequencies. All associations were consistently present in all brain lobes in the lower frequencies and in most lobes in the higher frequencies, and were independent of cognitive function and cardiovascular risk factors. In voxel-based analyses we found associations of hearing impairment with smaller white volumes and some smaller and larger grey volumes, yet these were statistically non-significant. Our findings demonstrate that hearing impairment in older adults is related to smaller total brain volume, independent of cognition and cardiovascular risk factors. This mainly seems to be driven by smaller white matter volume, throughout the brain.

INTRODUCTION

Age-related hearing impairment is common in the middle-aged and elderly population[1-3]. This typically starts with loss of hearing sensitivity in the higher frequencies, and progresses over time to the mid- and lower frequencies. Simultaneously, the ability to understand speech in noise declines[4], leading to communication difficulties that have a large impact on a person's social, psychological, and physical well-being[5].

Primarily, age-related hearing impairment has been described as a condition caused by damage in the peripheral auditory system, in particular the outer hair cells, stria vascularis, or cochlear neurons[6]. Subsequently, several risk factors for age-related hearing impairment, including noise exposure, cognitive function, and genetic predisposition, have been identified[4, 7, 8]. More recently the focus of research on age-related hearing impairment has expanded toward changes in the central auditory and cerebral system. One of the most commonly studied cerebral regions with regard to hearing impairment is the central auditory pathway, yet the evidence remains inconsistent. Some studies demonstrated a relation between hearing impairment and smaller grey matter volume in this region[9-11], whereas others found an association with smaller white matter volume[10, 12], or no association with any brain volume[13]. One longitudinal study reported an association between hearing impairment and decline in grey matter volume in the right temporal lobe was found[14]. Apart from these contrasting results, an extra consideration which applies to these studies, is that these were performed in relatively small populations who were of various age, and that the effects of important other factors, including cognition, alcohol consumption, and cardiovascular risk factors, were not always taken into account. Hence, larger scale population-based data on older adults with the ability to account for these additional factors are needed. These results will contribute to a further understanding of the link between age-related hearing impairment and structural brain changes. Therefore, we set out to investigate the association between age-related hearing impairment and morphological brain differences within the large population-based Rotterdam Study.

MATERIALS AND METHODS

Study Design and Subjects

This study was embedded in the Rotterdam Study[15], a population-based prospective cohort study. The study started in 1990 with 7,983 participants that were aged 55 years and older. In 2001, the cohort was extended with 3,011 participants of 55 years and older. A third cohort expansion was performed in 2006 with 3,932 participants aged 45 years and older. Follow-up examinations are performed every 3–4 years in all participants. From 2005 onward, brain MRI has been incorporated into the core study protocol. Moreover, from 2011 onward, we have

been performing hearing assessments in all participants visiting the research centre. The current study comprises those participants that underwent both a hearing assessments and brain MRI (N = 3,168) until 2014. Ninety-six percent of the MRIs were conducted before or within less than 3 months after hearing assessment (median: 1 month; interquartile range (IQR) -17 months; 2 months). The Rotterdam Study was approved by the medical ethics committee according to the Population Screening Act: Rotterdam Study, executed by the Ministry of Health, Welfare, and Sports of the Netherlands. A written informed consent was obtained from all participants.

Hearing Assessment

All audiometric measurements were performed in a soundproof booth by one trained health care professional. A computer-based clinical audiometry system (Decos Technology Group, version 210.2.6 with AudioNigma interface) and TDH-39 headphones were used. To determine hearing thresholds in decibels (dB) pure-tone audiometry was performed. Thresholds were measured according to the ISO-standard 8253-1[16]. Air conduction (frequencies 0.25, 0.50, 1, 2, 4, and 8 kilohertz (kHz)) and bone conduction (only two frequencies due to limited time: 0.50 and 4 kHz) were tested for both ears. Masking was done according to the method of Hood[17]. Thresholds for the 4 kHz bone conduction were increased with 10 dB afterward based on the discussion on the reference value[18, 19]. We determined the best hearing ear by taking the mean threshold over all frequencies. If both ears were equal, we alternately chose right and left. Furthermore, we determined low- (mean of 0.25, 0.50, and 1 kHz), speech- (mean of 0.50, 1, 2, and 4 kHz) and high frequency hearing thresholds (mean of 2, 4, and 8 kHz). We excluded subjects with an air-bone gap of 15 dB or more (N = 240), to eliminate clinically relevant conductive hearing loss.

Brain MRI Acquisition and Processing

All participants underwent non-contrast enhanced MRI scanning on a 1.5T-scanner (GE Healthcare, Milwaukee, WI, USA). The full MRI protocol has been described extensively before[20]. Briefly, the protocol included a T1- weighted sequence, a proton density-weighted sequence, a FLAIR sequence, and a T2 -weighted gradient echo sequence. For all sequences the slice thickness was 1.6 mm (zeropadded to 0.8 mm), except for the FLAIR sequence for which this was 2.5 mm. We used an automated brain tissue classification method, based on a k-nearest-neighbor-classifier algorithm[21], to quantify the following: total intracranial volume (ICV), total brain volume, grey matter volume, white matter volume, and cerebrospinal fluid volume (in cubic millimetres). To facilitate more regionalized analysis of total brain, grey matter, and white matter volumes, we segmented individual lobes, by non-rigidly registering a template image in which the lobes have been manually outlined (Figure 1)[22, 23]. Voxel-based morphometry (VBM) was performed according to an optimized VBM protocol[24]. FSL software[25] was used for VBM data processing, all grey matter and white matter density maps were non-linearly registered

to the standard ICBM MNI152 grey matter and white matter template (Montreal Neurological Institute) with a 1 mm × 1 mm × 1 mm voxel resolution. Subsequently, a spatial modulation and smoothing procedure with 3 mm (FWHM 8 mm) isotropic Gaussian kernel were applied to all images.

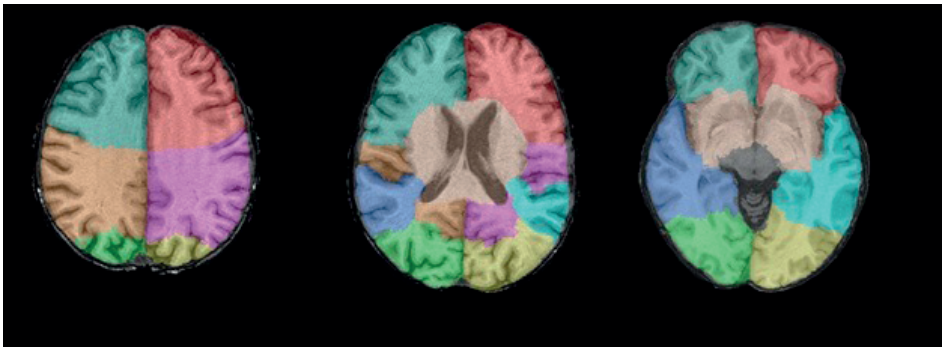

Figure 1. The template image for the individual lobes as seen from three axial coupes. Blue-grey = right frontal lobe; red = left frontal lobe; brown = right parietal lobe; purple = left parietal lobe; green = right occipital lobe; yellow = left occipital lobe; blue = right temporal lobe; turquois = left temporal lobe.

Other Measurements

We collected detailed information on relevant covariates by interview, physical examination, and blood sampling[15]. Assessment of systolic and diastolic blood pressure, Body mass index (BMI), cognition (Mini-Mental State Examination (MMSE)), smoking, and alcohol consumption was done at the research centre the day the hearing tests were conducted. Smoking was categorized as never, former, or current. Alcohol consumption was categorized as non-consumer, light consumer (1 unit of alcohol per day for women and 1–2 units of alcohol per day for men), or above-average (more than 1 unit of alcohol per day for women and more than 2 units of alcohol per day for men)[26]. Level of education was categorized as having completed primary educational level, secondary educational level, or higher education. Fasting blood samples were obtained and serum total cholesterol and high density lipoprotein (HDL) cholesterol were measured using an automatic enzymatic procedure (Hitachi analyzer, Roche Diagnostics). Glucose was determined enzymatically by the Hexokinase method. We calculated the cholesterol ratio by the quotient of the total and high density lipoprotein cholesterol. Diabetic mellitus was defined as fasting glucose was 7 mmol/L or more, or non-fasting glucose was 11 mmol/L or more, or subjects used antidiabetic medication, diabetes was stated present.

Population for Analysis

We performed audiometric measurements and brain MRI in 3,168 subjects. From these, 240 subjects with conductive hearing loss and 20 with an incomplete pure-tone audiogram were excluded, leaving 2,908 subjects for analyses.

Statistical Analysis

To allow direct comparison of effect estimates, we calculated Z-scores for the different brain volumes (total brain volume, grey matter volume, and white matter volume). Missing data on covariates in 305 (10.5%, maximum 7.1% per variable) subjects were entered using multiple imputation (iterations = 5). The difference in standardized brain volume and 95% confidence intervals (CI) were calculated per decibel increase in hearing threshold. This was done for the all tone average-, low-, speech-, and high frequency average. Higher thresholds indicate worse hearing. Model 1 was adjusted for age (linear and quadratic terms), sex, time between the conduction of MRI and hearing assessment, and ICV. Model 2 was additionally adjusted for MMSE, educational level, systolic and diastolic blood pressure, presence of diabetes mellitus (DM), cholesterol ratio, BMI, smoking, and alcohol consumption. In the VBM analysis the same linear regression models were fitted with voxel values of grey matter and white matter density as the dependent variable. Statistical significant threshold for family wise error correction was calculated by performing 10,000 random permutation tests, resulting to a *p*-value threshold of 3 × 10−7. Data analysis was done using IBM SPSS Statistics version 21 (IBM, Armonk, NY, USA), and R version 3.1.2 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Descriptives

The mean age at the time of the hearing assessment was 64.9 years (SD 7.3) and 56% of the subjects were female. Table 1 displays all relevant characteristics of the study population.

Hearing Function and Brain Volumes

Table 2 shows how hearing impairment is related to brain volume. We found that a higher hearing threshold (*i.e.,* worse hearing) was significantly associated with a smaller brain volume (difference in standardized brain volume per decibel increase in hearing threshold in the age-sex adjusted model: −0.003; CI 95% −0.004; −0.001). When brain tissues were analysed separately, the association with the pure-tone audiogram appeared to be driven by white matter volume only (difference in standardized brain volume per decibel increase in hearing threshold −0.004; CI 95% −0.006; −0.001). Above associations were present in all frequencies, however, the effect size was strongest in the lower frequencies. Adjustment for cardiovascular risk factors, alcohol consumption, education and MMSE score did not alter the associations (Table 2, model 2).

Table 1. Characteristics of the study population (N = 2,908).

Characteristics	
Sex, female	1631 (56.1%)
Age, years	64.9 (±7.3)
Age range, years	52-99
Body mass index, kg/m^2	27.4 (±4.2)
Educational level	
Secondary	1343 (46.1%)
Higher	747 (25.7%)
MMSE score, median (IQR)	29 (27;29)
Systolic blood pressure, mmHg	138.7 (±20.4)
Diastolic blood pressure, mmHg	82.9 (±11.0)
Diabetes mellitus, yes	253 (8.7%)
Cholesterol ratio	3.97 (±1.25)
Smoking	
Former	1473 (50.7%)
Current	483 (16.6%)
Alcohol consumption	
Light consumer	2078 (71.5%)
Above-average	259 (8.9%)
Intracranial volume, ml	1140.0 (±115.2)
Grey matter, ml	475.5 (±49.5)
White matter, ml	360.7 (±50.7)
Low frequency hearing impairment, dB	14.1 (±8.3)
High frequency hearing impairment, dB	32.4 (±16.9)
Hearing aid users	170 (5.8%)

Unless stated differently values are means (and standard deviation) for continuous variables or numbers (and percentage) for dichotomous variables. Data represent original data without imputed values. Missing values were present for Body mass index (0.1%), educational level (1.0%), MMSE score (0.5%), systolic and diastolic blood pressure (0.5%), cholesterol ratio (2.0%), smoking (0.2%) and alcohol consumption (7.1%). * Calculated in average grams a day. Light consumer for women is 0-10 g a day, for men 0-20 g a day. Above-average for women is more than 10 g a day, for men more than 20 g a day[26]. N, number; IQR, interquartile range; ml, millilitres; dB, decibel.

Table 2. Association between auditory function and brain volumes.

	Total brain volume		**Grey matter volume**		**White matter volume**	
	Difference (95% CI)	*p*	Difference (95% CI)	*p*	Difference (95% CI)	*p*
Per dB increase			**Model 1 (N = 2,908)**			
All frequencies	**-0.003 (-0.004;-0.001)**	**0.000**	-0.001 (-0.003;0.001)	0.434	**-0.004 (-0.006;-0.001)**	**0.003**
Low frequencies	**-0.004 (-0.006;-0.002)**	**0.000**	-0.001 (-0.003;0.002)	0.691	**-0.006 (-0.009;0.000)**	**0.000**
Speech frequencies	**-0.002 (-0.004;-0.001)**	**0.000**	-0.001 (-0.003;0.001)	0.323	**-0.003 (-0.005;-0.001)**	**0.016**
High frequencies	**-0.001 (-0.002;0.000)**	**0.002**	0.000 (-0.002;0.001)	0.770	**-0.002 (-0.004;0.000)**	**0.011**
			Model 2 (N = 2,908)			
All frequencies	**-0.002 (-0.004;-0.001)**	**0.001**	-0.001 (-0.003;0.002)	0.562	**-0.003 (-0.006;-0.001)**	**0.010**
Low frequencies	**-0.004 (-0.005;-0.002)**	**0.000**	0.000 (-0.002;0.003)	0.733	**-0.005 (-0.008;-0.002)**	**0.001**
Speech frequencies	**-0.002 (-0.003;-0.001)**	**0.003**	-0.001 (-0.003;0.001)	0.400	**-0.002 (-0.005;0.000)**	**0.046**
High frequencies	**-0.001 (-0.002;0.000)**	**0.012**	0.000 (-0.001;0.001)	0.969	**-0.002 (-0.003;0.000)**	**0.026**

Outcomes indicate the difference (and CI 95%) in standardized brain volume per decibel increase in hearing threshold (indicating worse hearing). Model 1 was adjusted for age, age^2, sex, time between MRI and audiometry and intracranial volume. Model 2 was adjusted as model 1, and additionally for educational level, MMSE score, systolic and diastolic blood pressure, BMI, DM, cholesterol ratio, smoking and alcohol consumption. Significant findings ($\alpha < 0.05$) are shown in bold. All frequencies (0.25, 0.50, 1, 2, 4 and 8 kHz); Low frequencies (0.25, 0.50 and 1 kHz); Speech frequencies (0.50, 1, 2 and 4 kHz); High frequencies (2, 4 and 8 kHz). CI, confidence interval; dB, decibel.

White Matter Volume in the Different Brain Lobes

Apart from total brain volume, the volumetric parameters of white matter in the frontal, temporal, parietal, and occipital lobe were analysed (Figure 2). We found similar and significant associations among all four brain lobes for low frequency hearing impairment, independently from the side of the hemisphere. Alike the first analysis, a higher hearing threshold (worse hearing) was significantly associated with smaller white matter volume. For high frequency hearing impairment, we also found associations for the frontal, temporal, parietal, and occipital lobe. Although these were not all significant, they point toward a similar effect: a higher hearing threshold (worse hearing) seems to be associated with smaller white volume.

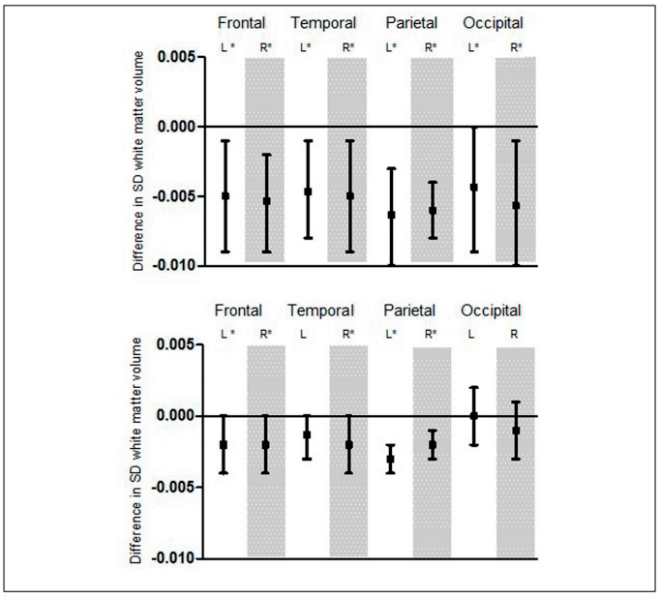

Figure 2. Association for hearing thresholds and white matter volume displayed for the different lobes. First: variation for low frequency pure-tone threshold. Second: variation for high frequency pure-tone threshold. Boxplots show the difference in SD white matter volume per decibel hearing threshold. Significant findings ($\alpha < 0.05$) are marked with *. This model was adjusted for age, age^2, sex, time between MRI and audiometry, intracranial volume, educational level, MMSE score, systolic and diastolic blood pressure, BMI, DM, cholesterol ratio, smoking and alcohol consumption. L, left; R, right; SD, standard deviation.

Voxel-Based Morphometry

After exploring the brain lobes, we conducted exploratory voxel-based analysis to identify if age-related hearing impairment was associated with certain grey matter and white matter regions on voxel level. The analysis showed association for smaller white matter in certain areas such as right pre and postcentral gyri, the right insula and the left posterior temporal lobe (Figure 3). Mainly, stronger associations were shown in the right hemisphere, while in the posterior temporal lobe this was in the left hemisphere. Again, associations were more pronounced in the lower than the higher frequencies. For grey matter, we saw association for both smaller and larger volumes in especially the superior frontal gyrus and medial orbital gyrus right, and the superior parietal gyrus left (Figure 4). However, none of the voxels reached the multiple-testing correction threshold (Supplementary Tables 1 and 2, which can be found online).

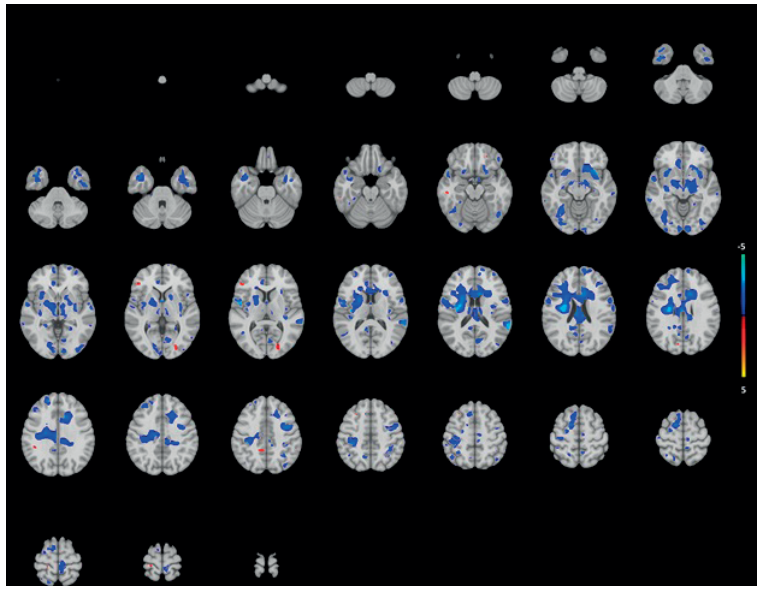

Figure 3. Projection of voxel-based white matter areas on axial coupes associated with age-related hearing impairment. Colours reflect the tendency of the association: blue for a negative direction (decrease of white matter), red for a positive direction (increase of white matter). See Supplementary Tables online for exact outcome per area.

