General discussion

GENERAL DISCUSSION

In recent years, age-related hearing loss in epidemiological research has been growing from a new kid on the block, into an established and relevant outcome assessed in population-based studies. Once regarded as an inevitable part of ageing, increased interest in the etiology and potential adverse outcomes of age-related hearing loss revealed to the scientific and medical world that hearing loss is a problem in the elderly population that should be acknowledged and treated properly. Several population-based studies reported that hearing loss is associated with social isolation, loneliness, and depression, but also with an increased risk of dementia.[2, 3] Especially the latter association has put hearing loss on the map as a condition seriously affecting quality of life, general health and psychosocial well-being in the elderly. Moreover, it has inspired interest into hearing loss as a potentially modifiable factor in neurological diseases.[4] However, the underlying pathway explaining this association remains unknown. Large, population-based studies provide the unique opportunity to further elucidate if and how hearing loss in the elderly is associated with an increased risk of dementia. As such, more can be said on whether hearing rehabilitative treatments may potentially alter or delay the progression of cognitive decline and dementia onset.

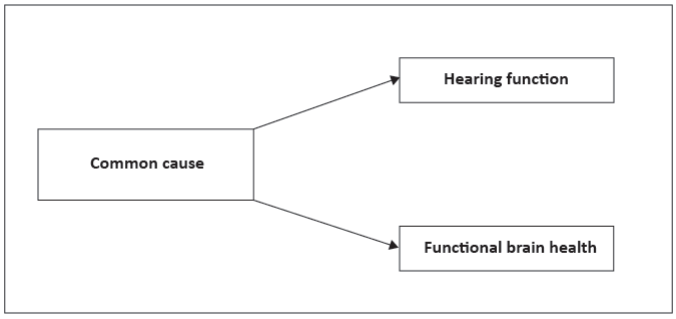

Figure 1. Common-cause hypothesis

The objective of this thesis was to gain new insights into the '*common-cause hypothesis*' (**figure 1**) and the '*sensory deprivation hypothesis*' (**figure 2**), two hypotheses proposing potential underlying mechanisms in the recently discovered association between hearing loss and dementia.[4] Specifically, I explored potential risk factors for hearing loss on the one hand, and risk factors for brain health on the other hand. Identifying common risk factors for both hearing function and brain health may shed more light on the *'common-cause hypothesis'*. Subsequently, I have addressed potential direct interrelations between hearing loss and brain health, to further explore the

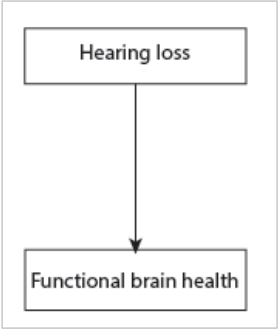

Figure 2. Sensory-deprivation hypothesis

'sensory-deprivation hypothesis'. Most studies described in this thesis were embedded within the prospective, population-based Rotterdam Study.[5] One study in this thesis was embedded within the Atherosclerosis Risk in Communities (ARIC) study from the United States of America.

In this chapter I will first review and discuss the main findings described in this thesis. Next, I will discuss methodological issues which should be considered when interpreting the findings. Finally, I will conclude with potential implications of my research with regard to clinical practice and future research.

MAIN FINDINGS

Risk factors for hearing function

Currently, several demographic- and lifestyle factors are known to contribute to elevated hearing thresholds in the elderly. One of the biggest demographic risk factors is age, reflected by exponentially increasing hearing thresholds with higher age.[6] Even though this is essential information to lay the foundation for further research into hearing loss by defining the prevalence and potential societal impact of hearing loss within an ageing population, it is obviously a non-modifiable risk factor. Therefore, other studies mostly focused on risk factors that are potentially modifiable. One of those well-established risk factors is smoking, reflected in a higher incidence of hearing impairment in smokers.[7-9] On top of this, smoking cessation virtually eliminates an increased risk of developing hearing impairment.[7] Following these promising results, I was interested in potential preventive effects of other lifestyle- and cardiovascular risk factors on hearing function.

The risk factors explored in the current thesis, for both hearing function and brain health, were selected based on existing knowledge. To be more specific, I was especially interested in factors known to be (also) associated with dementia. As such we might be able to draw conclusions about preventive factors for hearing function and brain health and eventually about the common-cause hypothesis.

Adherence to a healthy dietary pattern has been reported to lower the risk of dementia.[10] Thus, it may be hypothesized that diet is a potential common cause in the association between hearing loss and dementia. In the relatively few studies examining nutritional factors and hearing loss, it was seen that sufficient consumption of fish, meat, vitamin C, vitamin B_{12} and moderate intake of fat and alcohol was related with lower hearing thresholds.[11-15] The downside of assessing individual food components is that it does not acknowledge the complex interactions that occur across different food items and nutrients.[16] Surprisingly, overall dietary pattern as a risk factor for hearing loss is relatively unexplored. Two other population-based studies found cross-sectional associations between better diet quality and lower hearing thresholds, however they did