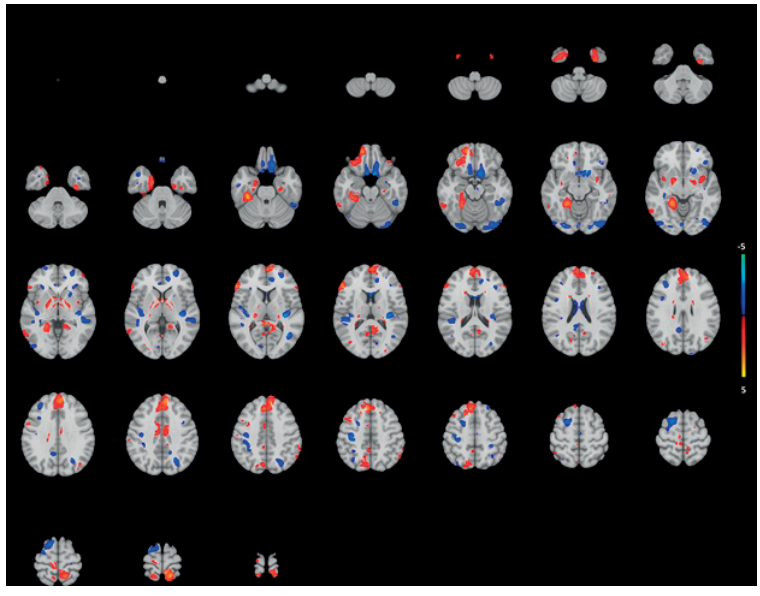

Figure 4. Projection of voxel-based grey matter areas on axial coupes associated with age-related hearing impairment. Colours reflect the tendency of the association: blue for a negative direction (decrease of grey matter), red for a positive direction (increase of grey matter). See Supplementary Tables online for exact outcome per area.

DISCUSSION

In a large sample of older adults, we found that hearing impairment was associated with a small total brain volume. These associations were driven by small white matter volumes, consistent over all hearing frequencies, and independent of cardiovascular risk factors, alcohol consumption, educational level, and MMSE score. The association between hearing impairment and white matter volume was present in all brain lobes. Although not significant, we found mainly an association in our voxel-based analysis in specific areas in the right pre and postcentral gyrus right, the right insula and the left temporal gyrus. Strengths of this study were the large sample size, the standardized assessment of hearing impairment with pure-tone audiograms, and the automated, volumetric assessment of brain volumes. Moreover, we were able to adjust for multiple determinants that are known to be associated with age-related hearing impairment[4]. Yet, some limitations of our study should also be addressed. First, although we took into account a large set of potential confounding factors, genetic factors may play a substantial role in the etiology of age-related hearing impairment[27]. We were unable to investigate this. Second, due to the cross-sectional design of this study, interpretation of the results with respect to cause and effect is not possible.

Total Brain, White Matter, and Grey Matter Volume

Although aging causes cortical grey matter atrophy[28] and is also strongly associated with hearing impairment[4], we found an association between hearing impairment and a small total brain volume independent of age. Additional adjustments for cognition, alcohol consumption, and cardiovascular risk factors did not influence this relation. When investigating brain volume more specifically, the relation between hearing impairment and smaller total brain volume was solely driven by white matter volume. This is in line with various other studies that reported age- and sex adjusted associations between hearing impairment and white matter volume[10, 12, 14, 29]. Interestingly, one other study[14] did find an significant association between hearing impairment and grey matter. They found hearing impairment to be related to a decrease of grey matter volume in specifically the right temporal lobe. We explain these differences in results through differences in study design. By performing a longitudinal study, Lin et al.[14] could correct for possible intra-individual brain volume differences, thereby eluding the effect of heterogeneity. Unfortunately, this is not to overcome by a cross-sectional design. Profant et al.[13] found results similar to ours, as they showed hearing impairment to be not associated with smaller grey matter volume. This was only influenced by age. Other cross-sectional studies that did find associations with hearing impairment and brain volumes mainly focused on grey matter in specific brain regions[9], and even found smaller and larger grey matter volumes contemporaneously in hearing impaired subjects[10, 30], something we found in our VBM analysis as well. Several potential mechanisms may be underlying the relation between hearing impairment and brain volume. First, hearing impairment and smaller brain volumes might be the results of mutual

risk factors, which is often referred to in the literature as the "*common-cause hypothesis*"[31]. This mechanism fits with our findings that suggest a generalized rather than a singular effect in specific brain areas. Such effect might be of microvascular origin, as this is a known process in both cerebral and peripheral auditory systems[32].

Second, brain atrophy might induce hearing impairment. This implicates that hearing impairment – as measured by the pure-tone audiogram – also reflects certain central auditory changes. It has been generally adopted that the pure-tone audiogram only reflects to peripheral auditory function, as it does not require higher central auditory processing[33]. It is difficult to justify that atrophy of the brain would lead to peripheral effects only. Third, peripheral hearing impairment may induce brain atrophy through neural deprivation of the auditory system by loss of sensory input[34]. This causative effect has already been described in animal studies, although its role is not clear for the aging human auditory system[35]. In this case we might expect to find initial atrophy in specific brain lobes that are involved in auditory processing such as the temporal lobe. Although we initially found comparable associations across all brain lobes in our main analysis, our voxel-based analysis revealed stronger associations in certain brain regions. Poorer hearing was associated with smaller white matter volume in the left temporal lobe, which is the location of the auditory cortex and thus involved in high-level auditory processing. The same goes for the right insula, which participates in key auditory processes[36] and the right pre and post gyri (speech relevant regions). This suggests that volume differences exist in specific brain regions that are more related to the process of hearing impairment than other regions. The associations in the voxel-based analysis were not significant, but we assume this is a power related problem. It would be interesting to study the effect of hearing aid use in relation to the hypothesis above, as this might reduce the process of neural deprivation. Unfortunately, only 6% (N = 170) of the participants in our study wore hearing aids and after excluding them, results did not change. As has been described previously, different types of age-related hearing impairment arise from different origins[6]. Strial presbycusis involves atrophy of the stria vascularis especially in the apex and thus affects the lower frequencies. Sensory presbycusis involves loss of outer hair cells especially in the base of the cochlea and thus affects the higher frequencies. As such, stronger associations between white matter volume and low frequency thresholds suggest at least some influence of a vascular factor. Although we adjusted for known traditional cardiovascular factors, these factors may not reflect well the more subtle differences in (micro)vascularization that might be involved in the case of age-related hearing impairment. Realistically, the above mentioned hypotheses are not mutually exclusive and could all take (a minor) part in the etiology of age-related decline in hearing and brain morphology.

CONCLUSION

Our findings demonstrate that age-related hearing impairment is associated with a smaller total brain volume, specifically white matter volume. Furthermore, though the association is found generalized throughout the brain, there is a suggestion of certain brain regions to be more strongly involved. Associations were independent of age, sex, cognitive function, cardiovascular risk factors, and alcohol consumption. Our results contribute to the culminating evidence that age-related hearing impairment and morphological differences in the brain interact. Additional research on this topic is needed to identify the relevant underlying causative mechanisms and possible preventive effects of early treatment, such as timely use of hearing aids.

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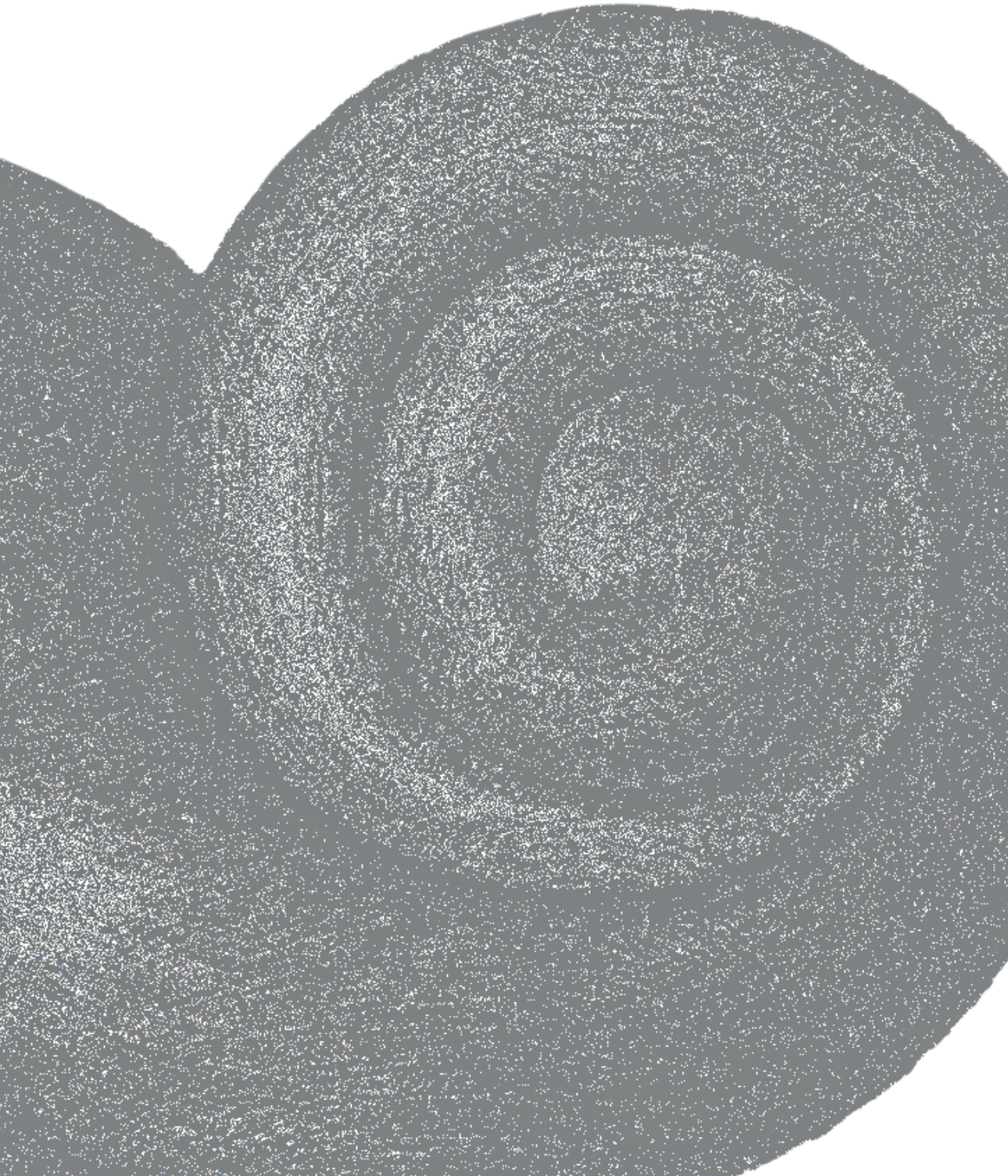

5

White matter microstructure and hearing acuity in older adults: a population-based cross-sectional DTI study

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ABSTRACT

To study the relation between the microstructure of white matter in the brain and hearing function in older adults we carried out a population-based, cross-sectional study. In 2,562 participants of the Rotterdam Study, we conducted diffusion tensor imaging to determine the microstructure of the white matter tracts. We performed pure-tone audiogram and digit-in-noise tests to quantify hearing acuity. Poorer white matter microstructure, especially in the association tracts, was related to poorer hearing acuity. After differentiating the separate white matter tracts in the left and right hemisphere, poorer white matter microstructure in the right superior longitudinal fasciculus and the right uncinate fasciculus remained significantly associated with worse hearing. These associations did not significantly differ between middle-aged (51-69 years old) and older (70-100 years old) participants. Progressing age was thus not found to be an effect modifier. In a voxel-based analysis no voxels in the white matter were significantly associated with hearing impairment.

INTRODUCTION

Progressive sensorineural hearing impairment is a common feature of aging. It is characterized by a gradual decline of hearing thresholds and worse understanding of speech, which seriously affects the quality of life[1]. Although cochlear damage is generally believed to cause age-related hearing impairment, there is strong evidence that age-related hearing impairment also has a central component in its pathogenesis[2]. Moreover, age-related hearing impairment seems to interact with the general cognitive function[3]. Multiple hypotheses on the mechanism between hearing acuity and brain alterations have been outlined. The "*common-cause hypothesis*" describes a mutual factor that affects both hearing acuity as well as brain alterations. This mutual factor could possibly be age, cognition, or an underlying pathological factor such as cardiovascular damage[4]. There are also 2 alternative hypotheses. The "*information-degradation hypothesis*" describes an indirect effect between hearing and the brain through a shift of cognitive functions. The "*sensory-deprivation hypothesis*" describes a direct causal relationship in which worse hearing acuity leads to brain alterations[5]. Previous studies using brain imaging have demonstrated that hearing acuity in the aged and middle-aged population relates to morphological brain changes (*e.g.* grey- or white matter atrophy)[6-9]. In a previous study in almost 3,000 people conducted by our group white matter atrophy, but not grey matter atrophy, was associated with age-related hearing impairment[9]. However, apart from the association with gross morphological differences, no conclusion on the underlying white matter microstructure could be made. White matter microstructure degenerates with aging[10, 11] and rates and timing of degradation vary regionally[12]. Reduced organization of white matter microstructure could repress communication between neurocognitive networks[13]. Previously, auditory and language functions have been ascribed to frontotemporal and parietal white matter connections[14], especially in the left hemisphere due to functional lateralization. In recent years, diffusion tensor imaging (DTI) has increasingly been used to study brain white matter tracts. This technique allows for estimation of the microscopic organization of neural tracts by providing information on the diffusion properties of water molecules in the tissue[15]. Parameters that are frequently derived from DTI include fractional anisotropy (FA) and mean diffusivity (MD). Worsening of white matter integrity is generally reflected in a lower FA and higher MD[15]. The study of Chang et al.[16] was one of the first to investigate the relation between white matter tracts and hearing function using DTI and pure-tone audiometry. They found a lower FA in the central auditory system in participants with sensorineural hearing impairment. However, they limited their region of interest to the higher auditory system rather than the whole brain. Due to a small sample size, they were not able to correct for confounders. Lin et al.[17] also studied this relation by comparing age-matched participants with hearing impairment and participants with normal hearing, using DTI and pure-tone audiometry. They also studied the auditory pathway instead of the whole brain and had similar results. Moreover, they found a linear relation between FA and the degree of hearing impairment. Husain et al.[7] conducted a third cross-sectional

study and performed DTI on the white matter association tracts. They found a different FA for both hemispheres. The association tracts into and out of the right temporal and frontal cortex had poorer white matter microstructure in participants with worse hearing thresholds when compared with participants with normal hearing. The same tracts in the left hemisphere were not associated with hearing impairment. These 3 studies have in common that the study samples were small (maximum N = 47), age ranges were wide (between 8 and 85 years old), and authors only focused on specific regions of interest (ROI) in the brain known for their auditory function instead of whole brain analysis. On the contrary, Profant et al.[18] found no significant associations between the organization of white matter tracts and age-related hearing impairment. They also investigated specific ROIs, and they used an equally small sample size, but they studied relatively old participants (mean age in the older group was 70.4 ± 1.3 years).

Although most of these studies show that microstructural changes in white matter and hearing loss are correlated, some essential issues remain to be investigated[19]. First, ROI's have not consequently been defined, which makes direct comparison of results impossible. It would be useful to additionally study potential changes in brain regions beyond those used for auditory processing. Second, different hearing outcomes have been used (*e.g*. speech- vs. high frequency thresholds) and speech-in-noise ability was not tested. Third, the relationship between cognitive decline, aging, and hearing impairment and their effect on brain structure and function is hard to investigate because of confounding effects. A population-based study could provide an unbiased evaluation of the association between white matter microstructure and age-related hearing acuity.

To address the above issues, we conducted a large population-based study on community-dwelling older adults. Our primary objective was to analyse the association between the global and tract-specific white matter microstructure and hearing acuity using DTI. Second, we aimed to investigate the effect of aging on this possible association, because aging is associated with both white matter degeneration and worse hearing acuity. In the analyses, we used both auditory thresholds (low-, speech-, and high frequencies) and the ability for speech recognition in noise, and we accounted for possible cognitive and cardiovascular covariates. We hypothesized that participants with worse hearing acuity would have a lower FA and higher MD, which corresponds with poorer white matter microstructure in the tracts. We assumed different outcomes for different tracts, based on anatomy and function, with stronger relations for association tracts directly or indirectly involved in auditory processing such as the superior longitudinal fasciculus, the inferior fronto-occipital fasciculus and the uncinate fasciculus. Furthermore, since we hypothesized that aging could amplify the effect between white matter microstructure and hearing acuity, we expected to find a larger effect in older than in middle-aged participants.

MATERIALS AND METHODS

Study population

This cross-sectional study is based on participants of the population-based Rotterdam Study, an ongoing prospective cohort study on healthy aging[20]. The Rotterdam Study includes inhabitants of 45 years and older of Ommoord, a Rotterdam district. It currently includes 14,926 participants. Participants undergo several measurements every 3-5 years. From 2005 onward, MRI scanning was added to the study protocol[21] and from 2011 onward, audiometry was incorporated as well. We considered eligible participants with brain MRI, including a diffusion-weighted sequence, and audiometry (N = 2,665). We excluded those with cortical infarcts on the scan (N = 61), with dementia (N = 25) or with conductive hearing loss (N = 17), leaving 2,562 participants for analysis. Dementia was ascertained as previously described using a 3-step protocol[22]. We excluded 104 participants from the analyses concerning the digits-in-noise (DIN) test. They failed to complete the DIN-test or the result was more than 4 standard deviations from the mean, making results less accurate[23]. The Rotterdam Study has been approved by the Medical Ethics Committee of the Erasmus MC and by the Ministry of Health, Welfare and Sports of the Netherlands, implementing the Wet Bevolkingsonderzoek: ERGO (Population Screening Act: Rotterdam Study). All participants provided written informed consent to participate in the study and to obtain information from their treating physicians.

MRI Acquisition and Processing

Multisequence MR imaging was performed in a 1.5 Tesla MRI scanner (GE Signa Excite). The MRI protocol included a T1-weighted image (T1w, repetition time 13.8 milliseconds (ms), echo time 2.80 ms, inversion time 400 ms, 96 slices of 1.6 millimeter (mm), matrix 256 x 256), a T2-weighted fluid-attenuated inversion recovery (FLAIR) sequence (repetition time 8000 ms, echo time 120 ms, inversion time 2000 ms, 64 slices of 2.5 mm, matrix 320 x 224), a proton density-weighted image (repetition time 21,300 ms, echo time 17.3 ms, 90 slices of 1.6 mm, matrix 416 x 256), and a spin echo planar diffusion-weighted image (repetition time 8575 ms, echo time 82.6 ms, 35 slices of 3.5 mm, matrix 64 x 96). Maximum b-value was 1000 s/mm^2 in 25 noncollinear directions. Three volumes were acquired without diffusion weighing (b-value = 0 s/mm^2)[21].

A number of preprocessing steps were performed before analysis[21]. In short, structural scans for each participant were spatially coregistered using rigid registration. After brain masking and nonuniformity correction scans were segmented in grey matter, white matter, cerebrospinal fluid, and background tissue using a supervised approach based on a k-nearest neighbor segmentation approach[24, 25] on the T1-weighted and proton density images. Intracranial volume, with the exclusion of the cerebellum and surrounding cerebrospinal fluid, was defined by the sum of grey and white matter and cerebrospinal fluid volumes. The brain tissue segmentation method was followed by a white-matter lesion segmentation. This was performed with an in-house

developed automated segmentation method using a 2-step protocol which relies on the brain tissue segmentation and the FLAIR image[26]. We used Elastix[27] to correct the diffusion images for subject motion and eddy currents, using an affine registration. Tensors were estimated using a Levenberg-Marquardt algorithm in ExploreDTI[28]. The same motion corrected diffusion data were also used to estimate the probabilistic model required for ProbTrackx tractography[29]. We performed tractography in native space, using standard space seed, target, stop, and exclusion masks as described previously[30]. The probabilistic tractography algorithm was run with default settings (step length 0.5, curvature threshold 0.2, maximum steps 200). Also, the diffusion model estimation (Bedpostx) was run with default options. Cortical infarcts were visually defined as focal parenchymal lesions <3 mm and >15 mm with involvement of cortical grey matter and with signal characteristics equal to CSF on all sequences and with a hyperintensive rim on the FLAIR image[31]. We computed global mean FA and MD in the normal appearing white matter. FA is the degree of anisotropy and is given as a ratio ranging from 0 (isotropic or non-directional) to 1 (unidirectional). MD is expressed in square millimeters per second. Furthermore, we used the diffusion data to segment 15 (of which 12 segmented bilaterally) white matter tracts using probabilistic tractography as previously described[32]. Tracts were grouped-based on anatomy or presumed functional groups into brainstem tracts (middle cerebellar peduncle and medial lemniscus), projection tracts (corticospinal tract, anterior thalamic radiation, superior thalamic radiation, and posterior thalamic radiation), association tracts (superior longitudinal fasciculus, inferior longitudinal fasciculus, inferior fronto-occipital fasciculus, and uncinated fasciculus), limbic system tracts (cingulate gyrus part of cingulum, parahippocampal part of cingulum, and fornix), and callosal tracts (forceps major, forceps minor) in the left and right hemisphere[32]. Due to tractography failures or (visually) rejected segmentations, tract-specific measurements were missing for on average 6.9 participants (ranging from 0 to 61 participants) per tract. We obtained tract-specific diffusion measures (mean FA and mean MD per tract)[32]. We standardized global and tract-specific diffusion measures (z-scores). We obtained tract-specific white matter volumes and tract-specific white matter lesion volumes (natural log-transformed) by combining tissue and tract segmentations. Varying seed masks were used to account for partial coverage of the medial lemniscus (one of the brainstem tracts), and this was considered as a potential confounder in the analyses in which the medial lemniscus was investigated.

Voxel-based Analysis

Voxel-based analysis (VBA) of DTI data was performed according to the voxel-based morphometry method[33] as previously described[34]. FSL software[29] was used for VBA data processing. All FA and MD maps were nonlinearly registered to the standard FA template from the FSL package with a 1 x 1 x 1 mm^3 voxel resolution. In addition, the Rotterdam Study tract template that was used for analysing the DTI measures per tract was mapped to MNI space, to assess location of association and compare VBA results with global DTI measures. Participant-specific tract segmentation masks[32] were registered to MNI template in the same way as FA and MD maps

and then merged to 1 tract template image. We used 90% probability thresholds to define the tract templates.

Audiometry

All audiometry was performed in a soundproof booth by a single qualified health professional. A clinical audiometer (Decos audiology workstation, version 210.2.6, with AudioNigma interface), TDH-39P earphones and B71 bone conductor were used. Pure-tone audiometry thresholds were measured according to the International Organization for Standardization 8253-1[35]. Air conduction (0.25, 0.50, 1, 2, 4, and 8 kHz) and bone conduction (only 2 frequencies due to limited time: 0.5 and 4 kHz) were tested for both the ears. Masking was done according to the method of Hood[36]. Bone conduction thresholds at 4 kHz were compensated with +10 decibel (dB) afterward[37]. We determined the best hearing ear by calculating the mean threshold over all frequencies. If both the ears were equal, right or left was alternately chosen. Of the best hearing ear, we then determined the low-(mean of 0.25, 0.50 and 1 kHz), speech- (mean of 0.50, 1, 2 and 4 kHz), and high frequency hearing thresholds (mean of 2, 4 and 8 kHz). We excluded participants with an air-bone gap of 15 dB or more to eliminate clinically relevant conductive hearing loss. In addition, the DIN-test was performed to detect the speech recognition ability in noise[38]. Again, this was done for the best hearing ear. The test measures a speech reception threshold by letting participants repeat digit triplets in an automated adaptive procedure and changing the signal to noise ratio according to the correctness of the answer. The speech reception threshold represents a speech-in-noise ratio for 50% correctly repeated triplets. A higher value represents a worse ability of understanding speech in noise. To avoid confounding for peripheral hearing acuity, we additionally adjusted for the high frequency hearing thresholds in the analyses with the DIN-test.

Other Covariates

Information on various covariates was collected through a home interview at enrollment of the study, or by recurrent physical examination and blood sampling at the study center. Education was qualified as having completed primary level, secondary level, or higher education. Mini-Mental State Examination (MMSE) score, body mass index, systolic and diastolic blood pressure, diabetes mellitus, cholesterol ratio, smoking habits, and alcohol consumption were reassessed every follow-up visit. Diabetes mellitus was stated present when fasting glucose was 7 mmol/L or more, or (if unavailable) when nonfasting glucose was 11 mmol/L or more, or when participants used antidiabetics. Cholesterol ratio was calculated via the quotient of serum total-cholesterol and high-density cholesterol. Smoking was categorized as never, former, or current. Alcohol consumption was categorized as non-consumer, light consumer (1 unit of alcohol per day for women and 1-2 units of alcohol per day for men) or above-average consumer (more than 1 unit of alcohol per day for women and more than 2 units of alcohol per day for men)[39]. We used the data on covariates from the same follow-up round as the MRI and audiometry measurements. Except for the MMSE score, which was registered 1 round earlier.

Statistical Analysis

Associations between DTI measurements (FA and MD) and hearing acuity were explored using multivariable linear regression models. Global and tract-specific FA and MD were regarded as independent variables, and pure-tone thresholds and score on the DIN-test as dependent variables. We calculated regression coefficients and 95% confidence intervals (CIs). Significance was set at $p < 0.05$ for the analyses concerning global DTI measurements. To account for multiple testing in the tract-specific analyses, we used the Sidak-correction, which was set at $p < 0.00248$ for the analyses in which we averaged left and right tract-specific measures and set at $p < 0.00156$ for the tract-specific analyses of left and right separately. To adjust for the covariates, we used 2 models. Model 1 was the 'simple' model and adjusted for age, gender, time between DTI and audiometry, intracranial volume, white matter volume and white matter lesions (log-transformed, global, or tract-specific). Model 2 was extended with possible confounders on the association between altered white matter tracts and hearing acuity. Specifically, we investigated the impact of potential vascular confounders, known for their association with altered white matter (De Groot et al., 2015) and hearing acuity (Gates and Mills, 2005). Model 2 further adjusted for: education, MMSE score, body mass index, systolic and diastolic blood pressure, the presence of diabetes mellitus, cholesterol ratio, and smoking and alcohol consumption. For analyses involving the medial lemniscus, we additionally adjusted for the varying position of seeds masks. In the analyses on the DIN-test, we adjusted for high frequency hearing loss as well. We repeated the analyses after stratification between middle-aged (51-69 year old) and older participants (70-100 years old). We examined the presence of multicollinearity and found no variance inflation factor larger than 4. For the VBA linear regression models were fitted with voxel values of FA and MD measures as dependent variables and pure-tone thresholds and score on the DIN-test as independent variables. Furthermore, we corrected the VBA models like the DTI models (mentioned previous). For this analysis, all voxels within the white matter mask were used. To estimate the threshold for significance, a nonparametric permutation test was performed independently for FA and MD. We shuffled the data randomly 5000 times and performed VBA. For every permutation, we saved the minimum *p*-value. Subsequently, we took the 5th percentile of this minimum *p*-value distribution to compute the family-wise error *p*-value threshold, which was 1.21×10^{-7} for FA and 1.23×10^{-7} for MD[40]. To map the significant voxels to the tract location, we created a tract study-specific atlas. Subject-specific tract segmentations[32] were registered to MNI template using FSL software. All these transformed images were merged and divided by number of participants to make a probabilistic tracts template. Due to between-participants variation in tract location, probabilistic templates allowed us to map voxels with different certainty.

Missing data were minimal (0.4% of total data) and were imputed in SPSS using fivefold multiple imputation with an iterative Markov chain Monte Carlo method, based on determinant, outcome, and included variables. Distribution of covariates was similar in the imputed and the

nonimputed data set. We pooled the data by aggregating the file in SPSS before analysing it in R. Data analysis was performed using IBM SPSS Statistics version 21 (IBM, Armonk, NY, USA), and R version 3.1.2 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

The demographic characteristics of the 2,562 participants are provided in Table 1. Hearing thresholds on the pure-tone audiogram were higher toward the higher frequencies, as typically seen in age-related hearing impairment (Figure. 1).

Table 1. Characteristics of the study population at baseline (N = 2,562).

Characteristics	
Age, years	69.3 (±9.6)
Sex, female	1412 (55.1%)
Educational level	
Primary	176 (6.9%)
Secondary	1762 (68.8%)
Higher	597 (23.3%)
MMSE score (median, IQR)	29 (27;29)
Body mass index, kg/m^2	27.3 (±4.0)
Systolic blood pressure, mmHg	144 (±21.4)
Diastolic blood pressure, mmHg	84 (±11.0)
Diabetes mellitus, yes	332 (13.0%)
Cholesterol ratio	3.90 (±1.21)
Smoking	
Never	863 (33.7%)
Former	1323 (51.6%)
Current	368 (14.4%)
Alcohol consumption	
Never	354 (13.1%)
Light consumer	2077 (77.9%)
Above-average	222 (8.7%)
FA, global white matter	0.34 (±0.016)
MD, global white matter ($x10^3$ mm^2/s)	0.75 (±0.027)
PTA, low frequencies, dB	17.2 (±10.7)
PTA, speech frequencies, dB	24.8 (±13.6)
PTA, high frequencies, dB	37.9 (±19.5)
DIN-score[a] (median, IQR)	-5.0 (-6.4;-2.4)

Unless stated differently values are means (and standard deviation) for continuous variables or numbers (and percentage) for categorical variables. Data represent original data without imputed values. Data were missing and imputed for systolic and diastolic blood pressure (0.1%), MMSE score (0.2%), educational level (1.1%), smoking (0.3%) and alcohol consumption (0.3%). dB, decibel; DIN, digits-in-noise test; FA, fractional anisotropy; IQR, interquartile range; MD, mean diffusivity; MMSE, Mini-Mental State Examination; PTA, pure-tone audiometry. [a] for DIN N = 2,408.

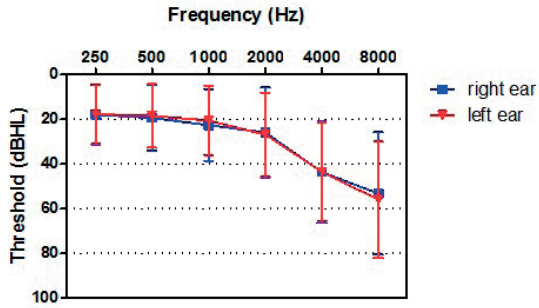

Figure 1. Mean hearing thresholds on the pure-tone audiogram of all participants (N = 2,562). Error bars indicates 95% CI. dBHL, decibel hearing level; Hz, Hertz.

The association between global DTI measures and hearing acuity is presented in Table 2. To compare the effect of the DTI measures, the betas of the most important covariates (age, gender, and MMSE score) are also shown. A lower FA was significantly associated with worse hearing acuity, that is, higher hearing thresholds on the pure-tone audiogram (beta per SD decrease in FA = 0.69 dB, 95% CI 0.24; 1.14) and worse performance on the DIN-test (beta per SD decrease in FA = 0.19 signal to noise ratio, 95% CI 0.05; 0.32). Adjusting for the covariates in model 2 showed stronger associations (beta per SD decrease in FA = 0.86 dB on the pure-tone audiogram, 95% CI 0.41; 1.30 and 0.23 signal to noise ratio on the DIN-test, 95% CI 0.09; 0.37). A higher MD was significantly associated with worse hearing acuity on the pure-tone audiogram for the speech and higher frequencies in model 2. MD and the outcomes of the DIN-test were not significantly associated.

Table 2. Association between global DTI measures and hearing acuity.

	PTA (N = 2,563)								DIN (N = 2,408)	
	All β (95% CI)	*p*	**Low** β (95% CI)	*p*	**Speech** β (95% CI)	*p*	**High** β (95% CI)	*p*	β (95% CI)	*p*
Covariate										
↓ In FA (model 1)	**0.69 (0.24;1.14)**	**0.002**	**0.42 (0.00;0.84)**	**0.049**	**0.72 (0.24;1.20)**	**0.003**	**0.97 (0.34;1.59)**	**0.002**	**0.19 (0.05;0.32)**	**0.008**
↑ In age, per year	**0.92 (0.86;0.99)**	**0.000**	**0.53 (0.47;0.60)**	**0.000**	**0.81 (0.74;0.89)**	**0.000**	**1.31 (1.21;1.40)**	**0.000**	-0.02 (-0.04;0.00)	0.054
Sex, male	**2.46 (1.51;3.41)**	**0.000**	**-1.32 (-2.20;-0.47)**	**0.003**	**2.29 (1.27;3.30)**	**0.000**	**6.25 (4.94;7.57)**	**0.000**	**-0.38 (-0.67;-0.08)**	**0.011**
↓ In FA (model 2)	**0.86 (0.41;1.30)**	**0.000**	**0.56 (0.14;0.97)**	**0.008**	**0.87 (0.40;1.36)**	**0.000**	**1.15 (0.53;1.78)**	**0.000**	**0.23 (0.09;0.37)**	**0.001**
↑ In age, per year	**0.90 (0.83;0.98)**	**0.000**	**0.51 (0.45;0.58)**	**0.000**	**0.80 (0.72;0.88)**	**0.000**	**1.30 (1.19;1.40)**	**0.000**	-0.02 (-0.04;0.00)	0.059
Sex, male	**1.97 (0.99;2.95)**	**0.000**	**-1.68 (-2.59;-0.77)**	**0.000**	**1.85 (0.80;2.90)**	**0.001**	**5.63 (4.26;6.99)**	**0.000**	**-0.39 (-0.70;-0.09)**	**0.010**
↑ In MMSE, per point	**-0.40 (-0.64;-0.16)**	**0.001**	**-0.27 (-0.49;-0.04)**	**0.018**	**-0.33 (-0.59;-0.08)**	**0.010**	**-0.53 (-0.84;-0.19)**	**0.002**	**-0.17 (-0.24;-0.09)**	**0.000**
↑ In MD (model 1)	0.43 (-0.09;0.94)	0.103	0.16 (-0.32;0.63)	0.524	0.41 (-0.14;0.96)	0.140	0.70 (-0.14;0.96)	0.055	0.03 (-0.13;0.18)	0.733
↑ In age, per year	**0.92 (0.85;0.99)**	**0.000**	**0.53 (0.47;0.60)**	**0.000**	**0.81 (0.74;0.89)**	**0.000**	**1.30 (1.20;1.40)**	**0.000**	-0.22 (-0.04;0.00)	0.075
Sex, male	**2.46 (1.51;3.41)**	**0.000**	**-1.33 (-2.22;-0.45)**	**0.003**	**2.28 (1.26;3.30)**	**0.000**	**6.26 (4.94;7.59)**	**0.000**	**-0.39 (-0.69;-0.10)**	**0.008**
↑ In MD (model 2)	**0.58 (0.07;1.09)**	**0.026**	0.29 (-0.18;0.77)	0.228	**0.57 (0.02;1.12)**	**0.042**	**0.87 (0.15;1.58)**	**0.017**	0.07 (-0.09;0.23)	0.377
↑ In age, per year	**0.90 (0.82;0.97)**	**0.000**	**0.51 (0.44;0.58)**	**0.000**	**0.80 (0.72;0.88)**	**0.000**	**1.29 (1.18;1.39)**	**0.000**	-0.02 (-0.04;0.00)	0.069

Table 2. Association between global DTI measures and hearing acuity. (*continued*)

	PTA (N = 2,563)								DIN (N = 2,408)	
	All		**Low**		**Speech**		**High**			
	β (95% CI)	*p*	β (95% CI)	*p*	β (95% CI)	*p*	β (95% CI)	*p*	β (95% CI)	*p*
Covariate										
Sex, male	**1.99 (1.00;2.97)**	**0.000**	**-1.68 (-2.59;-0.76)**	**0.000**	**1.87 (0.81;2.92)**	**0.001**	**5.66 (4.29;7.03)**	**0.000**	**-0.40 (-0.71;-0.10)**	**0.009**
↑ In MMSE, per point	**-0.39 (-0.63;-0.15)**	**0.001**	**-0.26 (-0.49;-0.04)**	**0.021**	**-0.33 (-0.59;-0.07)**	**0.013**	**-0.52 (-0.86;-0.18)**	**0.002**	**-0.16 (-0.24;-0.09)**	**0.000**

Outcomes indicates the change in hearing threshold (in decibel) for the PTA and the change in speech reception threshold for the DIN-test per standard deviation change of the DTI measures and most important covariates (and confidence intervals 95%). Significant findings ($p < 0.05$) are shown in bold. All, all frequency threshold average (0.25, 0.50, 1, 2, 4 and 8 kHz); Low, low frequency threshold average (0.25, 0.50 and 1 kHz); Speech; speech frequency threshold average (0.50, 1, 2 and 4 kHz); High, high frequency threshold average (2, 4 and 8 kHz). Model 1 is corrected for time between DTI and audiometry, white-matter volume (ml), white-matter lesion volume (log-transformed) and intracranial volume (ml). Model 2 is corrected as model 1 plus systolic and diastolic blood pressure, body mass index, diabetes mellitus, cholesterol ratio, education, score on MMSE, smoking and alcohol consumption. In the DIN-analyses high frequency hearing loss was also accounted for. DIN, digits-in-noise test; DTI, diffusion tensor imaging; FA, fractional anisotropy; MD, mean diffusivity; MMSE, Mini-Mental State Examination; PTA, pure-tone audiometry.