not replicate this association at follow-up.[17, 18] In **chapter 2.1**, it appeared that dietary composition did not affect hearing function, both at baseline and over time. Translating my results into clinically relevant measures of ageing within hearing function (+1 dB per year),[19] counterintuitively it appeared that adhering to a healthier dietary pattern was equivalent to 0.2 years of ageing. However, it is questionable whether such a small difference should be regarded as a clinically relevant effect on hearing abilities. Even though other studies confirmed protective effects of certain individual food components, it is questionable whether overall dietary pattern directly affects hearing function. Regardless of the non-significant association between diet quality and hearing levels, it is well-known that an unhealthy diet is the biggest contributor to obesity, which is currently one of the larger public health issues.[20] On top of this, obesity has been identified as a risk factor for dementia[20, 21] and it has been argued that obesity has a detrimental effect on hearing function,[22] making it a potential common cause. Most studies exploring the association between obesity and hearing loss used BMI as a measure of body composition.[22] However, BMI does not differentiate between metabolic healthy and unhealthy body mass. Therefore, dividing BMI further into fat mass index (FMI) and fat-free mass index (FFMI) may be a more accurate reflection of body composition. Especially since the cochlea is a heavily vascularized organ and consequently is prone to any change in cardiovascular health, associations between BMI and hearing loss may be largely explained by the effects of FMI. Indeed, in the Rotterdam Study I found that higher BMI, and especially a higher FMI, were related to higher hearing thresholds (**chapter 2.1**). However, a higher BMI and/or a higher FMI did not result in a statistically significant faster decline in hearing function over time. This may be partly due to a relatively short follow-up period (average of 4.4 years). Nonetheless, the results in this study can be considered relevant as the effect of obesity on hearing function is comparable to one year of ageing in hearing function.[19] Besides these nutritional- and cardiovascular risk factors, previous studies have focused on more direct, generalized markers of cardiovascular disease such as atherosclerosis. And indeed, during the last years, it has become clear that higher atherosclerotic burden leads to worse hearing function.[23] In light of the common-cause hypothesis, it is known from previous studies in the Rotterdam Study population that higher atherosclerotic burden leads to a higher risk of dementia.[24] On top of this, it was reported that carotid atherosclerosis is related with cognitive decline apart from normal age-related declines.[24, 25] In this thesis I found that higher plaque burden and increased intima media thickness of the carotid artery resulted in higher hearing thresholds (**chapter 2.2**). On top of this, atherosclerosis specifically seemed to exert its influence on hearing loss in the right ear, not in the left ear. Clinically, the effect of atherosclerosis is even more striking. Overall, higher atherosclerotic burden is related to 2 – 3.5 years of ageing in hearing function. From a clinical perspective, the impact of atherosclerosis seems to go beyond merely the risk of cardiovascular events.[26] Thus,

early detection and prevention of atherosclerosis by therapeutic- or lifestyle interventions carries the promise to not only lower the risk of clinical cardiovascular events and mortality, but also to delay the onset or slow down the progression of hearing loss by promoting and maintaining inner ear health.

Promoting hearing function

Unfortunately we are unable to cure hearing loss. Therefore it is of great importance to focus on the prevention of accelerated decline, beyond 'normal' age-related degeneration of hearing function by identifying modifiable risk factors. From the above studies it seems that promoting cardiovascular health through maintaining an optimal body composition and as such prevent cardiovascular disease may prove beneficial in promoting hearing function and maintaining inner ear health in the elderly population. Even though it is extremely important to adhere to a healthy dietary pattern for multiple reasons, based on our results it does not seem likely that diet quality is related to hearing function. Yet, we should keep in mind that an unhealthy diet is one of the largest contributors to obesity. Whereas diet quality might not have a direct effect on hearing function, it may exert its effects indirectly through body composition.

Risk factors for brain health

With the ageing of the population, not only the prevalence of hearing loss is increasing, also the number of dementia cases is showing a steep upward trend.[4] For this reason, research has focused on the prevention of cognitive impairment and dementia in the preclinical phases and identified some promising modifiable risk factors. For example, epidemiological evidence has shown that elevated blood pressure in mid-life increases the risk of cognitive impairment 20-30 years later.[27, 28] Thus, treating hypertension by medical- or lifestyle interventions may prevent cognitive decline and lower the risk or delay the onset of dementia. As such, preventing accelerated neurodegeneration, apart from 'normal' declines in brain volume and function with age, may prove as an effective strategy in lowering the risk of dementia. Yet, more in-depth knowledge on modifiable risk factors for brain health is needed.

Aside from the non-significant results between diet quality and hearing loss in **chapter 2.1**, the evidence in regard to dietary factors, brain health and dementia have been more conclusive. Specifically, we know that B vitamins, vitamin E, and the *n*-3 fatty acid docosahexaenoic acid that can be found in vegetables, fruit and seafood, have neuroprotective effects.[16, 29] However, people do not only consume fish, vegetables or vitamin E. Therefore, overall dietary pattern is a more realistic and accurate reflection of daily life. Evidence has shown that better adherence to the Mediterranean Diet in other European populations supports brain health, reflected in larger grey- and white matter volumes.[30, 31] Using the Rotterdam Study dietary guidelines in relation to brain

measures,[32] participants with healthier dietary patterns had larger brain tissue volumes. Specifically, adhering to a healthier diet was related to larger white matter volumes. Putting it differently, eating unhealthier appeared to be equivalent to 0.5 years of ageing in brain health.[33] Interestingly, diet quality did not seem to influence the volume of white matter hyperintensities, nor the presence of lacunes or microbleeds (**chapter 3.1**). Zooming in on specific dietary vitamins, it is known that vitamin D deficiency is associated with an increased risk of dementia and has previously been linked to worse hearing function, making vitamin D status a potential common cause.[34, 35] Unexpectedly, vitamin D in relation to brain health in dementia-free individuals remains relatively unexplored. In **chapter 3.2** I found that participants with vitamin D deficiency had on average smaller white matter volumes, which was equivalent to 1.6 years of ageing. Moreover, deficient vitamin D levels seemed to result in smaller hippocampus volumes, an area in the brain important for memory. Dietary pattern and vitamin D levels may be directly related to brain health through neuroprotective effects of both. Additionally, an indirect link may also be present. For example, it is plausible that the people with a healthy dietary pattern and high vitamin D levels may be higher educated and as such are more aware of the beneficial health effects of adhering to a healthy lifestyle. Concluding from my results, overall diet quality and vitamin D status may be a promising modifiable risk factor in the prevention of dementia by supporting brain health in the preclinical phases. As such, it is of importance to raise awareness of the beneficial effects of eating healthy and maintaining optimal vitamin D levels (possibly through vitamin D supplementation) in the general population and amongst general practitioners. Additionally, from an economic standpoint, promoting a healthy dietary pattern may be supported by lowering prices of healthy products and/or increase the prices of unhealthy products and possibly target (grocery store) advertisements at healthy foods and/or ban advertisements that recommend purchases of unhealthy products. Applying such strategies may also have additional beneficial effects in the battle against the so-called obesity epidemic.[20] As stated earlier, obesity may be a common-cause in the association between hearing loss and dementia.[21, 36] Previous studies mostly used BMI as a measure of obesity in relation to brain health.[36-38] Though, this does not take into account that in the elderly fat mass tends to decrease and lean mass tends to increase, making BMI a less suitable strategy to infer on obesity in the elderly.[21, 39] Additionally, it may be hypothesized that especially unhealthy fat mass may have negative effects on brain health through system wide cardiovascular disease.[25] Unexpectedly, differentiating between FMI and FFMI did not show an association (both statistically significant and clinically relevant) between higher FMI and changes in brain volume, white matter microstructure, nor the presence of markers of cerebrovascular disease such as white matter hyperintensity volume, lacunes and microbleeds (**chapter 3.3**). This may be partly explained by selection bias in the study population as the sample with a follow-up MRI scan were younger and healthier

than the participants with just a baseline MRI scan. Moreover, equal to **chapter 3.1**, we might be dealing with an insufficient follow-up time to capture a potential small, but significant effect of obesity on brain health.

Promoting brain health

With increasing age, our brain will undergo so-called normal age-related changes, such as decreasing cell function and volume, increasing cerebrospinal fluid volume, the formation of white matter hyperintensities, decreased microstructural organization, and potential formation of lacunes and microbleeds (**figure 3** shows an example of A; a microbleed, and B; white matter hyperintensities).[40] Nowadays, no treatment exists to prevent this age-related neurodegeneration. However, great promise may lay in preventing accelerated neurodegeneration when no cognitive decline or cognitive impairment is present yet. From our results, in a dementia-free population, it can be concluded that adhering to a healthy lifestyle by consuming an overall healthy dietary pattern and maintaining sufficient vitamin D levels might directly support brain health. Although we could not confirm an effect of obesity on neurodegeneration, maintaining a healthy body composition may indirectly support brain health as it is plausible that all lifestyle factors are highly intertwined with one another.[21]

Age related hearing loss and brain health: the common-cause hypothesis

Identifying potential common-causes in the association between hearing loss and dementia is important to truly establish whether hearing loss is directly related to brain health, cognitive function, and eventually dementia. Based on my results it is doubtful

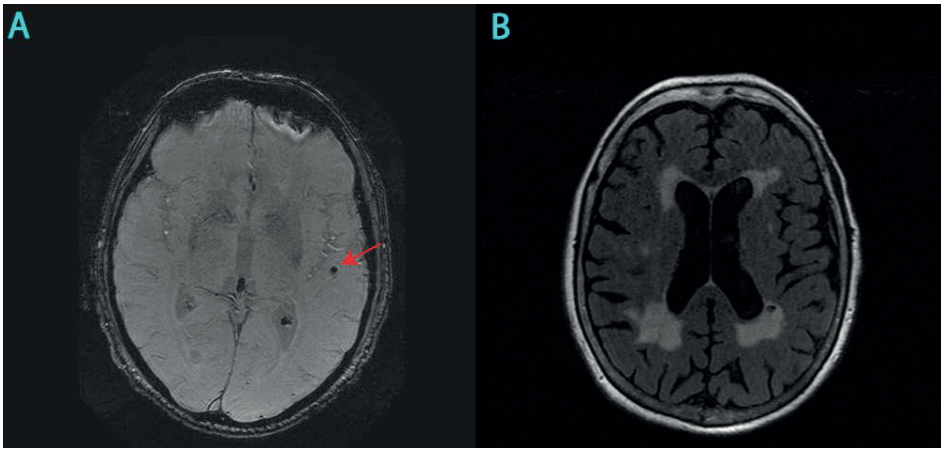

Figure 3. A) Axial slice of a susceptibility weighted image (SWI). The red arrow indicates a microbleed. B) Axial slice of a T2-weighted fluid attenuated inversion recovery (FLAIR) image on which white matter hyperintensities are visible. Images were obtained by means of a 1.5 tesla MRI scanner.

that dietary pattern and obesity on their own are a third factor causing both hearing loss and cognitive impairment. Yet, cardiovascular disease and vitamin D levels may actually be a common-cause as they both relate to worse hearing function and diminished brain health. As such, they might also be important confounders in previously found associations between hearing loss and dementia. Even though I did not find a direct relation of obesity and diet quality on either brain health or hearing function, we should not disregard them entirely as a potential common-cause. It is plausible that the accumulation of several lifestyle factors and cardiovascular risk factors all together exerts its effects on neurodegeneration and/or hearing loss. In future studies exploring hearing loss as a modifiable risk factor for dementia, it might be worthwhile to adjust for cardiovascular disease, vitamin D status and other lifestyle factors. If positive associations continue to exist after this adjustment, then there is more ground to make statements about a potential direct association between hearing function and brain health. Moreover, it might be of interest to explore whether hearing loss could act as a mediator in the association between cardiovascular risk factors, cardiovascular disease and dementia.