Subsequently, we analysed the association between tract-specific DTI measurements and hearing acuity (Supplemental Tables 1 and 2). The association of a lower FA and worse hearing acuity was primarily found in the association tracts: superior longitudinal fasciculus, inferior longitudinal fasciculus, inferior fronto-occipital fasciculus, and uncinate fasciculus (Table 3). However, only the association between the superior longitudinal fasciculus and worse hearing on the pure-tone audiogram and the association between the uncinate fasciculus and worse performance on the DIN-test were still significant after the multiple testing correction (p < 0.0024). When differentiating the tracts between left and right hemisphere (Supplemental Tables 3 and 4), a lower FA of the right superior longitudinal fasciculus remained significantly (p < 0.00156) associated with worse hearing on the pure-tone audiogram. A higher MD of the right uncinate fasciculus was also significantly (p < 0.00156) associated with worse hearing on the pure-tone audiogram, whereas the MD of the left and right uncinate fasciculus combined was not (Supplemental Table 2). Both significant tracts (superior longitudinal fasciculus and uncinate fasciculus) are displayed by a tractographic reconstruction in Figures. 2 and 3.

Table 3. Association between the FA of the association tracts and hearing acuity.

	PTA (N = 2,563)								DIN (N = 2,408)	
	All		**Low**		**Speech**		**High**			
	β (95% CI)	*p*	β (95% CI)	*p*	β (95% CI)	*p*	β (95% CI)	*p*	β (95% CI)	*p*
Association tract										
SLF (model 1)	0.70 (0.20;1.19)	0.005	0.37 (-0.09;0.83)	0.114	0.62 (0.24;1.20)	0.021	1.02 (0.34;1.71)	0.003	0.00 (-0.15;0.15)	0.994
SLF (model 2)	**0.84 (0.35;1.34)**	**0.000**	0.49 (0.03;0.95)	0.036	0.76 (0.24;1.29)	0.004	**1.20 (0.52;1.89)**	**0.000**	-0.04 (-0.11;0.19)	0.571
ILF (model 1)	0.58 (0.11;1.05)	0.015	0.42 (-0.02;-0.85)	0.060	0.57 (0.07;1.07)	0.026	0.74 (0.09;0.74)	0.026	0.08 (-0.07;0.22)	0.287
ILF (model 2)	0.62 (0.16;1.09)	0.008	0.46 (0.03;0.89)	0.037	0.62 (0.12;1.12)	0.015	0.79 (0.14;1.44)	0.017	0.10 (-0.05;0.24)	0.182
IFO (model 1)	0.59 (0.10;1.08)	0.018	0.43 (-0.03;0.89)	0.066	0.65 (0.12;1.17)	0.016	0.75 (0.07;1.44)	0.031	0.13 (-0.03;0.28)	0.102
IFO (model 2)	0.67 (0.18;1.16)	0.007	0.50 (0.04;0.95)	0.033	0.73 (0.20;1.25)	0.006	0.84 (0.16;1.53)	0.015	0.15 (0.00;0.30)	0.049
UNC (model 1)	0.28 (-0.21;0.77)	0.257	0.19 (-0.26;0.65)	0.405	0.34 (-0.19;0.86)	0.208	0.37 (-0.31;1.05)	0.283	0.19 (0.04;0.34)	0.011
UNC (model 2)	0.41 (-0.08;0.90)	0.097	0.30 (-0.16;0.75)	0.198	0.46 (-0.06;0.98)	0.084	0.52 (-0.15;1.20)	0.128	**0.23 (0.08;0.38)**	**0.002**

Outcomes indicates the change in hearing threshold (in decibel) for the PTA and the change in speech reception threshold for the DIN-test per standard deviation decrease of FA. Significant findings (p < 0.05) are shown in normal font, findings that survived multiple testing (p < 0.00156) are shown in bold. All, all frequency threshold average (0.25, 0.50, 1, 2, 4 and 8 kHz); Low, low frequency threshold average (0.25, 0.50 and 1 kHz); Speech; speech frequency threshold average (0.50, 1, 2 and 4 kHz); High, high frequency threshold average (2, 4 and 8 kHz). Model 1 is corrected for age, sex, time between DTI and audiometry, white-matter volume (ml), white-matter lesion volume (log-transformed) and intracranial volume (ml). Model 2 is corrected as model 1 plus systolic and diastolic blood pressure, body mass index, diabetes mellitus, cholesterol ratio, education, score on MMSE, smoking and alcohol consumption. In the DIN-analyses high frequency hearing loss was also accounted for. DIN, digits-in-noise test; DTI, diffusion tensor imaging; FA, fractional anisotropy; IFO, inferior fronto-occipital fasciculus; ILF, inferior longitudinal fasciculus; PTA pure-tone audiometry; SLF, superior longitudinal fasciculus; UNC, uncinated fasciculus.

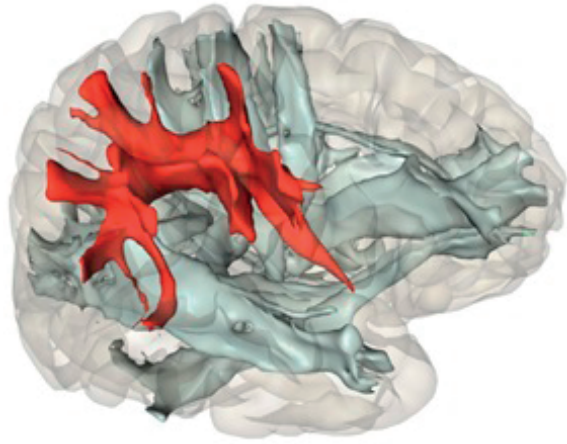

Figure 2. Tractographic reconstruction of the right superior longitudinal fasciculus, sagittal view.

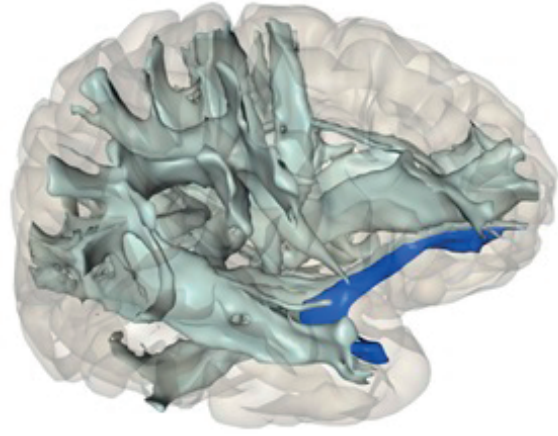

Figure 3. Tractographic reconstruction of the right uncinate fasciculus, sagittal view.

To address our second objective -examining whether there is a different effect caused by progressive aging- we stratified our results into a middle-aged (51-69 years old, N = 1,390) and older (70-100 years old, N = 1,172) group. The associations between global DTI measurements and pure-tone audiogram were significant in the middle-aged group, but not in the older group. On the other hand, the associations between global DTI measurements and the DIN-test were significant in the older group, but not in the middle-aged group. However, interaction was not significant (Supplemental Table 5). Finally, we performed VBA on the white matter tracts to examine whether specific tract-subregions showed primarily associations with worse hearing acuity. FA and MD in the VBA were not associated with hearing acuity on both the pure-tone audiogram and the DIN-test.

DISCUSSION

Our objective was to investigate the association between brain white matter microstructure and hearing acuity in middle-aged and older adults in a large population-based study. We found that poorer white matter microstructure, in particular in association tracts, was significantly associated with worse hearing acuity. Altered white matter microstructure in the right superior longitudinal fascisulus and the right uncinate fasciculus were associated with worse hearing acuity, when differentiating for the white matter tracts in the left and right hemisphere. Progressive aging did not seem to be an effect modifier. In the VBA there were no single voxels in the white matter tracts that were significantly associated with hearing acuity. Our results contribute to the discussion on how white matter microstructure and hearing acuity are related. We found an association in specific auditory and language-related tracts. This could argue against the "*common cause hypothesis*". Otherwise, we would have expected more widespread effect throughout the brain. Moreover, we corrected our analyses for potential confounders and possible components of the "*common cause hypothesis*", such as age and hypertension. The fact that we still found significant associations between poorer white matter microstructure and worse hearing acuity makes the "*common cause hypothesis*" as the main explanation less likely. We acknowledge that we might not have included several unknown confounders. Altered white matter microstructure was both associated with worse hearing on the pure-tone audiogram as well as worse hearing on the DIN-test, which reflects central auditory processing and cognitive skills[41]. The brain alterations may thus have an effect on higher auditory and cognitive functions. This would plead for the "*information-degradation hypothesis*" over a mere loss of sensory deprivation with worse hearing. To further explore the stated hypotheses, a comparative neuroimaging study in hearing impaired participants with or without hearing aids may help narrow possible pathways. Different white matter tracts have a variable susceptibility to age-related structural decline[10]. This could be caused by the location and function of the tracts. It also suggests that different tracts may play a different role in age-related diseases. We found that primarily association tracts, among these the superior longitudinal fasciculus and uncinate fasciculus, were related to hearing acuity. Association tracts connect the different cortical regions of the same hemisphere and are typically located in watershed areas, implying that their blood supply relies on small and deep lenticulostriate arteries. Association tracts may therefore be more vulnerable to insults and vascular damage[42]. The superior longitudinal fasciculus connects the frontal lobe with the temporal, parietal and occipital lobe. Multiple processes, such as language, emotion, and attention have been ascribed to the superior longitudinal fasciculus[43]. The uncinate fasciculus is an association tract that connects the limbic regions in the frontal lobe to the temporal lobe[44]. Its function is not exactly clear, however it seems to be involved in limbic tasks such as emotional processing and memory, including linguistic-related tasks such as naming people[45], semantic processing such as mnemonic associations[46] and better overall language development in children[47]. This is interesting, since we found an asso-

ciation with the uncinate fasciculus and our speech-in-noise test. A lower FA in the right superior longitudinal fasciculus in hearing impaired participants was also found by Husain et al.[7]. They also found associations with the inferior fronto-occipital tract, the corticospinal tract, and the anterior thalamic radiation. However, the authors only published *p*-values and no raw data, making direct comparison of effect sizes not possible. They did not find an association with the uncinate fasciculus. They did not perform a test on speech recognition in noise, such as the DIN-test, for which we primarily found an association with the uncinate fasciculus. This association could suggest that this tract is involved in higher order auditory function, including certain verbal memory functions needed to recall the digits in noise. Our second objective was to investigate the effect of aging on the association between white matter microstructure and hearing acuity. We hypothesized a possible progression of white matter damage in worse hearing acuity with age. Besides correcting for age as a possible confounder in multivariable models 1 and 2, we also stratified our results between middle-aged and older participants to investigate if age is a possible effect modifier. We found no significant interaction, despite the fact that increased FA was significantly associated with a worse outcome on the DIN-test in the older group, whereas in the middle-aged group, this significant association was found in the pure-tone thresholds. Thus, progressive aging does not seem to act as an effect modifier. Profant et al.[18] likewise noticed the differences in the relation between FA and hearing acuity among younger and older participants. Although they compared their older group with a much younger group (mean age 67.9 vs. 24.3) than ours, they also did not find a significant effect. We suggest further research on this relation by performing longitudinal studies, since cross-sectional studies do not allow age changes within individuals to be studied. To our knowledge, we performed the largest study so far on tract-specific white matter microstructure and hearing acuity. Furthermore, we tried to optimize the design. First, we investigated the whole brain instead of the central auditory system and thereby provided an overview of the brain. Second, we explored both peripheral and central hearing function. A pure-tone audiogram reflects more on the peripheral auditory function, whereas a speech-in-noise test informs on higher functions of the auditory system. Third, the tract-specific measurements were performed with fully automated and publicly available methods[10]. Finally, we corrected for cognition and cardiovascular risk factors[19]. Still, our study has several limitations. Within the tracts that we have studied, there was no specific auditory tract. This we tried to preempt by additionally performing an analysis on the voxel level using voxel-based morphometry. No significant voxels were found when we used 90% probability thresholds to define the tract templates (corresponding voxels had to belong to a tract in 90% of the participants). When lowering these thresholds to 10%, we found significant voxels in areas that belong to the right superior fasciculus and right inferior longitudinal fasciculus. However, this means that in only 10% of the participants this was a predefined white matter tract by the anatomical template. We made the choice for a 90% threshold so we were sure that we looked at white matter tracts and not at voxels possibly belonging to other brain areas. An explanation for finding different results with the tract-specif-

ic and voxel-based analysis may be that due to multiple comparisons corrections, the threshold for the voxel-based analysis is too conservative. To detect significant voxels, a bigger sample size would be required. To decrease the number of tests, another method with low resolution can be used, such as for example tract profiles estimation[48]. Third, our study was performed with 25 diffusion gradient directions, and this may have lowered the precision to detect crossing fiber populations. However, probabilistic tractography was performed with a good reproducibility of 0.89[32]. Therefore, we are confident that we could reconstruct the tracts of our interest accurately. Unfortunately, it was not possible to differentiate in our specific-tract data for subcomponents, for example, the 3 segments of the SLF that are presumed to have different functions[49]. Finally, the study design is cross-sectional, making it impossible to state a conclusion on the direction of the effect. Therefore, longitudinal research is required.

CONCLUSION

In 2,562 participants of the Rotterdam Study, poorer white matter microstructure was associated with worse hearing acuity, specifically in the right superior longitudinal fasciculus and uncinate fasciculus. Progressive aging was not found to be an effect modifier.

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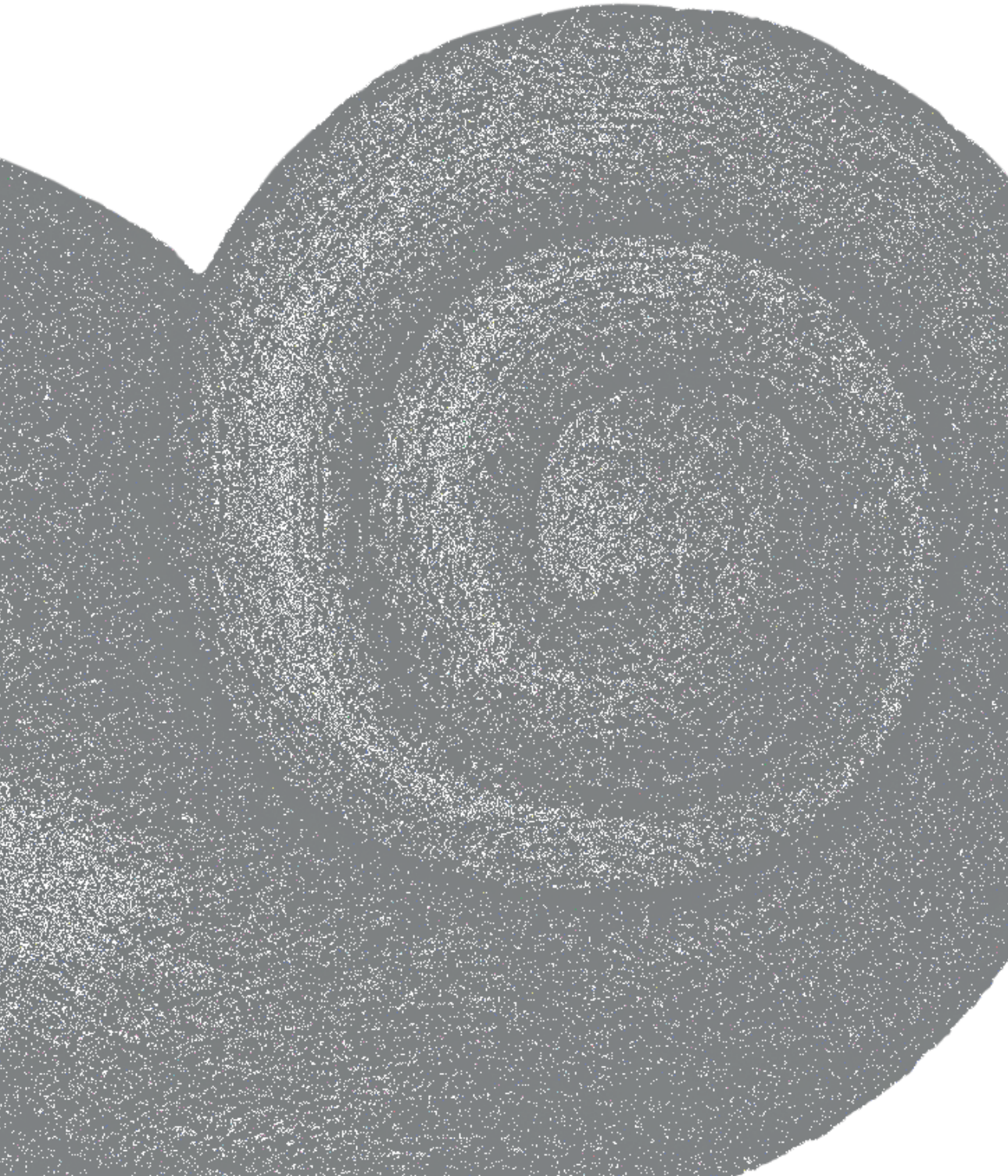

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The effect of hearing aid use on the association between hearing loss and brain structure in older adults

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ABSTRACT

Recent studies have shown an association between poorer hearing thresholds and smaller brain tissue volumes in older adults. Several underlying causal mechanisms have been opted, a "*sensory deprivation hypothesis"* as one of the most prominent. If hearing deprivation would lead to less brain volume, hearing aids could be hypothesized to moderate this pathway by restoration of hearing. This study aims to investigate whether such a moderating effect of hearing aids exists. The authors conducted a cross-sectional study involving aging participants of the population-based Rotterdam Study. Hearing aid use was assessed by interview and hearing loss was quantified using pure-tone audiometry. Total brain volume, grey matter and white matter volume and white matter integrity (fractional anisotropy (FA) and mean diffusivity (MD)) were measured using magnetic resonance imaging. Only participants with a pure-tone mean at 1, 2 and 4 kHz ($PTA_{1,2,4}$) of ≥ 35 dB HL were included (N = 479). Associations of hearing loss with brain volume and global measures of white matter integrity were studied using linear regression analysis, stratified for hearing aid use. Models were adjusted for age, sex, time between audiometry and MRI, level of education, depression, MMSE, and cardiovascular risk factors. The authors included 479 participants with mean age (range) 71.5 (52 to 97). Forty-one percent were female. Distributions of age and sex among hearing aid users (N = 181) did not significantly differ from those without hearing aids. $PTA_{1,2,4}$ was not associated with a difference in total brain volume, grey matter volume, white matter volume, FA or MD. Additional analyses did not reveal any statistical interaction effects between $PTA_{1,2,4}$ and hearing aid use on brain volume and global white matter integrity. The authors found no evidence for a modifying effect of hearing aids on the relationship between hearing loss and brain structure in a population of older adults. Future longitudinal research is needed to confirm these results.