Interrelations between hearing function and brain health

Even though there is support for the common-cause hypothesis, it has been demonstrated that age-related sensory degeneration is also at least in part independent of cognitive degeneration. Such independent effects would not be observed if there is a single common-cause underlying all decline.[41] Hence, in recent years, interest has also increased in a potential direct link between hearing function and brain health. It has been argued that impoverished auditory input results in permanent cognitive changes, possibly through neuroplastic changes that disadvantage general cognition in favour of processes supporting speech perception.[41] Such chronic reallocation of cognitive resources may produce permanent changes in structural and functional brain health over time. Even though research on the association between hearing loss, cognition and dementia has increased exponentially, it is necessary to replicate previously found findings in various population-based samples.

Tinnitus and brain health

Besides hearing impairment, tinnitus is a common auditory disorder in the adult population.[42] It is characterized by the perception of a sound, without an objective corresponding sound source being present. Research has shown that hearing loss is one of the biggest risk factors for tinnitus: 90% of the people with tinnitus also have hearing loss.[42] Besides peripheral involvement, it has been argued that there is a central process contributing to the pathogenesis of tinnitus.[43] A cross-sectional analysis within the Rotterdam Study reported associations between higher levels of hearing loss and smaller brain tissue volumes.[44] As hearing loss is highly related to tinnitus, it might be

argued that the same central processes occur in individuals with tinnitus as in those with hearing loss, i.e. having tinnitus is associated with smaller brain volumes. Interestingly, I found the opposite. In **chapter 4.1** I have described how in the Rotterdam Study population, having tinnitus is associated with larger instead of smaller brain volumes. These associations were independent of age and amount of hearing loss. Another study reported no significant associations between tinnitus and brain volumes.[45] These authors suggested that smaller brain volumes may be explained by comorbid hearing loss, which is largely determined by age. Other studies also proposed that grey matter changes, which is known to degenerate with age,[40] are attributable to age-related hearing loss rather than the tinnitus per se.[45, 46] This might suggest that tinnitus has more of a neurodevelopmental origin potentially increasing the risk of developing future tinnitus in people with larger brain tissue volumes from a young age onwards. My results add to the knowledge on the pathophysiology of tinnitus. Nonetheless, it is plausible that tinnitus does not play a role in the association between hearing loss and dementia.

Hearing loss and brain health

Typically, research in ageing of the brain has mostly focused on macro structural neurodegeneration, e.g. cell loss and the formation of white matter hyperintensities visible on MRI-scans. Besides degeneration of the macrostructure, changes in the underlying microstructure occur which are invisible to the human eye. These changes even take place before macro structural cell loss or the formation of white matter hyperintensities sets in.[47] Therefore, it has been suggested that degeneration of the underlying microstructure is an earlier, more sensitive marker of neurodegeneration.[47] Following this, it was seen in the Rotterdam Study that higher levels of hearing loss were related to diminished white matter microstructural integrity, independent of macro structural brain measures.[48] Until recently, this was the only large population-based study exploring the association between hearing loss and microstructural integrity of the brain. In an American population-based sample, I identified that hearing loss had a negative effect on white matter microstructure in the temporal lobe and in several white matter limbic fibres (**chapter 4.2**). Moreover, I found that hearing loss was associated with lower grey matter microstructure of the hippocampus. Research on diffusion imaging so far mostly focused on the white matter microstructural degeneration of the brain. Fewer studies researched grey matter microstructure, even though there is evidence that grey matter microstructure degenerates with increasing age.[49] Therefore, it is unclear whether found associations with lower grey matter microstructural integrity in the hippocampus are also clinically relevant. Nonetheless, my results support the sensory-deprivation hypothesis, describing a direct causal relationship in which diminished auditory input leads to neuroplastic changes in the brain.

Hearing loss and cognitive decline

Moving further downstream from brain health towards cognitive function, it has been repeatedly reported that hearing loss is associated with accelerated cognitive decline.[4] Whilst this is an important and promising finding in the search towards preventive factors for dementia, it is important to realize that both hearing- and cognitive function are heavily dependent on age.[50, 51] Therefore, it remains unclear whether the effects of hearing loss on cognitive function are independent of concurrent ageing effects. Whilst adjusting for baseline age takes account of differences in hearing- or cognitive function due to age at baseline, it fails to take into account that older people will decline faster in cognitive function over time compared to their younger counterparts. Adding an interaction of age and follow-up time into statistical models will filter out these ageing effects over time. This is supported by our findings in **chapter 4.3**. Even though we saw that any hearing loss accelerated decline of memory functioning, this association disappeared after adding above mentioned interaction into our models. Yet is important to acknowledge that our relatively short follow-up time (4.4 years) and limited amount of repeated measurements (2 cognitive assessments) may have resulted in these non-significant results. Cognitive decline with age is gradual,[52] thus studies with sufficient follow-up time are needed to identify potential small, but significant effects. Indeed, a study with 8-year of follow-up time did not find a significant association between hypertension, a well-known risk factor for dementia,[4] and risk of cognitive impairment.[53] On the other hand, in a study with 20-30 years of follow-up researchers reported an increased risk for cognitive impairment related to hypertension during mid-life.[27, 28] This underlines the need for sufficient follow-up time to capture an effect of hearing loss on cognitive decline.

Age related hearing loss and brain health: the sensory-deprivation hypothesis

In this thesis I have found some promising evidence pointing towards a direct link between hearing loss and brain health, namely an independent association between higher levels of hearing loss and diminished brain health as reflected in lower micro-structural integrity. On top of this, hearing loss had a negative impact on cognitive function. Yet, age-related hearing loss did not accelerate cognitive decline over time. This finding underlines the need for two things to truly establish whether hearing loss is independently related to brain health, cognitive decline and dementia. First, longitudinal data with repeated measurements with sufficient follow-up time is warranted. Second, in statistical models it is essential to take the strong effects of ageing and other confounders into account. As I will describe in more detail below, it is difficult to truly filter out the confounding effects of ageing. Due to these strong effects, it should be considered that age might act as a third factor, a common-cause, in the association between hearing loss and brain health.

METHODOLOGICAL CONSIDERATIONS

Study design

All studies described in this thesis are embedded within population-based cohort studies. Most of them (**chapter 2.1 & 2.2; chapter 3.1 – 3.3; chapter 4.1 & 4.3**) were part of the Rotterdam Study; an ongoing prospective population-based cohort study in the area of Ommoord, Rotterdam, the Netherlands, initiated in 1989.[5] **Chapter 4.2** was embedded within the Atherosclerosis Risk in Communities (ARIC) study, an ongoing cohort study from four US communities (Washington County, Maryland; Forsyth County, North Carolina; Jackson, Mississippi; and Minneapolis, Minnesota) from 1987 onwards.[3, 54] Population-based cohort studies provide the unique opportunity to accurately study the incidence, but also the etiology of a large variety of diseases. Besides this, another specific advantage of population-based studies is that the findings may be generalized to a large portion of the population.[55] Despite these advantages, there are also some limitations that should be acknowledged.

Population-based studies, like all other studies, may be subject to specific types of bias. To be more specific, selection bias, information bias and confounding may play a role in associations between a determinant and an outcome and increase the risk of potential false negative results or false positive results. Despite the best efforts to minimize these biases through procedures such as random sampling from the general population, blinded measurements, maintaining high response rates, and adjustment for potential confounders in statistical analyses, the results in any study may still suffer from some residual confounding and/or bias.

A number of studies in this thesis are of a cross-sectional design. Even though the Rotterdam Study and the ARIC study have a considerable history of data collection, hearing assessment has only been added into the core study protocol in both studies in 2011 and in 2016, respectively. Moreover, magnetic resonance imaging (MRI) of the brain has been included into the core study protocol of the Rotterdam Study in 2005 and in ARIC in 2011 (see **figure 4** for an overview of the Rotterdam Study). As such, few follow-up data is available for particularly hearing function, limiting some of our studies towards a cross-sectional design (**chapters 2.2; 3.1; 3.2; 4.1; 4.2**). A well-known limitation of cross-sectional studies is the lack of the ability to establish a temporal effect, i.e. determine whether the determinant actually precedes the outcome. In above mentioned chapters, it can only be speculated that the determinants and outcomes are related to one another in that specific order. However, biologically it is very unlikely that for example in **chapter 2.2** higher levels of hearing loss will lead to increased plaque burden and higher intima media thickness in the carotid artery, or that in **chapter 4.2** lower microstructural integrity will cause more hearing loss.[41]