INTRODUCTION

Age-related hearing loss is highly prevalent among the aging population[1, 2]. With population numbers growing and life expectancy globally shifting upwards, an increasing number of adults suffer from impaired hearing. Age-related hearing loss has been linked to decreased participation in everyday life, social isolation, loneliness, and depression[3], and cognitive decline[4] and dementia[5]. It is thought that such cognitive impairment might be a reflection of structural changes in the brain related to hearing loss[6, 7]. Indeed, several studies among older adults have found associations between hearing loss and reduced grey matter volume[8-10], white matter volume[11] or loss of white matter integrity[12, 13].

The underlying causative mechanisms for these alterations of the brain in the presence of hearing loss are still unclear, although various theories have been postulated[7, 14, 15]. One of the most prominent theories, the sensory-deprivation hypothesis, proposes that cognitive function in hearing impaired older adults declines due to changes in brain structure as a consequence of reduced sensory input[15, 16]. If this is the case, one could reason that timely use of hearing aids could partly prevent, slow down or even reverse these changes by preventing deprivation. Therefore, the aim of our study is to investigate whether hearing aid use is an effect modifier in the association between hearing loss and smaller brain volume or between hearing loss and reduced white matter integrity in older adults.

MATERIALS AND METHODS

Study Design

This study was set up as a cross-sectional study within the larger population-based Rotterdam Study, a prospective cohort study in the Netherlands[17]. Persons aged 45 and older living in the Ommoord district in the city of Rotterdam were invited to take part in the Rotterdam Study. All participants within the Rotterdam Study undergo repeated measurements every 3 to 5 years. Brain MRI is performed on all participants without contra-indications from 2005 onward[18]. Starting in 2011, pure-tone audiometry was added to the core study protocol.

The current study comprises data collected between 2011 and 2014. Follow-up data was not included, as the process of collecting and analysing data was still ongoing at the time of writing. MRI data was available for 4115 of all participants who enrolled within this period. Of those, 3217 participants also underwent pure-tone audiometry. Only participants who had an MRI scan and an audiogram conducted within a timeframe of 36 months or less were considered (N = 2913). Eighty-three percent of the included MRIs were conducted within 6 months before or after the hearing assessments (median 2 months, inter quartile range (IQR) 1 month; 2

months). We limited our study population to those with hearing loss severe enough for hearing aid reimbursement (N = 479). The threshold for hearing aid reimbursement in the Netherlands is set at a pure-tone mean at 1, 2 and 4 kHz ($PTA_{1,2,4}$) of 35 dB HL.

Standard Protocol Approvals, Registrations, and Participant Consents

The Rotterdam Study has been approved by the medical ethics committee of the Erasmus MC (registration number MEC 02.1015) and by the Dutch Ministry of Health, Welfare and Sport (Population Screening Act WBO, license number 1071272-159521-PG). The Rotterdam Study has been entered into the Netherlands National Trial Register (NTR; www.trialregister.nl) and into the WHO International Clinical Trials Registry Platform (ICTRP; www.who.int/ictrp/network/primary/en/) under shared catalogue number NTR6831. All participants provided written informed consent to participate in the study and to have their information obtained from treating physicians.

Hearing Aid Use

During a home interview at enrollment of the study, participants were asked the question "*Do you use hearing aids*?". Out of a total of 4,836 responding participants, 391 (8.1%) answered with yes. These participants were asked to answer a Dutch translation of the International Outcome Inventory of Hearing Aids (IOI-HA)[19]. This questionnaire had to be filled out at home and handed in at the time of the first visit to the research center. Seventy-seven percent (N = 140) of all hearing aid users included in the current study handed in a response to the IOI-HA questionnaire.

MRI Acquisition and Processing

Brain MRI scanning was performed on a 1.5T-scanner with a dedicated 8-channel head coil (software version 11x; General Electric Healthcare, Milwaukee, WI)[18]. The scan protocol included a T1-weighted sequence (Tw, repetition time 13.8 ms, echo time 2.80 ms, inversion time 400 ms, 96 slices of 1.6 mm, matrix 256 × 256), a fluid-attenuated inversion recovery (FLAIR) sequence (repetition time 8000 ms, echo time 120 ms, inversion time 2000 ms, 64 slices of 2.5 mm, matrix 320 × 224), a proton density-weighted image (repetition time 21,300 ms, echo time 17.3 ms, 90 slices of 1.6 mm, matrix 416 × 256), a single shot, diffusion-weighted spin echo-planar sequence (repetition time 8575 ms, echo time 82.6 ms, 35 slices of 3.5 mm, matrix 64 × 96) with gradients (maximum b = 1000 s/mm^2) applied in 25 noncollinear directions, and 3 volumes acquired without diffusion weighting (b = 0 s/mm^2).

We used an automated brain tissue classification method-based on a k-nearest-neighbor-classifier algorithm[20] for tissue segmentation and to quantify the total intracranial volume, total brain volume, grey matter volume and white matter volume. To obtain measures of microstructural integrity, diffusion tensor imaging (DTI) (voxel size 3.3 x 2.2 x 3.5 mm3) was used.

Using a standardized processing pipeline, diffusion data were preprocessed. This data was combined with the tissue segmentation to derive FA and MD in the normal-appearing white matter[21]. FA is the degree of anisotropy in the normal-appearing white matter and is given as a ratio ranging from 0 (isotropic or non-directonal) to 1 (uni-directional). MD is expressed in square millimeters per second. In general, lower FA and higher MD are thought to reflect poorer white matter integrity.

Visual evaluation of all scans was performed to assess the presence and number of lacunes, cortical infarcts, and cerebral microbleeds, using a rating approach that has been described before in detail[18].

Pure-Tone Audiometry

Pure-tone thresholds were measured in a soundproof booth by a single qualified health professional. Measurement conditions were compliant with ISO standard 8253-1[22]. A clinical audiometer (Decos Audiology Workstation, version 210.2.6, with AudioNigma interface), TDH-39P earphones and B71 bone conductor were used. Air conduction (0.25, 0.5, 1, 2, 4, and 8 kHz) and bone conduction values (0.5 and 4 kHz) were measured in dB HL for both the ears. Masking was done according to the method of Hood[23]. Thresholds for the 4 kHz bone conduction were adjusted by +10 dB afterward[24, 25]. We excluded participants with conductive hearing loss, defined by an mean air bone gap > 15 dB (N = 15). We calculated the pure-tone mean at 1, 2 and 4 kHz ($PTA_{1,2,4}$). For each participant we determined the best hearing ear based on the lowest $PTA_{1,2,4}$ on either the left or right side. When both ears had equal hearing thresholds, we alternately chose the left or the right ear.

Covariates

We collected information on medication and level of education through a home interview at enrollment of the study[26]. Participants were asked to report and show all medication used during the week preceding the interview. Level of education was categorized as having completed primary level, secondary level, or higher education. On the day of audiometry testing, height (cm) and weight (kg) were measured, from which body mass index (kg/m2) was calculated. Alcohol intake and smoking habits were assessed at the research center on the same day. Daily alcohol intake in grams was calculated using an extensive food-frequency questionnaire[27]. Smoking habits were categorized as never, former, or current. Cognition and depressive symptoms were assessed by means of Mini-Mental State Examination (MMSE) and Center for Epidemiological Studies Depression Scale (CES-D)[28]. Systolic and diastolic blood pressure were measured using a random-zero sphygmomanometer. Fasting blood samples along with challenged samples were collected and glucose was determined using the hexokinase method. Diabetes mellitus was considered present when participants used antidiabetics, when fasting glucose was equal to or higher than 7 mmol/L, or when non-fasting glucose was 11 mmol/L or

more. Serum total cholesterol and high-density lipoprotein cholesterol were measured from fasting blood samples using an automatic enzymatic procedure[26]. Cholesterol ratio was calculated by taking the quotient of serum total cholesterol and high-density lipoprotein cholesterol.

Statistical Analysis

Characteristics of the study population were compared for the group with hearing aids (N = 181) versus the group without hearing-aids (N = 298) using independent samples t-test for the normally distributed continuous variables, Mann-Whitney *U* test for continuous variables that were not normally distributed, and χ^2-test for the categorical variables.

Total brain volume, grey matter volume, and white matter volume were expressed as percentage of intra-cranial volume in order to normalize for head size differences between individuals. Linear regression models were used to explore associations of $PTA_{1,2,4}$ with brain tissue volumes and global white matter integrity, while stratifying for hearing aid use. The difference in brain tissue volumes, FA and MD, and 95% confidence intervals (CI) were calculated per 10 dB increase in $PTA_{1,2,4}$. Model 1, the more basic model, was adjusted for age, sex, and the time interval between MRI and audiometry. In addition, model 2 included cardiovascular risk factors, known to be associated with hearing loss[29] and changes in white matter[30], and other possible confounders on the association between hearing loss and changes in brain structure: education level, MMSE, CES-D score, systolic and diastolic blood pressure, diabetes, cholesterol ratio, body mass index, smoking, and alcohol intake. Missing values were present for FA and MD (6,4%), alcohol intake (15.7%), cholesterol ratio (1.9%), CES-D (1.0%), level of education (1.0%), MMSE (0.6%), smoking (0.6%), systolic and diastolic blood pressure (0.2%). Multiple imputation (5 iterations) was used for alcohol intake, cholesterol ratio, and systolic and diastolic blood pressure.

In a separate linear regression model, we added a term for interaction between $PTA_{1,2,4}$ and hearing aid use to the basic model (model 1). We applied this extended model to the combined population of hearing aid users and non-users, as an additional means to test whether hearing aid use is an effect modifier in the associations between hearing loss and brain volume or between hearing loss and white matter integrity. We performed sensitivity analyses on all models to assess whether the regression outcomes were affected by the presence of cortical infarcts, or by correcting for self-reported daily hours of hearing aid use. Data analysis was performed using IBM SPSS Statistics version 24 (IBM, Armonk, NY, USA).

RESULTS

The characteristics of the study population are displayed in Table 1. Out of 479 included participants with $PTA_{1,2,4}$ ≥ 35 dB HL, forty-one percent (N = 196) were female. Mean age (range) was 71.5 (52 to 97). One hundred eighty-one (37.7%) participants responded that they used hearing aids. The age and sex distribution of hearing aid users did not significantly differ from those without hearing aids. $PTA_{1,2,4}$ was higher ($p < 0.001$) for the group that used hearing aids. For those without hearing aids, the distribution of $PTA_{1,2,4}$ was mostly concentrated around the milder hearing losses (IQR 37 dB HL; 45 dB HL), with the highest outliers at a maximum of 75 dB HL. The distribution of hearing losses was wider for the group with hearing aids (IQR 45 dB HL; 60 dB HL) with a maximum $PTA_{1,2,4}$ of 93 dB HL (Figure 2).

Table 1. Characteristics of the study population (N = 479).

Characteristics	Without hearing aids (N = 298)	With hearing aids (N = 181)
Gender, male	116 (38.9%)	80 (44.2%)
Age, years	70.3 (66.4;75.2)	71.0 (66.2;78.7)
Educational level		
Secondary	113 (38.3%)	51 (28.5%)
Higher	52 (17.6%)	38 (21.2%)
MMSE	28 (27;29)	28 (27;29)
CES-D score	3.0 (1.0;6.0)	3.5 (1.0;9.9)
Body mass index, kg/m^2	27.7 (25.4;29.8)	27.3 (25.3;29.6)
Systolic blood pressure, mmHg	145 (131;160)	146 (132;158)
Diastolic blood pressure, mmHg	84 (77;92)	84 (76;92)
Diabetes mellitus, yes	38 (12.8%)	29 (16.0%)
Cholesterol ratio	3.81 (3.13;4.62)	3.76 (2.98;4.59)
Smoking		
Former	161 (54.4%)	110 (61.1%)
Current	55 (18.6%)	23 (12.8%)
Alcohol intake, g/d		
High Fletcher Index, dB	40 (37;45)*	52 (45;60)*

Median (IQR) for continuous variables and number (percentage) for dichotomous variables. Mann-Whitney U test and X^2 –test were used to compare characteristics for hearing aid users and non-users. CES-D, Center for Epidemiological Studies Depression Scale; dB, decibel; mmHg, millimetres of mercury; MMSE, Mini-Mental State Examination. * Indicates a significant difference ($p < 0.01$).

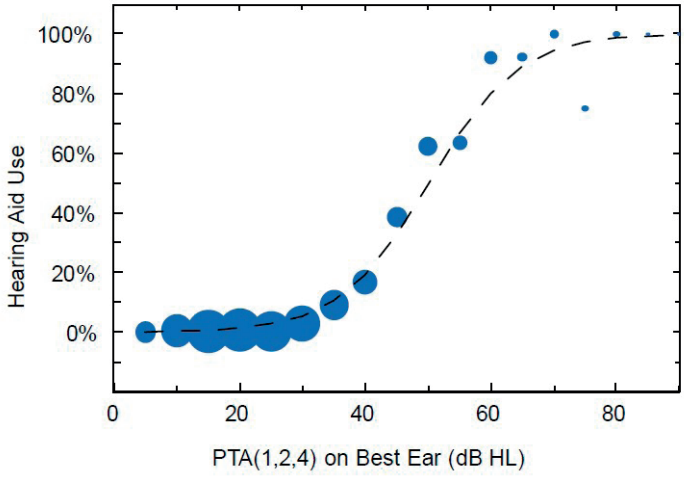

Figure 1. Percentage use of hearing aids as a function of the pure-tone mean at 1, 2 and 4 kHz ($PTA_{1,2,4}$) . Blue circles show which fraction of participants (y axis) with a certain $PTA_{1,2,4}$ (x axis) were using hearing aids. A larger circle represents a larger number of participants with $PTA_{1,2,4}$ falling within ± 2.5 dB range of the value displayed on the x axis. The circles were fitted manually by a logistic distribution (dashed line). The graph includes data for all 2,899 participants who underwent both pure-tone audiometry and MRI within a time span of 36 months, and who did not show conductive hearing loss.

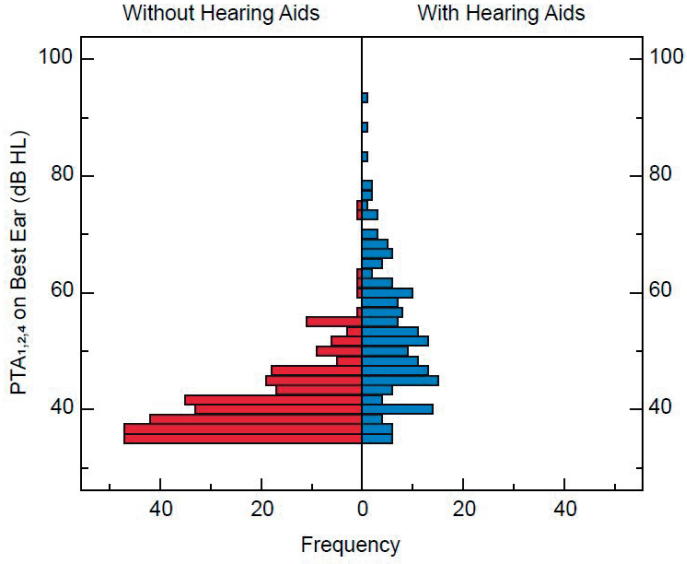

Figure 2. Distribution of pure-tone mean at 1, 2 and 4 kHz ($PTA_{1,2,4}$) for non-hearing aid users vs. hearing aid users. Red bars show the $PTA_{1,2,4}$ distribution for participants who answered 'no' to the interview question: '*Do you use hearing aids?*'. Blue bars show the $PTA_{1,2,4}$ distribution for participants who answered 'yes'. Only participants with hearing loss higher than 35 dB HL, the minimum threshold for hearing aid fitting in the Netherlands, were included.

Table 2 shows the association of $PTA_{1,2,4}$ with total brain volume, grey and white matter volume and global FA and MD, stratified for hearing aid use. In both model 1 and model 2, $PTA_{1,2,4}$ was not associated with a difference in total brain volume for those without hearing aids (difference in percentage of intracranial volume per 10 dB increase in $PTA_{1,2,4}$: 0.32; CI 95% -0.20; 0.84), nor for those who did use hearing aids (0.26; CI 95% -0.18; 0.70), neither was there an association for grey matter or white matter in particular.

Table 2. Association between amount of hearing loss and brain structure measures, stratified for hearing aid use.

		Without hearing aid (N = 298)		**With hearing aid (N = 280)**	
	Total brain volume	Grey matter	White matter	FA	MD (x 10-3 mm^2/s)
Per 10 dB ↑					
$PTA_{1,2,4}$ (model 1)	0.32 (-0.20;0.84)	-0.10 (-0.68;0.48)	0.42 (-0.29;1.13)	0.001 (-0.002;0.004)	-0.001 (-0.005;0.003)
$PTA_{1,2,4}$ (model 2)	0.35 (-0.23; 0.94)	0.08 (-0.56;0.73)	0.27 (-0.54;1.08)	0.002 (-0.001;0.005)	-0.002 (-0.007;0.002)
		With hearing aid (N = 181)		**With hearing aid (N = 168)**	
	Total brain volume	Grey matter	White matter	FA	MD (x 10-3 mm^2/s)
Per 10 dB ↑					
$PTA_{1,2,4}$ (model 1)	0.26 (-0.18;0.70)	-0.06 (-0.44;0.33)	0.32 (-0.12;0.76)	**-0.003** **(-0.006;-0.001)**	0.003 (-0.001;0.006)
$PTA_{1,2,4}$ (model 2)	0.09 (-0.48; 0.66)	-0.20 (-0.72;0.32)	0.29 (-0.30;0.88)	-0.002 (-0.005;0.001)	0.001 (-0.004;0.005)

Data represent difference in volume, expressed in percentage of intracranial volume (95% confidence interval) per 10 dB change of the amount of hearing loss ($PTA_{1,2,4}$). Results are stratified for hearing aid use yes / no. Significant results ($p < 0.05$) are shown in bold. Model 1 was adjusted for age, sex and time between MRI and audiometry. Model 2 as adjusted as model 1 and additionally for educational level, MMSE, CES-D score, systolic and diastolic blood pressure, diabetes, cholesterol ratio, BMI, smoking and alcohol consumption. Missing values were presented for alcohol consumption (15.7%), cholesterol ratio (1.9%), CES-D (1.0%), educational level (1.0%), MMSE (0.6%), smoking (0.6%), systolic and diastolic blood pressure (0.2%). CES-D, Center for Epidermiological Studies Depression Scale; FA, fractional anisotropy; MD, mean diffusivity; MMSE, Mini-Mental State Examination.