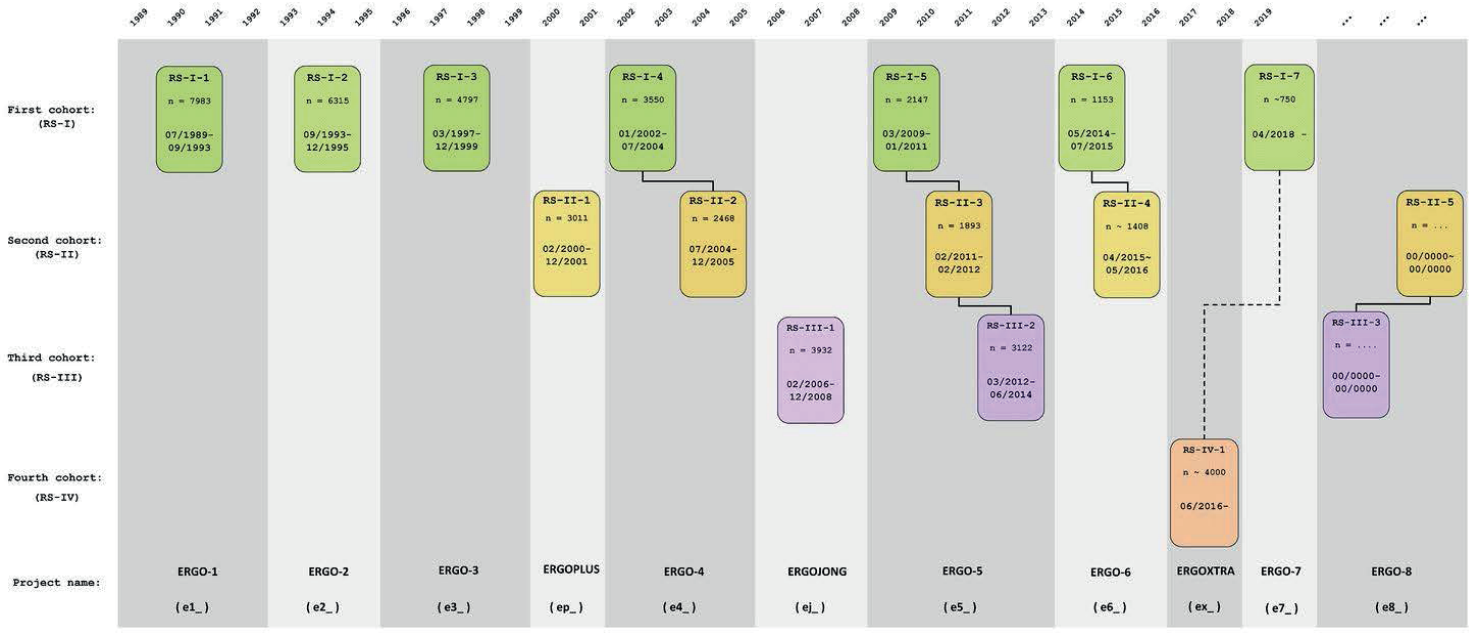

Figure 4. Overview of the Rotterdam Study cohorts and follow up scheme

Effects of age in cross-sectional studies

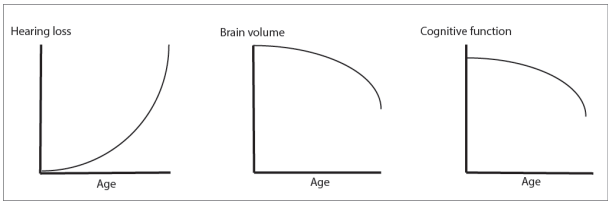

Figure 5. Hypothetical trend of hearing function, brain volume and cognitive function with ageing

Besides these limitations in the cross-sectional studies concerned, I might be dealing with residual confounding by age effects. Especially when I am exploring potential direct associations between hearing loss, brain health and cognitive function. The amount of hearing loss increases, and brain volume and cognitive function decreases in a non-linear fashion with older age (see for a hypothetical example: **figure 5**).[40, 50, 51, 56, 57] Adjusting for the linear term of age or the non-linear term of age (age^2 or the spline of age) in statistical models will sufficiently adjust for baseline age differences, i.e. it will take into account that due to age, older people will have smaller brain volumes or a lower cognitive function at baseline. However, residual confounding due to strong, far-reaching effects of age might still be present. Not only hearing loss, brain health and cognitive function are heavily dependent on age, the confounders in our statistical models are highly related to age as well. In **Table 1**, I have listed every determinant, outcome or confounder used in any of my studies ordered by age group. Measurements of these variables have been obtained during research visit 5 (e5; **figure 3**) of the Rotterdam Study, the same study visit as when hearing assessment was added to the study protocol. In this table we see that the levels, amount or presence of almost every factor increases substantially with age. So for example, we see in the eldest group of the Rotterdam Study population (80 – 99 years), lower levels of physical activity (median MET h/week of 20.0), higher plaque burden (median plaque score of 2.5), higher levels of hearing loss (mean hearing threshold of 45.8 dB), and a lower score on the 15-word learning test (mean score of 5.9) as compared to the youngest participants of the Rotterdam Study (51 – 65 years; MET h/week: 42.0; plaque score: 1.0; hearing threshold: 18.0 dB; 15-word learning test score: 9.0, respectively). So it is extremely complex in cross-sectional studies to truly adjust for effects of ageing as it is highly intertwined with every variable in the different studies throughout this thesis. Following this reasoning, we might be looking at effects of ageing instead of a direct effect of vitamin D deficiency (**chapter 3.2**) on brain health as the lowest levels of vitamin D are measured in the eldest age group. This might also be the case in **chapter 4.2** in which I report associations between higher levels of hearing loss and lower microstructural integrity. Both hearing function and brain health decline steeply with age (presence of severe hearing impairment in youngest participants: 0.4%; vs in oldest participants: 11%; total brain volume in youngest participants: 959.8 mL; vs in

Table 1. Overview of characteristics of participants (cohort I, II, and III) of the Rotterdam Study during visit 5 (2009-2015) by age groups.

	Entire sample	Participants 51 - 65 years	Participants 65 - 80 years	Participants 80 – 99 years
	N = 6,279 (100%)	N = 1,996 (31.8%)	N = 3,379 (53.8%)	N = 904 (14.4%)
Demographic				
Age, years	69.6 (9.2)	59.3 (3.6)	71.8 (4.4)	84.5 (3.5)
Female, N (%)	3,593 (57.2)	1,140 (57.1)	1,898 (56.2)	555 (61.4)
Educational level, N (%)				
Primary	538 (8.6)	141 (7.1)	252 (7.5)	145 (16.0)
Lower/intermediate	2,475 (39.4)	627 (31.4)	1,459 (43.2)	389 (43.0)
Intermediate vocational	1,830 (29.6)	612 (30.7)	975 (28.9)	273 (30.2)
Higher vocational	1,341 (21.4)	609 (30.5)	644 (19.1)	88 (9.7)
Lifestyle factors				
Physical activity, MET h/week*	40.1 (15.7 – 79.4)	42.0 (18.0 – 76.7)	44.4 (17.5 – 85.5)	20.0 (8.3 – 49.3)
Smoking yes, N (%)	3,270 (52.1)	942 (47.2)	1,820 (53.9)	508 (56.2)
Alcohol consumption, grams p/day*	6.8 (0.9 – 17.4)	8.0 (1.3 – 19.2)	7.3 (0.9 – 17.5)	2.7 (0.0 – 11.6)
Dietary adherence score*	7.0 (6.0 – 8.0)	7.0 (6.0 – 8.0)	7.0 (5.0 – 8.0)	7.0 (5.0 – 8.0)
Vitamin D status, nmol/L	60.9 (27.7)	59.4 (27.2)	64.5 (28.5)	54.2 (31.1)
Cardiovascular risk factors				
Body mass index, kg/m^2	27.5 (4.3)	27.3 (4.5)	27.7 (4.2)	27.0 (4.0)
Fat mass index, kg/m^2	10.0 (3.3)	9.8 (3.4)	10.1 (3.2)	9.9 (3.1)
Fat-free mass index, kg/m^2	17.5 (2.1)	17.5 (2.2)	17.5 (2.0)	17.1 (1.9)
Systolic blood pressure, mmHg	143.9 (22.2)	132.4 (18.2)	147.8 (21.0)	155.9 (23.5)
Diastolic blood pressure, mmHg	83.5 (11.2)	82.1 (10.8)	84.4 (11.1)	83.3 (11.9)
Anti-hypertensive medication use, N (%)	2,962 (47.2)	638 (32.0)	1,741 (51.5)	583 (64.5)
Total cholesterol, mmol/L	5.4 (1.1)	5.6 (1.1)	5.4 (1.1)	5.2 (1.1)
HDL-Cholesterol, mmol/L	1.5 (0.4)	1.5 (0.5)	1.5 (0.4)	1.5 (0.4)
Statin use, N (%)	1,756 (28.0)	384 (19.2)	1,094 (32.4)	278 (30.8)
Diabetes mellitus, N (%)	557 (8.9)	141 (7.1)	325 (9.6)	91 (10.1)
Lipid lowering medication use, N (%)	1,926 (30.7)	482 (24.1)	1,159 (34.3)	285 (31.5)
Cardiovascular disease				
Maximum intima media thickness*	1.0 (0.9 – 1.1)	0.9 (0.8 – 1.0)	1.0 (0.9 – 1.1)	1.1 (1.0 – 1.3)
Plaque score*	1.5 (0.5 – 2.5)	1.0 (0.0 – 2.0)	1.5 (0.5 – 3.0)	2.5 (1.0 – 4.0)
Hearing function				
All frequency hearing loss, dB	25.7 (13.5)	18.0 (9.1)	29.3 (12.1)	45.8 (13.9)
Low frequency hearing loss, dB	15.6 (10.6)	11.1 (7.0)	17.4 (9.9)	29.9 (15.6)
Speech frequency hearing loss, dB	22.8 (13.3)	16.0 (8.9)	25.9 (12.3)	42.0 (15.2)
High frequency hearing loss, dB	34.7 (19.0)	23.8 (13.8)	40.3 (17.2)	60.5 (15.2)
Degree of hearing loss, N (%)				
Normal hearing (0 – 20 dB)	1,631 (26.0)	1,145 (57.4)	482 (14.3)	4 (0.4)
Mild hearing loss (20 – 35 dB)	1,607 (25.6)	550 (27.6)	1,004 (29.7)	53 (5.9)
Moderate hearing loss (35 – 50 dB)	702 (11.2)	68 (3.4)	500 (14.8)	134 (14.8)
Severe hearing loss (>50 dB)	249 (4.0)	14 (0.7)	134 (4.0)	99 (11.0)

Table 1. Overview of characteristics of participants (cohort I, II, and III) of the Rotterdam Study during visit 5 (2009-2015) by age groups. (continued)

	Entire sample	Participants 51 - 65 years	Participants 65 - 80 years	Participants 80 – 99 years
	N = 6,279 (100%)	N = 1,996 (31.8%)	N = 3,379 (53.8%)	N = 904 (14.4%)
Brain tissue volume				
Total brain tissue volume, mL	920.5 (62.9)	959.8 (97.4)	912.1 (101.8)	853.9 (92.7)
White matter volume, mL	393.9 (65.9)	414.8 (63.0)	390.4 (63.3)	354.6 (63.3)
Grey matter volume, mL	526.6 (62.9)	545.1 (63.3)	521.7 (60.0)	499.4 (59.8)
Cognitive function				
Mini-mental state examination score*	28.0 (27.0 – 29.0)	29.0 (28.0 – 30.0)	28.0 (27.0 – 29.0)	27.0 (25.0 – 29.0)
Word Learning Test – delayed recall	7.6 (3.0)	9.0 (2.7)	7.2 (2.8)	5.9 (2.8)

Values are mean (standard deviation) for normally distributed continuous variables or median (interquartile range) when indicated (*), percentages for dichotomous variables. MET: metabolic equivalent of task. nmol: nanomole. L: litre. kg: kilogram. m: meter. mmHg: millimetres of mercury. mmol: millimole. dB: decibel. mL: millilitre.

oldest participants: 853.9 mL; **Table 1**). Therefore, to elucidate whether determinant and outcomes of interest are truly directly related to one another, independent of age and other confounding factors, longitudinal studies are preferred above cross-sectional designs as they have the potential to filter out effects of ageing more thoroughly for which I will present an example below.

Effects of age in longitudinal studies

Multiple studies have shown that higher levels of hearing loss are related to accelerated cognitive decline and an increased risk of dementia.[2-4, 58, 59] These studies have only taken baseline age (whether it being the linear or non-linear term of age) into account as a confounding factor in their analyses. However, it is plausible that older people will decline faster over time on cognitive function compared to their younger counterparts. For example, hypothetical participant Y (80 years) will decline faster on cognitive functioning between T0, T1 and T2 then hypothetical participant X (65 years old) as a consequence of his or her older age (**figure 6**). Not taking into account this faster decline in cognition in older participants, may result in an overestimation of the true effect of hearing loss on cognitive decline. This faster decline due to age can be accounted for by adding the interaction between age and follow-

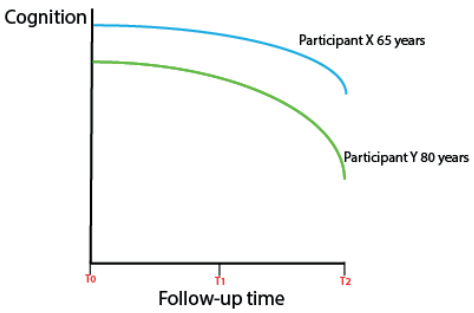

Figure 6. Hypothetical difference in cognitive trajectories over time in two participants.

up time into statistical models. In **chapter 4.3** I explored the longitudinal association between hearing function and cognitive decline in two steps. First, I applied a model similar to statistical models in previous studies and found comparable results, namely an accelerated decline on memory function due to moderate hearing loss as compared to normal hearing abilities. However, when adding the interaction between age and follow-up time in a second model, hearing loss was no longer significantly associated with an accelerated decline on memory function. This likely indicates that the association in my study was driven by (residual) effects of age on cognitive function. As such, I believe it is important, when investigating factors influencing brain health, cognitive decline or risk of dementia, to thoroughly adjust for strong effects of ageing.