$PTA_{1,2,4}$ was not associated with MD in either of the models for both hearing aid users (difference of MD in 10^{-3} mm^2/s per 10 dB increase in $PTA_{1,2,4}$: 0.003; CI 95% -0.001; 0.006) and non-users (-0.001; CI 95% -0.005; 0.003). Model 1 did yield a significant association of $PTA_{1,2,4}$ with lower FA (difference of FA per 10 dB increase in $PTA_{1,2,4}$: -0.003; CI 95% -0.006; -0.001) for those using hearing aids, while no significant result was found for FA in the without hearing aids stratum (0.001; CI 95% -0.002; 0.004). However, the effect found for hearing aid users was not significant after correcting for additional covariates in model 2 (-0.002; CI 95% -0.005; 0.001).

When testing for interaction between $PTA_{1,2,4}$ and hearing aid use in the combined population of hearing aid users and non-users, no significant interaction effect was found for total brain volume, grey or white matter volume, FA or MD (results not shown). Excluding participants with cortical infarcts (N = 12) did not affect any of the outcomes. Results of our study did

not change significantly when including only hearing aid users who responded to the IOI-HA questionnaire (N = 140), nor did the outcome change when correcting for self-reported daily hours of hearing aid use, with 75.7% of the respondents indicating a daily use of more than 4 hours per day. Hence, all of the 181 self-reported hearing aid users were included in the final analysis described here.

DISCUSSION

In a population-derived sample of older adults with moderate to severe hearing loss ($PTA_{1,2,4} \geq$ 35dB HL) , we found no modifying effect of hearing aid use on previously described associations between hearing loss and smaller brain tissue volumes[8-11], or on associations between hearing loss and reduced white matter integrity[12, 13].

The current study used MRI to investigate possible anatomical differences in the brain in relation to hearing aid use. Previous studies on the possible effect of hearing aids consider cognitive measures to quantify differences in brain function rather than anatomy. Results of these studies do not lead to clear conclusions[31]. Longitudinal research by Amieva et al.[32] and a cross-sectional study by Dawes et al.[33] yielded associations of hearing aid use with better cognitive performance. A recent longitudinal trial[34] found that some cognitive measures remained stable or improved among a small group of first time hearing aid users. None of these studies included a control group. Also, cognitive tests may be subject to learning effects. A review of earlier literature[35], concluded that observed associations between hearing aid use and cognitive measures mostly concern short-term interactions, while no strong evidence for long-term effects was found. Lin et al.[36] did not find an association between hearing aid use and cognitive performance within a cross-sectional study, as neither did others find in their longitudinal analysis[37]. Our results are in line with the lack of consistent evidence that hearing aids have a modifying effect on age-related cognitive decline or brain atrophy. Factors such as daily hours of hearing aid use and level of amplification are relevant to the success of hearing aids and may be a source of variability among studies, but are often not recorded. In our study, self-reported daily hours of hearing aid use were recorded, while other factors were not.

Although Rigters et al. found independent associations of hearing loss with smaller white matter volume and poorer white matter integrity within the same Rotterdam Study cohort[11, 12], we were not able to replicate these findings in our smaller and more selected sample, which included only participants with moderate to severe hearing loss. This made it highly unlikely to find any possible modifying effect of hearing aid use on white matter. Other studies that did report changes in white matter related to hearing loss, did not consider hearing aid use. These studies were performed within smaller and in some cases considerably younger study

populations[38, 39], hence results are difficult to compare to ours. Research by Husain et al.[40] and Profant et al.[41] did comprise older, however relatively small populations, and did not account for possible confounders such as education or cardiovascular risk factors .

While the eventual size of our studied population was still large, the number of participants in our analysis has been brought down significantly by including only those eligible for hearing aid imbursement. When stratified by hearing aid use, the groups of hearing aid users and non-users showed significantly different distributions of $PTA_{1,2,4}$. This is a logical consequence of the fact that hearing-aid use is frequent at high levels of hearing loss, but only marginal at lower levels just above the border of hearing aid indication (35 dB HL). In our population, a $PTA_{1,2,4}$ of 50 dB HL appeared to be the tipping point above which the majority of participants were provided with hearing aids. Matching hearing aid users and non-users by amount of hearing loss without significant loss of power was not feasible.

The Rotterdam Study collects longitudinal data, but the process of collecting and analysing follow-up data was still ongoing at the time of writing. As a consequence, the current study only considers cross-sectional data, which is an important limitation. When follow-up data becomes available, our conclusions may be verified more accurately by longitudinal analysis of the MRI-data.

CONCLUSION

In conclusion, we were able to collect pure-tone audiometry, MRI-data and information about hearing aid use for a large group of older adults in a population-based setting. In a cross-sectional analysis among 479 older adults with moderate to severe hearing loss, we could not find evidence for our hypothesis that hearing aids have a modifying effect on the association of hearing loss with brain volume or on the association of hearing loss with white matter integrity. Analysis of longitudinal MRI-data is needed to confirm these results. Such a longitudinal study should ideally include information regarding onset and duration of hearing loss, and start and duration of hearing aid use.

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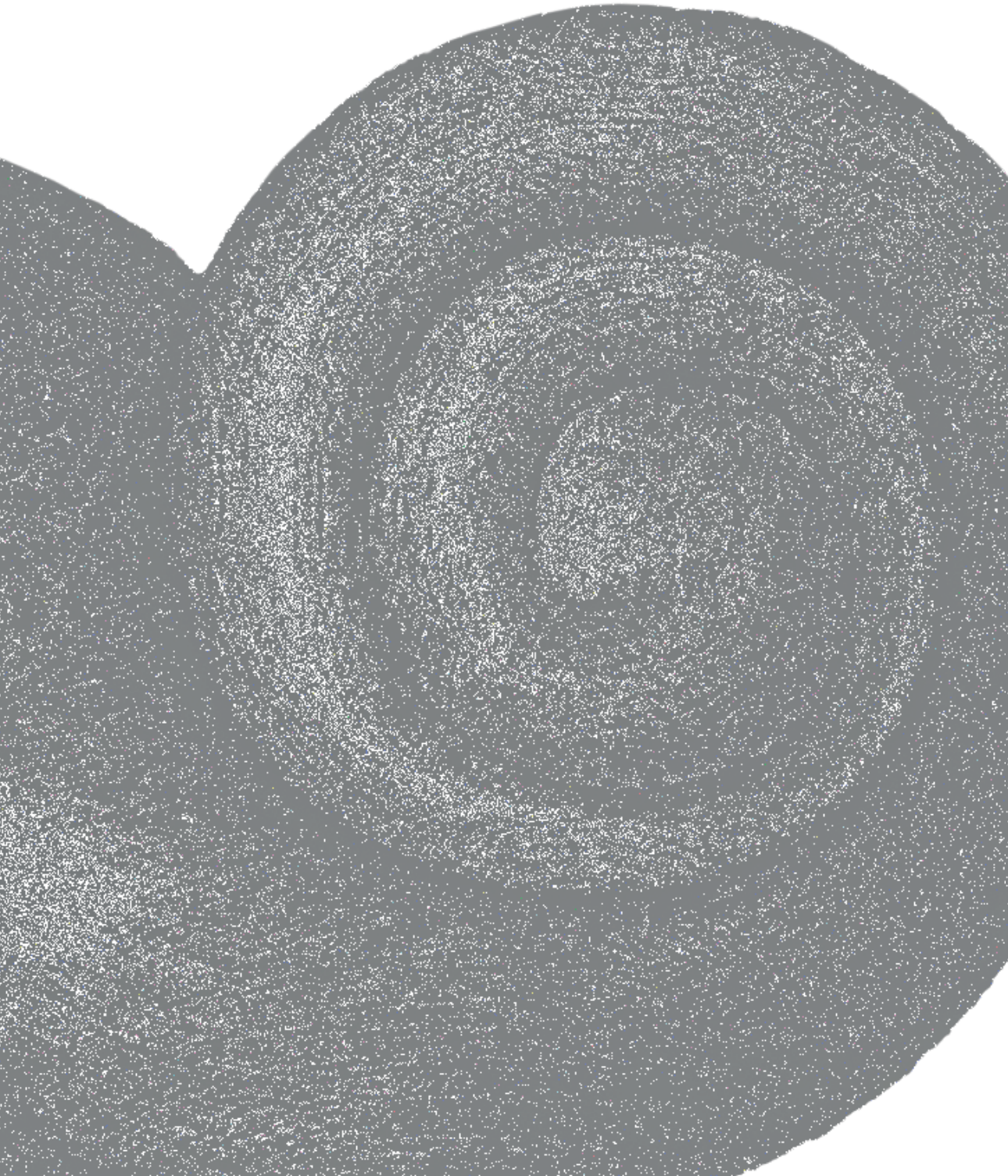

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General discussion

Although age-related hearing loss is a common health problem, few people know it is a complex disorder with a multifactorial character. Overall it is a progressive type of hearing loss, mostly bilateral and of neuro-sensory origin. In general it is characterized by gradually reduced hearing sensitivity affecting higher frequencies first and lower frequencies later on. As a result, speech understanding in noise diminishes and localization of sound is more difficult. Despite the fact that age-related hearing loss has been studied on large scale, its etiology and interindividual variability is not fully understood. The term "*age-related*" adequately suggests an association with age, but there must be other factors influencing hearing loss when aging. After all, people of the same age can vary greatly in hearing acuity. With this thesis we wanted to study what other in- and extrinsic factors affect the hearing acuity of older adults. To account for both peripheral and more central auditory processing, we studied the general risk factors for age-related hearing loss, other than age itself, and the relation of hearing acuity to brain health.

RISK FACTORS OF AGE-RELATED HEARING LOSS

To address the question on the multifactorial etiology and possible risk factors of age-related hearing loss we studied the audiograms of 3,315 community-dwelling adults with an average age of 65 year (range 52 – 99). They lived near the research centre in Ommoord, an area in the city of Rotterdam. This population holds healthy aging individuals, but also individuals that suffer from all kind of medical diseases such as cardiovascular diseases, osteoporosis and (pre-)dementia. This makes it a good representation of a normal healthy population in the Western society. At first we examined the interaction of hearing loss with several lifestyle and cardiovascular determinants in a cross-sectional study (**Chapter 2**). The choice of presumable risk factors was based on existing knowledge. Unsurprisingly, the largest effect on hearing was that of aging; per decade of age a person had an average of 3 (low frequencies) till 13 (high frequencies) dB worse hearing thresholds. It is common knowledge that hearing diminishes with the rising of age. Notable in our research was that this effect was decelerated as participants had worse initial hearing levels. In our longitudinal study we saw that a baseline difference of approximately 16 dB resulted in 1 dB less progression over the 4 years of our follow-up. This amount of deceleration is substantial in view of the average of 3 till 13 dB decline of hearing loss per decade. This finding could imply a so called ceiling effect in age-related hearing loss and has been described before[1, 2]. Hearing loss may be protected against its own deterioration since the exposure decreases as hearing worsens.

According to the concept of different pathophysiological processes involved in cochlear degeneration, as first studied by Schuknecht, we studied the effect of our determinants on peripheral hearing loss separately for low- and high frequency hearing loss. In our cross-sectional study low frequency hearing loss in men was associated with a higher systolic blood pressure, while

high frequency hearing loss was associated with smoking and a lower educational level. For women, more determinants were associated with hearing loss and larger effect sizes were found. Smoking and higher BMI were associated with both low- as high frequency hearing loss. A lower educational level was associated with worse hearing in the lower frequencies. Moderate alcohol consumption was associated with less low frequency hearing loss - when compared to non-consumers – so this seemed protective. Having diabetes was associated with worse hearing in the higher frequencies. Also in our longitudinal study, having diabetes and smoking were associated with worse hearing for both men and women in low and high frequencies.

Usually, the reported prevalence and severity of age-related hearing loss is worse in men. In our study population specifically high frequency hearing loss was worse for men, while low frequency hearing loss was worse for women. An explanation for the difference in high frequency hearing loss could be a more prominent history of occupational noise exposure in men compared to women. Both occupation and amount of noise damage were not adequately registered in the Rotterdam Study. We therefore used educational level as a proxy[3] and found a lower education background was associated with worse hearing. Of course, this result can also be affected by a confounding effect of a less healthy lifestyle that lower educated people in general have, but most of this effect was corrected for by the various other lifestyle-related factors used in our regression analyses. In women, not high- but low frequency hearing loss was more severe. Compared to other earlier studies the thresholds of our female population were worse. It has been suggested this is due to a lifestyle women nowadays live, that is more comparable to that of men 20 to 30 years ago[4]. The overall hearing loss in the female group was also influenced by more determinants and with stronger effects (*e.g.* diabetes mellitus, BMI, smoking and alcohol consumption). In general, the lifestyle-related determinants of hearing loss could point to a dominantly vascular cause of hearing loss, that is more prominent at low frequencies, at least among women. Effects of vascular-related influences could be different throughout the cochlea, because the vascularization of the cochlea is different for the apex where the lower frequencies are situated than for the base where the higher frequencies are situated[5]. While the coil and base of the cochlea receive blood through two branches, the apex of the cochlea is vascularized through one branch and thus could be more vulnerable to ischemic effects. Our findings were in line with previous studies that found associations of worse hearing with vascular-related factors such as cardiovascular risk factors[6, 7], diabetes mellitus[8, 9], obesity[10], smoking[7, 11-13] and a protective effect of moderate alcohol consumption[12, 14, 15]. Some studies found the same gender-specific pathophysiological findings, but there was not always differentiated between low- and high frequency hearing loss. Above mentioned determinants could lead to hypoperfusion or changes in blood viscosity which can affect the blood supply of the cochlea[16, 17]. A normal blood supply is essential to maintain the right endocochlear potential in the cochlea at a level that is needed for the transmission of sound. In diabetes mellitus narrowed capillaries seem to cause hypoperfusion. This also leads to neuro-, retino- and ne-

phropathy, common complications of the disease. In obesity the same mechanism of narrowed capillaries is believed to affect the vascular circulation of the cochlea. In smoking direct damage through the ototoxic effect of nicotine or through vascular damage by changed blood viscosity and less available oxygen is the hypothesized pathway. Even after correcting for cardiovascular risk factors, associations with smoking and the consumption of alcohol remained[15]. Smoking was dose-related to the level of hearing loss. Most studies on alcohol showed the same protective effect of moderate alcohol consumption on hearing loss as we did, even after correcting for occupational noise and general health. Considering these outcomes, we expected to find at least some effect of the determinants on the progression of hearing loss in our longitudinal study (**Chapter 3**). We studied the audiograms of 675 older adults, from who 78.8% showed progression of hearing loss within the follow up time. The average progression was 0.29 till 1.35 dB per year, depending on the frequency looked at. Although age-related hearing loss was well presented – 53.6% among participants aged 66-69 years, 65.5% among participants aged 70-79 years and even 84.8% among participants aged 80-87 years - no effect was found of any of the determinants on the rate of progression. We believed the negative results were due to the relatively short follow up time of approximately four years in combination with the small amount of participants (=675) in contrast to other earlier published studies[18, 19].

It is not easy to compare epidemiologic studies on age-related hearing loss among each other. Design, study groups and cut-off values are often different. The strength of this kind of research however lies in replication: with every consistent repeating of outcomes, results get more solid. Yet we must not ignore a possible publication bias. Studies finding associations have a higher chance of being published. Therefore, it is possible that certain associations may be slightly less consistent than they appear based on literature. Furthermore, we must realize a considerably part of the variance in hearing is explained by heritability or a genetic cause. This was not taken into consideration in our study. Literature on heritability shows an estimated 25 – 75% of the age-related hearing loss cases has a genetic component[20]. There even is evidence epigenetics plays a role in age-related hearing loss. Here, environmental factors can influence gene expression. In a multi-center cohort genome-wide association study including almost 10,000 participants, researchers found 7 specific loci for age-related hearing loss[21]. These loci were different for low and high frequently hearing loss, again indicating different pathophysiological mechanisms.

Concluding, our results confirm earlier assumptions. There are multiple important influences on age-related hearing loss on cochlear level. Although the clinical effect size (the amount of hearing loss in decibels) of most of our results is small, our results do show us the possible pathways behind the clinical variation in age-related hearing loss. Biological aging, health-related causes (predominantly lifestyle-related factors) and genetics are either a sole cause for age-related hearing loss, or synergetic in the pathophysiology. So potentially lifestyle factors

could influence our hearing. Keeping a healthy lifestyle (*e.g.* a normal blood glucose level, not smoking, moderate alcohol use, healthy weight and noise protection) is a good idea anyway and possibly it will lessen the amount of hearing loss. Second, above outcomes contribute to the understanding which individuals are at risk of more rapid deterioration of hearing loss. This is important because this gives an extra reason for counselling individuals to discuss the rehabilitation of hearing and treatment of the underlying condition.

AGE-RELATED HEARING LOSS AND BRAIN HEALTH

Auditory processing starts at the level of the cochlea and is proceeded through the higher auditory system up to the auditory cortex in the brain. There is great interest into the possible relation between age-related hearing loss and brain health. Deficits in the higher auditory system and brain may also explain why some older adults have more trouble in processing sound than others, while having similar cochlear thresholds. Hence, there are studies that showed associations between age-related hearing loss and cognition or dementia, suggesting a possible involvement of brain functioning[22, 23]. Speculative, there are three possible hypotheses proposed on a causal relationship between hearing loss and brain health. In the first there is assumed that hearing loss generates less sensory input peripheral which leads to neural deprivation and neuroplastic changes in the brain. This is called the *"sensory-deprivation hypothesis"*. There is even the possibility of reallocation of certain brain areas because of chronic changes in the use of them[24]. The second hypothesis is called the *"central-component hypothesis"*. Here it is opted that changes in brain health lead to peripheral hearing loss. The third hypothesis states that there is a mutual risk factor or factors causing both altered hearing and brain health; the *"common-cause hypothesis"*. To explore these hypotheses we examined structural changes in the brain (brain morphology) to study brain health in relation to hearing loss. We used several markers for this; brain volume, grey and white matter volume and quality of the white matter tracts.

In this thesis an association between hearing impairment and a smaller brain volume overall is shown (**Chapter 4**). This result was driven by smaller white matter volume and not by differences in grey matter atrophy. In the general aging process, certain morphological changes such as brain atrophy of grey and white matter, and reduced quality of white matter microstructure play a role[25, 26]. To exclude this effect, analyses were corrected for age. Despite this correction, associations between hearing loss and white matter volume remained. Therefore we believe that our results cannot solely be explained by the natural aging process. Our results were consistent for both low- as high frequency hearing loss and independent of cognition and cardiovascular risk factors. In earlier cross-sectional studies an association between worse pure-tone hearing thresholds and smaller grey matter volume was found in the auditory cortex bilaterally[27, 28], but

also in non-auditory regions such as the frontal and occipital lobe and corpus callosum[28, 29] or only with high frequency hearing loss in the frontal gyrus[30]. However, others found an increase of the grey matter in the limbic area's[29] or no significant association between hearing loss and grey matter volume[31, 32]. The only longitudinal study published showed with a six-year follow up MRI of 126 older adults (age 56 – 86 years) an accelerated grey matter volume decline in particular the right temporal lobe in hearing impaired participants when compared to normal hearing participants[33]. While most studies focused on the relation of hearing loss with grey matter atrophy, we found a relation with poorer white matter. The mechanism underlying the association of hearing loss and brain atrophy is not known and remains speculative. Comparison of earlier studies among each other and with ours is hampered by the different criteria that have been used as it comes to the specific regions of interest in the brain, definition and measurement of hearing loss, study population and correction for possible confounders such as cognition, cardiovascular risk factors and alcohol consumption. This could very well explain the heterogeneous results on the relation between hearing loss and *e.g.* grey matter volume.

As stated above, the association of a lower whole brain volume in our results was driven by a lower white matter volume. This result was consistent in all four brain lobes; frontal, temporal, parietal and occipital. It was present for both low- and high frequency hearing loss, but more outspoken in the lower frequencies. Besides degeneration of the white matter volume we further on focused on the microstructure of the white matter by studying the white matter tracts using diffusion-weighted MRI (**Chapter 5**). These tracts function as a communication network between the grey matter areas. The finding of lower fractional anisotropy and higher mean diffusivity corresponds with worse organization of the tract fibres. Interestingly, we found associations between hearing loss and a poorer level of organization of this microstructure. Most studies that have examined age-related hearing loss in relation to the white matter tracts reported similar results[28, 34, 35]. However, the studies were small (N maximum = 47), not particularly focused on older adults and not always able to correct for possible confounders such as cognition. We do have to realize most of these studies were done when the use of the diffusion-weighted MRI was still in its infancy. Spatial resolution, detecting complex crossing white matter tracts and the knowledge on different aging pattern among tracts could have been less developed or known[36]. Also, the above prior studies did not test the speech-in-noise ability. This test is of particular interest because it is a relatively simple way to test higher auditory functions instead of solely the peripheral hearing function like pure-tone audiometry does[37]. One recent longitudinal study in where they did test speech-in-noise found worse hearing was associated with worse quality of the uncinated fasciculus[38]. This is the exact same tract we found. The uncinate fasciculus is important in semantic processing. It supports with recalling names and mnemonic associations[39]. Furthermore, we found hearing loss was associated with worse quality of the superior longitudinal fasciculus. This tract is involved in processes such as language, memory and attention[40]. Because longitudinal data on brain morphology in the

Rotterdam Study was not yet available, we could not explore causality between hearing and brain health. We tried to account for all possible mutual factors such as age, cardiovascular risk factors and cognition, thereby ruling out the *"common-cause hypothesis"*. We must recognize there will almost certainly always be factors we could or did not account for. Speculative, there are some clues which could provide insight on what causal pathway is plausible. The first clue is the location of the affected areas in the brain. It seems more logical that local effects in the brain, *e.g.* in the auditory associated locations such as the temporal lobe, are caused by disordered peripheral sensory input. While widespread effects throughout the brain could be an indication for the *"central-component hypothesis"* or *"common-cause hypothesis"*. We found both: in our general analyses we found a poorer white matter macro- and microstructure throughout the brain and in the specific analyses (voxel-based) we found associations with locations such as the right pre- and postcentral gyri, the left temporal lobe, the right superior longitudinal fasciculus and right uncinate fasciculus. From which the superior longitudinal fasciculus and uncinate fasciculus, as well as the left temporal lobe are related to auditory functioning[41, 42]. The second clue can be found in the comparison to other sensory age-related diseases, *e.g.* macular degeneration. Here, similar associations with altered brain morphology are found, suggesting that a common cause may be present affecting brain morphology and general sensory functions. However, because of the cross-sectional design of the studies no conclusions on the causality could be made here either[43, 44]. For a third clue, comparable studies on animals can be considered. But also here difficulties for determining the causal pathway are faced and although it seems at least a central origin plays a role, no direct conclusions could be made[45].

As all above hypotheses on the possible mechanism between hearing loss and brain health remain speculative since they were based on cross-sectional research, we were interested in hearing aid usage in our cohort. Because usage is highly dependent on individual preference both users and non-users are common in the normal population, even at higher ages and increased hearing thresholds. Our idea was that if the *"sensory-deprivation hypothesis"* would be accurate, the changes in the brain can be slowed down or maybe even reversed by preventing deprivation and restoring the sensory input, *e.g.* by wearing hearing aids. In this case, hearing aids could be hypothesized to moderate this pathway. However, among the 479 older adults tested (**Chapter 6**), there was no statistical interaction effect of wearing hearing aids on the relation between hearing loss and brain health. A major study design issue here was the unequal distribution of hearing loss among users and non-users. As expected, hearing loss was more severe in the first group. Although age and sex were evenly distributed, it was not possible to match the groups in terms of hearing loss without losing too much power. We believe it would be worthwhile to repeat the study with a larger and more equally distributed group in terms of hearing loss and to focus on specific brain area's such as the temporal lobe, besides the general brain health. Maybe, effects are so small they could be averaged out if the primary

outcomes are too general. It is believed by some that wearing hearing aids is associated with better cognitive performance. A recent longitudinal study[46] found that hearing aid users had stable or improved cognitive outcomes. Because there was no use of a control group, we should bear in mind that confounding might have played a role here. People with a better cognition could be in better capability of asking for help and start a hearing revalidation trajectory. The relation between age-related hearing loss and cognition is a very interesting one and research on this topic is emerging rapidly. The relation is presumably a very complicated one: not only is it possible they have a mutual common cause (*e.g.* aging of the brain or vascular causes), but there is also an hypothesis that states that less sensory input leads to permanent cognitive changes through changed neuroplasticity in the brain[47]. Hence, we should also be aware of the fact that there is an effect of hearing on the outcomes of cognition tests[48]. Age-related hearing loss is described as a risk factor for developing dementia with an attributable factor of 9%[23]. In line with our thoughts on hearing aid usage and brain health, it was even suggested that hearing aids are potentials to lower the risk for dementia. This puts hearing loss on the map as an important modifiable factor in preventing or delaying dementia.

LESSONS LEARNED, FUTURE PERSPECTIVES AND CLINICAL IMPLICATIONS

We were fortunate to be able to distract data from the population-based Rotterdam Study. It is designed to study the etiology, natural history and course and potential risk factors for chronic diseases in a healthy aging group[49]. Many possible confounders are well registered and could be taken into account, however there are some limitations that should also be acknowledged. Although the overall response rate of 72% is comparable to other population-based studies, we must realize the potential selection bias of non-participants, *e.g.* because of poorer health, is present. Moreover, most of the cohort concerns Caucasians, so the results are especially applicable to this group. And although many confounders are registered, it is always possible others have been missed. More specifically in our studies, in order to study other risk factors, the effect of age on hearing acuity was accounted for, but it is difficult to be absolutely sure this effect is truly covered. We believe our data set is a true reflection of the general Dutch elderly population, based on the distribution of age and hearing loss.

In all the studies in this thesis we used the hearing thresholds of the better ear. Since hearing is binaural, this was believed to give the most accurate view of a person's hearing sensitivity. After all, one's hearing in daily life is mainly determined by the better ear. However, as a consequence the role of unilateral / asymmetrical decline of hearing has not been taken into account. In our studies, hearing was tested through a pure-tone audiogram as well as the digits-in-noise-test. The latter is a variation on the speech-in-noise test and a very practical option for population

research. The test is low in effort, time and costs, compared to other more extended tests for higher auditory functions (*e.g.* brainstem audiometry). For the DTI we are aware that although it is a very good method to measure microstructural changes in the brain, it is also very sensitive for artifacts and noise. It has been acknowledged that it is difficult to calculate the exact FA and MD of tracts that cross each other, leading to possible incorrect estimates within the tractography. This is called the "*crossing-fibers problem*". This is, however, a fundamental problem if the DTI and a limitation every study needs to cope with.

The follow-up data collection of the Rotterdam Study is highly valued. During the writing of this thesis for audiometry only two follow-up rounds were available, but more rounds are expected. If this data comes available, it would be of great interest to perform a study with longitudinal audiometry and MRI / DTI data to get more information on a possible causal pathway between age-related hearing loss and altered brain health. We would expect to find that multiple or maybe all of the discussed hypotheses are contributing in the mechanism of age-related hearing loss and brain health.

This thesis provided to a better understanding in the peripheral and central aspects of age-related hearing loss. It points out this disorder has not a simple singular etiology, but multiple possible pathways could play a role in its development. Furthermore, with this thesis we showed an effect of age-related hearing loss further than degeneration of the auditory pathway, namely also alterations in brain morphology. There is a relation between age-related hearing loss and brain health, and with the more upcoming concept of the relation between age-related hearing loss and loss of cognition or risk on dementia, this is a very important finding. We assume the amount of contribution of the in- and extrinsic risk factors is very small and will only have a minor effect on hearing loss, nevertheless a healthy lifestyle is always important.

I believe the discussed pathways or hypotheses on age-related hearing loss and brain health in this thesis are not mutually exclusive. Hearing is a complex process and covers not only the auditory pathway. It also involves the interpretation of noise and speech, the filtering of background noise, and is related to the cognitive function.
In the future we could consult patients differently. First, physicians should advise a healthy lifestyle strongly, since it beholds the modifiable risk factors for hearing loss. Second, physicians need to keep in mind the role of brain health and cognition. Hearing aids should be discussed and prescribed sooner to contribute in an early stage to prevention of (further) hearing loss. In the future hearing aids could be developed and used differently, as more smart-working devices, since we are finding out the role they can play in preserving cognition and preventing dementia.

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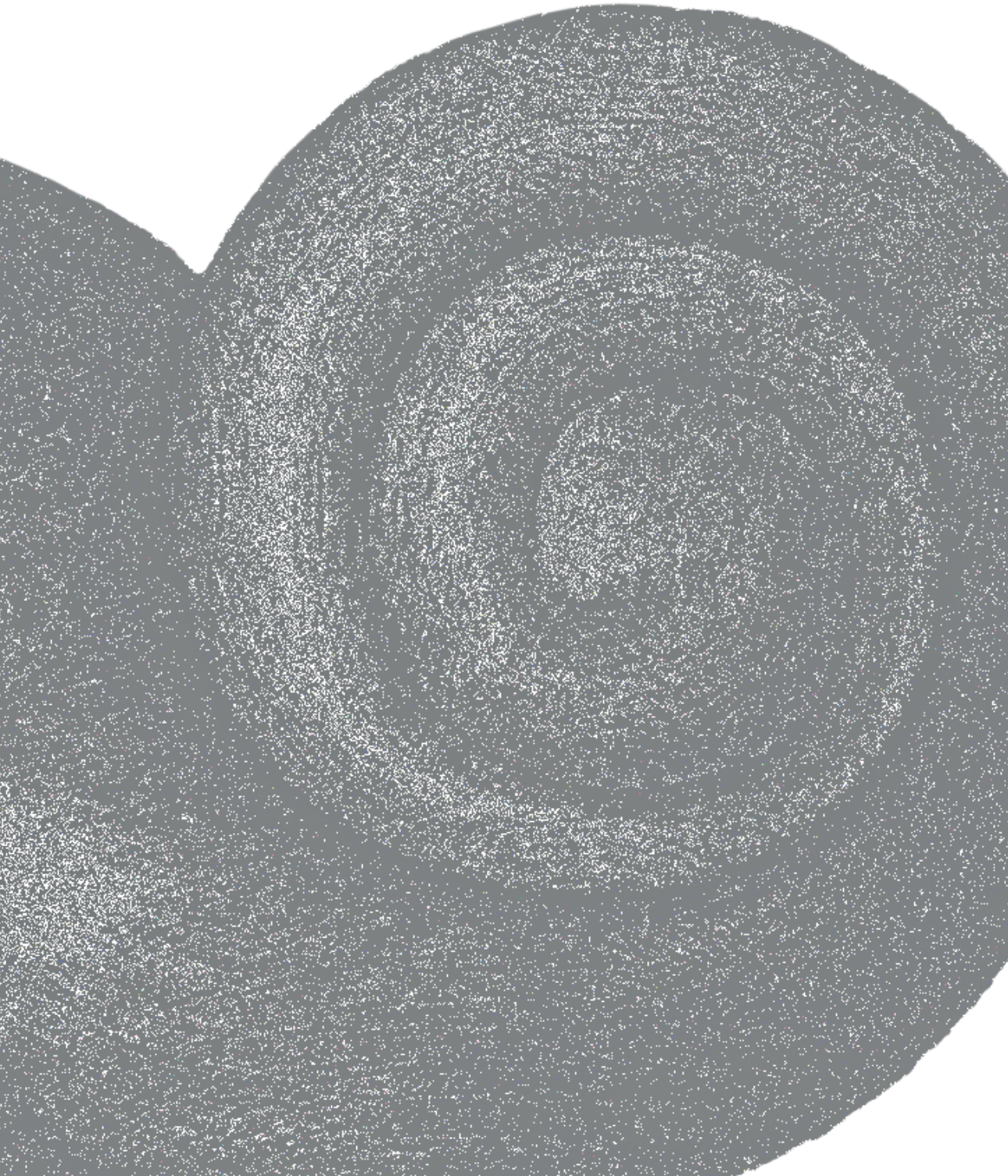


8

Summary
Samenvatting

Presbycusis, or age-related hearing loss, is highly prevalent and currently affecting an estimated 1.27 billion people worldwide. What is less known is that age-related hearing loss is one of the leading causes of disability globally. Furthermore, the prevalence is expected to rise in the near future due to the increasing life expectancy. Within this thesis we attempted to contribute to a better understanding of the distribution, but also in the variance in age-related hearing loss. Obviously aging itself is a principal cause, but there are other factors likely to contribute as well. We studied the in- and extrinsic factors affecting the hearing ability of aging adults, as well as the relation of hearing ability with brain health. Processing of sound does not only occur in the cochlea and inner ear, but also in the higher auditory system stretching into the brain. Different exposures might explain the variety in hearing acuity among older adults the same age.

Chapter 1 gives a brief insight in the epidemiology, pathophysiology and current ideas on age-related hearing loss being a disease with a multifactorial etiology.

In **Chapter 2** we examined the hearing of 3,315 older adults by analysing their pure-tone audiogram. We studied several patient and environmental determinants as possible risk factors for age-related hearing loss. Results substantially differed for low- and high frequency hearing loss, and also between men and women. Low frequency hearing loss in men was associated with age and a higher systolic blood pressure. High frequency hearing loss was associated with age, a lower educational level and being a smoker. For women, low frequency hearing loss was associated with age, a lower educational level, higher BMI and being a smoker. Alcohol consumption was reversibly associated. High frequency hearing loss was associated with age, having diabetes mellitus, higher BMI and being a smoker. These results confirm the hypothesis of different mechanisms being involved in the etiology of age-related hearing loss. Subsequently, the effect of those determinants on the rate of progression of age-related hearing loss was studied in a longitudinal study in **Chapter 3**. As known age-related hearing loss is progressive and irreversible. Since the diminishing rate of our hearing varies, it is of interest to find out who could be more prone to rapid deterioration and why. Of 675 older adults two different pure-tone audiograms and speech-in-noise tests over a substantial period of time were studied for possible associations with the same determinants as in the prior study. It appeared none of our studied determinants influenced the rate of progression; we attributed this to the relatively short follow-up time of four years. Remarkably, we saw initial worse hearing had an effect of deceleration on the progression rate of hearing loss. This could imply a so called ceiling-effect, where diminished hearing reserve results in slower rates of decrease.

In the two previous chapters we focused on cochlear damage in relation to age-related hearing loss. But there is increasing evidence that changes in the central auditory and cerebral system are also involved in the process of hearing loss at an older age. Earlier studies were mostly small in size and data from a population perspective was limited. In **Chapter 4** we explored the rela-

tionship of age-related hearing loss with the brain health of 2,908 older adults. Brain health was qualified in brain morphology. With a brain MRI we determined the whole brain volume, and cerebral grey and white matter volume. We found age-related hearing loss was associated with a smaller brain volume. This was driven by a smaller white matter volume. This effect was found throughout the whole brain and not just in the temporal lobe. The effect size was stronger in the lower hearing frequencies. To further analyse the relation of hearing loss with white matter, in **Chapter 5** we focused on the white matter microstructure by examining the separate white matter tracts in the brain. By using diffusion-weighted MRI the microstructure becomes visible. We compared the quality of the microstructure to the hearing acuity of 2,562 older adults. Poorer white matter microstructure, especially in the right superior longitudinal fasciculus and the right uncinated fasciculus (auditory and language associated tracts) was associated with worse hearing in the pure-tone audiogram and speech-in-noise test. The found effects in both these chapters were independent of age, cognition and the earlier mentioned determinants. The mechanism underlying these associations is not known. The first opted hypothesis is the "*central-component hypothesis"*. Here, it is assumed changes in the brain or brain health lead to peripheral hearing loss. The second is the "*common-cause hypothesis"* where a mutual risk factor or factors causes both altered hearing and brain health. The third opted hypothesis in literature, the "*sensory-deprivation hypothesis"*, assumes hearing deprivation affects the brain by diminished sensory input which can lead to reorganization of the brain.

To explore this hypothesis, we conducted the following study in **Chapter 6**. We speculated that restoring the hearing, *e.g.* by wearing hearing aids, could modify the pathway of less sensory input and thereby affect the brain health. We studied 479 older adults with an average hearing loss of 35 decibels or more, where one group wore hearing aids and the other did not. The relation between hearing loss and brain health was explored. Again, brain volumes and white matter microstructure were studied. The analyses did not reveal any interaction effects of hearing aid use. We believe longitudinal research is needed to confirm nor reject the hypothesis.

Finally, in **Chapter 7** we discuss our main findings and the three hypotheses on the relation of age-related hearing loss with altered brain morphology. Our results contribute to the idea of age-related hearing loss being a multifactorial condition and to the culminating evidence that age-related hearing loss and brain health interact. Future research should focus on longitudinal studies to identify the underlying causative mechanisms and possible preventive effects of early treatment, such as timely use of hearing aids.

CONCLUSIONS OF THIS THESIS

- The most important determinant in hearing loss among older adults is age(ing).
- Different in- and extrinsic factors have influence on age-related hearing loss (*e.g.* diabetes mellitus, blood pressure, BMI, smoking, alcohol consumption and educational level).

- Within short follow-up time (4 years in our case) studied determinants have no effect on the progression of age-related hearing loss.
- Age-related hearing loss is associated with smaller brain volume, independent of age and the cognition of a person.
- This effect is driven by smaller white matter volume and worse organized white matter tracts in the brain.

Ouderdomsgehoorverlies, ook wel presbyacusis genoemd, is een veelvoorkomende ziekte en treft momenteel naar schatting 1,27 miljard mensen wereldwijd. Het is daarmee een van de meest voorkomende aandoeningen onder ouderen. Bovendien is het vooruitzicht dat door de alsmaar stijgende levensverwachting dit aantal nog meer zal worden. Met dit proefschrift wilden we bijdragen aan een beter begrip van presbyacusis; waardoor wordt de variatie van deze aandoening verklaard? Wat zijn de risicofactoren? Veroudering is overduidelijk een van de voornaamste oorzaken, maar er zijn zeer waarschijnlijk ook andere factoren die een rol spelen. In dit proefschrift bestudeerden we welke in- en extrinsieke factoren het gehoor van ouderen beïnvloeden. Daarnaast bestudeerden we ook de relatie tussen presbyacusis en de gezondheid van het brein. Het verwerken van geluid vindt namelijk niet alleen plaats in de cochlea, maar ook in het hogere auditieve systeem wat zich uitstrekt tot de temporale kwab in de hersenen. Verschillen in bovenstaande factoren zou de variatie in gehoor onder ouderen van dezelfde leeftijd kunnen verklaren.

Hoofdstuk 1 geeft een overzicht van de pathofysiologie, epidemiologie en eerdere literatuur aangaande presbyacusis als ziekte met een multifactorieel karakter.

In **Hoofdstuk 2** bestudeerden we het gehoor van 3.315 deelnemers aan de Rotterdam Studie (een populatiestudie), door de toondrempels van hun toonaudiogram te analyseren. Deze vergeleken we met mogelijke risicofactoren voor presbyacusis. De resultaten verschilden voor lage- en hoge tonen gehoorverlies, als mede voor mannen en vrouwen. Lage tonen gehoorverlies bij mannen was geassocieerd met hogere leeftijd en met een hogere systolische bloeddruk. Hoge tonen gehoorverlies bij mannen was geassocieerd met hogere leeftijd, een lager opleidingsniveau en roken. Bij vrouwen was lage tonen gehoorverlies geassocieerd met hogere leeftijd, een lager opleidingsniveau, een hoger BMI en roken. Matige alcohol consumptie was juist geassocieerd met een beter gehoor. Hoge tonen gehoorverlies bij vrouwen was tot slot geassocieerd met een hogere leeftijd, het hebben van diabetes mellitus, een hoger BMI en roken. Deze resultaten bevestigden de gedachte dat er mogelijk verschillende mechanismen betrokken zijn bij de etiologie van presbyacusis. Hierop volgend werd het effect van bovenstaande risicofactoren op de progressie van presbyacusis bestudeerd in **Hoofdstuk 3**. Presbyacusis wordt progressief en irreversibel verondersteld. Aangezien het tempo waarmee het gehoor afneemt wel per persoon varieert, waren we geïnteresseerd wie er vatbaarder is voor een snelle achteruitgang en waarom. Van 675 deelnemers werden twee toonaudiogrammen en spraak-in-ruis testen in relatie tot de eerdere risicofactoren bestudeerd met een tussenliggende periode van circa 4 jaar. Echter, geen van de eerdere risicofactoren voor presbyacusis had een significante invloed op de progressie van het gehoorverlies. Mogelijk is dit toe te schrijven aan de relatieve korte follow-up tijd. Opmerkelijk was wel dat een slechter gehoor tijdens de eerste meting was geassocieerd met een minder snelle progressie. Dit zou kunnen betekenen

dat er een zogenaamd 'plafondeffect' bestaat, waarbij minder gehoor reserve resulteert in een langzamere afname.

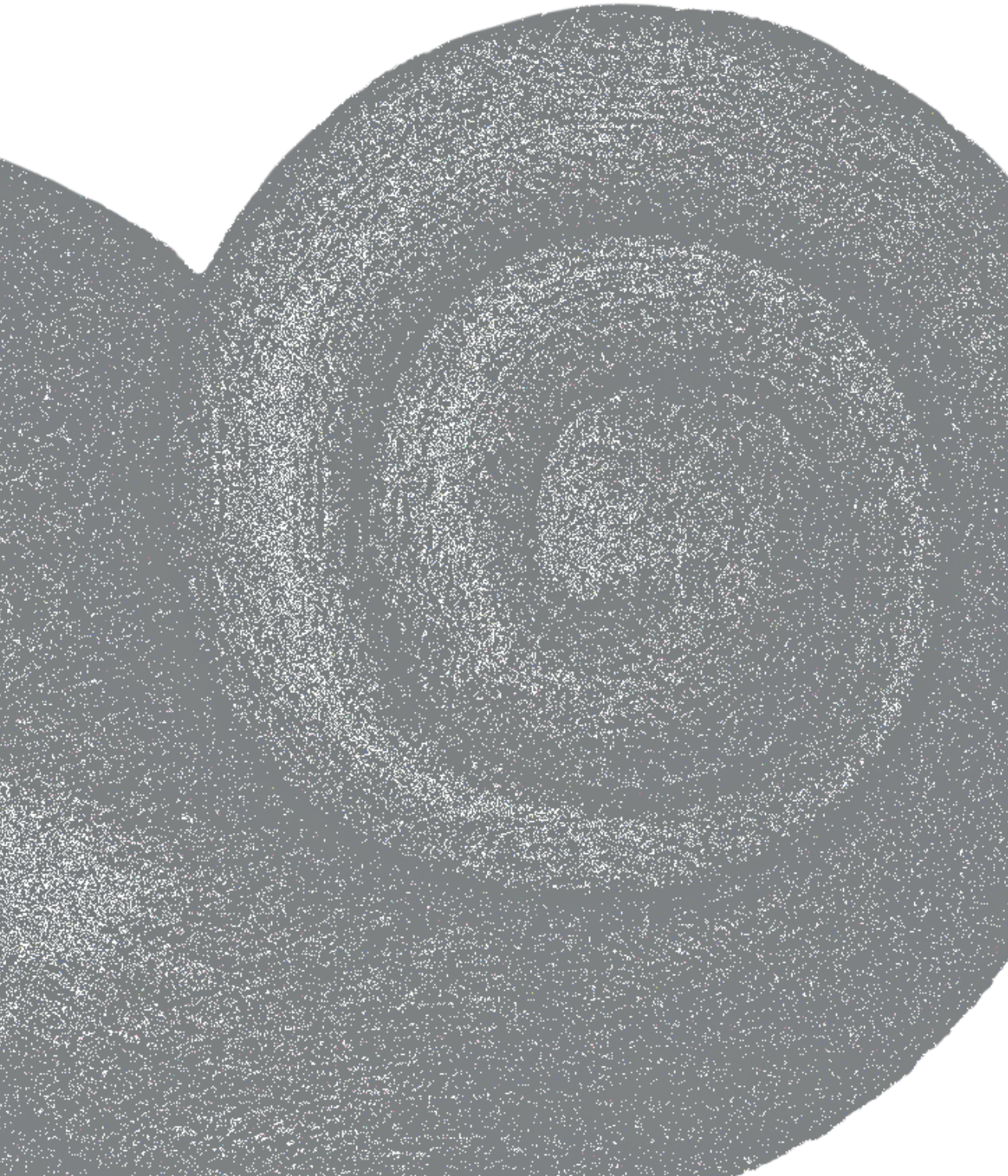
In de voorafgaande twee hoofdstukken richtten we ons met name op cochleaire schade in relatie tot presbyacusis. Er zijn echter steeds meer aanwijzingen dat ook veranderingen in het centraal auditieve systeem en in het brein een rol spelen bij presbyacusis. Eerdere studies waren vaak van kleine omvang en er zijn amper gegevens op populatieniveau. In **Hoofdstuk 4** hebben we daarom de relatie tussen presbyacusis en de gezondheid van het brein onderzocht onder 2.908 ouderen. Als kwalificatie van de gezondheid van het brein gebruikten we morfologische bepalingen zoals het breinvolume en grijze en witte stof volume. Dit werd bepaald middels een MRI-brein. We ontdekten dat presbyacusis was geassocieerd met een kleiner volume van het brein. Dit bleek te worden veroorzaakt door een kleiner volume aan witte stof. Dit effect was zichtbaar in het hele brein en niet alleen in bijvoorbeeld de temporaal kwab. Het effect was het grootst bij gehoorverlies in de lage tonen. Om deze relatie verder te bestuderen, concentreerden we ons in **Hoofdstuk 5** op de microstructuur van deze witte stof. We onderzochten daarvoor de afzonderlijke witte stof banen met behulp van een diffusie-gewogen MRI. We analyseerden de relatie van presbyacusis met de microstructuur van deze witte stof banen bij 2.562 ouderen. Een slechtere kwaliteit van de microstructuur, in het bijzonder in de rechter superieure longitudinale fasciculus en de rechter uncinate fasciculus (auditieve en taal gerelateerde banen) was geassocieerd met een slechter gehoor op zowel het toonaudiogram als bij de spraak-in-ruis test. De gevonden associaties waren onafhankelijk van leeftijd, cognitie en de eerder onderzochte risicofactoren. Het causale verband tussen deze associatie is tot op heden onbekend. Er bestaan een aantal hypotheses. Bij de '*central-component hypothese*' wordt verondersteld dat veranderingen in het brein c.q. de gezondheid van het brein kunnen leiden tot perifeer gehoorverlies. Bij de tweede hypothese, de '*common-cause hypothese*' wordt verondersteld dat een of meer gezamenlijke risicofactoren de afwijkingen in gehoor en brein veroorzaken. Bij de derde hypothese, de '*sensory-deprivation hypothese*' wordt verondersteld dat de verminderde sensorische input bij gehoorverlies kan leiden tot reorganisatie van (bepaalde gebieden van) de hersenen.

Om deze laatste hypothese te toetsen, hebben we een studie uitgevoerd die staat beschreven in **Hoofdstuk 6**. We veronderstelden dat herstel van de sensorische input, bijvoorbeeld door het dragen van hoortoestellen, zou kunnen leiden tot betere gezondheid van het brein. We onderzochten daarvoor 479 ouderen met een gemiddeld gehoorverlies van 35 decibel of meer, waarbij de ene groep uit hoortoestellen-dragers bestond en de andere groep deze niet gebruikte. Opnieuw bestudeerden we de relatie tussen presbyacusis en de gezondheid van het brein. Onze analyses toonden geen interactie-effect van hoortoestel gebruik. Mogelijk is er longitudinaal onderzoek nodig om bovenstaande hypothese verder te onderzoeken.

Tot slot bespreken we in **Hoofdstuk 7** onze belangrijkste bevindingen en reflecteren op de eerder benoemde hypotheses. Onze resultaten dragen bij aan het concept dat presbyacusis een multifactoriële aandoening is en dat het een relatie heeft met de gezondheid van ons brein. Toekomstig onderzoek zou zich bij voorkeur moeten richten op longitudinale studies om de causale verbanden te verduidelijken en zo mogelijke preventieve effecten van een behandeling, zoals het tijdig gaan gebruiken van hoortoestellen, te identificeren.

CONCLUSIES VAN HET PROEFSCHRIFT

- Eén van de belangrijkste bepalende factoren voor de mate van presbyacusis is leeftijd.
- Er zijn ook verscheidene andere risicofactoren voor presbyacusis (diabetes mellitus, hoge bloeddruk, BMI, de consumptie van alcohol en opleidingsniveau).
- Binnen een relatief korte tijd (in ieder geval 4 jaar follow-up) hebben deze risicofactoren geen invloed op de mate van progressie van presbyacusis.
- Presbyacusis is geassocieerd met een kleiner breinvolume, onafhankelijk van de leeftijd en cognitie van iemand.
- Dit effect wordt veroorzaakt door een kleiner witte stof volume en slechtere kwaliteit van de witte stofbanen daarin.



9

Appendices

Abbreviations
List of publications
Phd portfolio
Dankwoord
Over de auteur

ABBREVIATIONS

BMI	body mass index
CI	confidence interval
dB	decibel
DIN	digits in noise
DM	diabetes mellitus
DTI	diffusion tensor imaging
FA	fractional anisotropy
HDL	high-density lipoprotein
HL	hearing level
ICV	intracranial volume
IQR	inter quartile range
kHz	kilo Hertz
MD	mean diffusivity
MMSE	Mini-Mental State Examination
MRI	magnetic resonance imaging
ROI	region of interest
SD	standard deviation
SRT	speech reception threshold
VBA	voxel-based analysis
VBM	voxel-based morphometry

LIST OF PUBLICATIONS

2016 **Contributing determinants to hearing loss in elderly men and women: results from the population-based Rotterdam Study.**
Rigters SC, Metselaar M, Wiering MH, Baatenburg de Jong RJ, Hofman A, Goedegebure A.
Audiology and Neurotology 2016; 21: 10-15.

2017 **Hearing impairment is associated with smaller brain volume in aging.**
Rigters SC, Bos D, Metselaar M, Roshchupkin GV, Baatenburg de Jong RJ, Ikram MA, Vernooij MW, Goedegebure A.
Frontiers in Aging Neuroscience 2017; 9: 131.

2018 **White-matter microstructure and hearing acuity in older adults: a population-based cross-sectional DTI study.**
Rigters SC, Cremers LGM, Ikram MA, van der Schroeff MP, de Groot M, Roshchupkin GV, Niessen WJN, Baatenburg de Jong RJ, Goedegebure A, Vernooij MW.
Neurobiology of Aging 2018; 61: 124-131.

2018 **Progression of hearing loss in the aging population – repeated auditory measurements in the Rotterdam Study.**
Rigters SC, van der Schroeff MP, Papageorgiou G, Baatenburg de Jong RJ, Goedegebure A.
Audiology and Neurotology 2018; 23: 290-297.

2020 **Hearing loss and microstructural integrity of the brain in a dementia-free older population.**
Croll PH, Vernooij MW, Reid RI, Goedegebure A, Power MC, Rigters SC, Sharrett AR, de Jong RJP, Mosley TH, de Groot M, Lin FR, Deal JA.
Alzheimer's & Dementia 2020; 16: 1515-1523.

2021 **The effect of hearing aid use on the association between hearing loss and brain structure in older adults.**
De Boer TG, Rigters SC, Croll PH, Niessen WJ, Ikram MA, van der Schroeff MP, Vernooij MW, Goedegebure A.
Manuscript under revision at Ear and Hearing.

PHD PORTFOLIO

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Department:	Otolaryngology and Head & Neck Surgery
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PhD period:	2013 – 2021
Total ECTS:	65.8

GENERAL ACADEMIC COURSES (6.4 ECTS)	**YEAR**
EndNote, Pubmed, search in other databases	2013
BROK	2014
English Language	2014
Biomedical English Writing and Communication	2015

THESIS-RELATED COURSES (1.4 ECTS)	
Introduction to Clinical Research	2014
Biostatistics for Clinicians	2014

MASTER OF SCIENCE (35.5 ECTS) *Clinical Epidemiology (NIHES)*	
Principles of Research in Medicine	2014
Methods of Public Health Research	2014
Fundamentals of Medical Decision Making	2014
The Practice of Epidemiological Analysis	2014
Health Economics	2014
Biostatistics Methods I	2014
Courses for the Quantative Researcher	2014
Biostatistics Methods II	2014
Principles of Epidemiological Data-Analysis	2015
Missing values in Clinical Research	2015
Logistic Regression	2015
History of Epidemiology	2015
Cohort Studies	2015
Clinical Practice-Relevant Therapeutic Trials	2015
Study Design	2015
Clinical Epidemiology	2015
Methodological Topics in Epidemiological Research	2015
Research Proposal	2016
Psychopharmacology	2016
Bayseian Statistics	2016

ENT-RELATED COURSES (7.0 ECTS)	YEAR
Course on Basic Life Support	2013
Basic Surgical Exam	2017
Course on Functional Endoscopic Sinus Surgery	2018
Health-Law (Desiderius School)	2018
Medical Ethics (Desiderius School)	2019

PRESENTATIONS (4.0 ECTS)	
Patient presentations	2013-2021
Research presentations, e.g. ENT science day	2013-2021

(INTER)NATIONAL COURSES (4.0 ECTS) *Oral presentations*	
228th Scientific Meeting of Dutch Society for ENT	2016
"*Presbyacusis en structurele cerebrale veranderingen"*	
HEAL 2016 (Como, Italy)	2016
"Structural brain changes and hearing impairment in aging – Results from the Rotterdam Study"	
ENT Congress 2017 (Port Elizabeth, South Africa)	2017
"*Age-related hearing loss and morphological brain changes in the elderly population."*	
232th Scientific Meeting of Dutch Society for ENT	2018
"*Presbyacusis & het brein"*	

AWARDS (1.0 ECTS)	
Posterprijs, 1st Prize, Dutch Society for ENT	2017

TEACHING (2.0 ECTS)	
Supervising practical's 3th and 5th year medical students	2013-2021
Traumatic ENT for staff first aid department	2013-2021

SUPERVISION (4.0 ECTS)	
Coaching bachelor medicine students	2016-2018
Supervisor of Tom de Boer, audiologist	2017-2018
Coaching bachelor medicine students	2020-now

OTHER (0.5 ECTS)	
Review of paper for BMJ Open	2017

DANKWOORD

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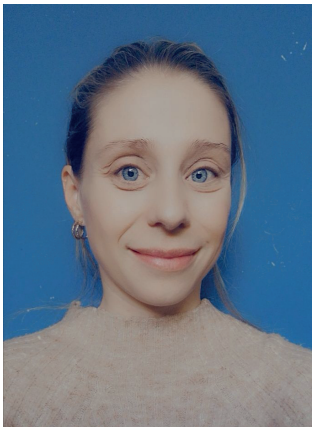
OVER DE AUTEUR



Stephanie Claire Rigters werd geboren op de eerste dag van het nieuwe jaar in 1987 te Leiderdorp als dochter van Lisette Dhont en Tom Rigters. Samen met haar jongere broertjes Martijn en Wouter groeide zij op in Leiderdorp. Gedurende haar tijd op de middelbare school, het Stedelijk Gymnasium te Leiden, was biologie haar lievelingsvak en de vervolgstap om Geneeskunde te studeren, lag dan ook voor de hand. Zij vertrok op 17-jarige leeftijd naar Amsterdam, maar werd helaas uitgeloot. Het eerste jaar startte ze daarom met Biomedische Wetenschappen. Voorafgaand aan haar tweede studiejaar kon Stephanie, middels de decentrale selectie, alsnog beginnen met Geneeskunde. Tijdens haar co-schappen wekte het vak KNO gelijk haar interesse. Naast haar oudste co-schap KNO in het AMC, heeft ze ook drie maanden co-schappen gelopen in Zambia, waar ze met één van de drie(!) KNO-artsen dat het land telt, kon meelopen.

Naast Geneeskunde, wilde ze ook graag Spaans leren. Na een keuzevak op de Universiteit van Amsterdam is ze dan ook voor haar wetenschappelijke stage vier maanden in Buenos Aires gaan wonen om deze twee te combineren. In 2012 studeerde ze af en vond haar eerste baan als arts-assistent op de afdeling thoraxchirurgie in het Erasmus MC. In 2013 werd ze aangenomen voor het huidige promotietraject en voor de opleiding tot KNO-arts onder leiding van prof. R.J. Baatenburg de Jong en dr. R.M. Metselaar. Deze laatste begeleidde in eerste instantie ook haar onderzoek, samen met dr.ir. A. Goedegebure. Later werd ook dr. M.P. van der Schroeff haar co-promotor. Tijdens haar promotietraject behaalde zij tevens de master ‘Clinical Epidemiology’ aan de Erasmus Universiteit. Inmiddels bevindt zij zich in het vierde jaar van haar opleiding tot KNO-arts.

Stephanie woont samen met haar vriend Chiel Kalter in Rotterdam. Samen kregen zij in 2019 dochter Evi en afgelopen juli (2021) zoon Filip.

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