Measuring hearing function

Throughout this thesis, I have used a somewhat crude measure of hearing loss, namely the average over all-, low-, speech-, or high frequencies. As such, I have disregarded potential subtypes of hearing loss, which have been described previously.[57] These subtypes encompass the metabolic-, the sensory-, and a mixed phenotype of age-related hearing loss.[60] The metabolic type is thought to result from the deterioration of the stria vascularis in the cochlear lateral wall (**figure 6**), which normally produces endolymph to maintain the endocochlear potential. Elderly with a metabolic type of hearing loss typically show audiograms that exhibit mild, flat hearing loss at the lower frequencies (10-40 dB) and gradually sloping hearing loss at higher frequencies (30-60 dB).[60] The sensory phenotype is thought to be related to damage to sensory cells in the inner ear (**figure 7**) and loss of the cochlear amplifier due to environmental exposures, such as excessive noise or ototoxic drugs, resulting in steeply sloping 50-70 dB thresholds shifts that predominantly affect the higher frequencies. The mixed phenotype is thought to reflect combined metabolic declines and sensory damage. This leads to audiograms marked by mild, flat hearing loss at the lower hearing frequencies and steeply sloping hearing loss at the higher hearing frequencies. Interestingly, it is thought that audiometric phenotypes are stable over time, although hearing thresholds do increase with older age.[60] Yet, if a transition is seen between phenotypes, it is usually observed in the sensory phenotype. Re-

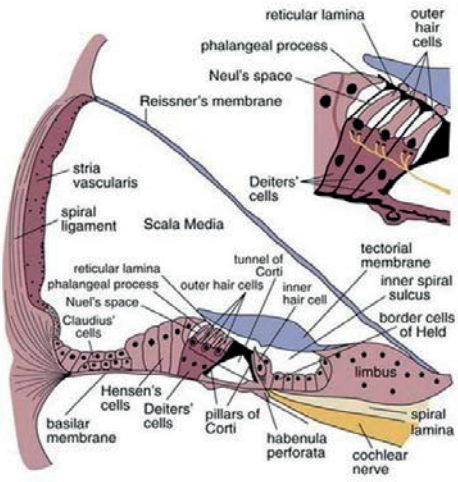

Figure 7. Cochlear anatomy. Source: Clinical Anatomy & Operative Surgery

searchers have proposed that sensory hearing loss might be relatively unaffected by ageing.[60] Nevertheless, from 70 years of age onwards, individuals with a sensory form of hearing loss also start to exhibit hearing loss typical for the metabolic phenotype, thus transitioning from the sensory type, to the mixed phenotype. Moreover, the metabolic and the mixed phenotype is most often seen in the older ages and are therefore regarded as the phenotypes which are typical for age-related hearing loss.[60] Indeed, the Rotterdam Study participants do have hearing thresholds typical for age-related hearing loss. As can be seen in **Table 1**, the increase in hearing thresholds with age is largest in the high frequencies (from 23.8 dB towards 40.3 dB and 60.5 dB per increasing age group) whereas thresholds in the low frequencies increase in a slower fashion (from 11.1 dB towards 17.4 dB and 29.9 dB per increasing age group). Unfortunately, there is no data available on noise exposure within the Rotterdam Study leading to the inability to differentiate between a metabolic and sensory phenotype. Nevertheless, exploring differences in results between the low- and high hearing frequencies may serve as a proxy to discern between these phenotypes. If certain factors would specifically harm hearing thresholds within age-related hearing loss, it can be expected that the largest effect is seen for the high hearing frequencies as compared to the low hearing frequencies. In **chapter 2.1** and **chapter 2.2** I examined differences between low- and high frequencies in regard to the effect of body composition and cardiovascular disease on hearing function. Regardless of the fact that the Rotterdam Study population does show hearing thresholds typical for age-related hearing loss, no differences were seen in the effect on high- versus low hearing frequencies for both body composition and cardiovascular disease. If certain factors would be more detrimental for a specific phenotype of hearing loss, I did not find evidence in this thesis pointing towards such a phenomenon.

Measuring brain health

Magnetic resonance imaging

Throughout this thesis I have mostly used MRI data from the Rotterdam Study. In the dedicated research centre, MRI scans are made with a 1.5 tesla MRI scanner.[61] Even though a 1.5 tesla MRI scanner is widely used, both in research and in clinical settings, a higher field strength would have the advantage to more sensitively image relatively small structures or markers of cerebral small vessel disease such as microbleeds.[62-64] The potential lower detection of the scanner used could explain the absence of any association between the determinants of interest and the risk of having microbleeds (**chapter 3.1, 3.2 and 3.3**). Moreover, in **chapter 4.2,** in which I had data available on brain microstructure imaged with a 3 tesla MRI scanner from the ARIC study, I saw an effect of hearing loss in the white matter microstructure of the limbic tracts, a relatively small white matter area. The study of Rigters et al.,[48] did not find such an association, which may (partly) be explained by the fact that this study used diffusion data obtained

by a 1.5 tesla MRI scanner. Thus, I might have missed particular associations in the Rotterdam Study between risk factors, hearing loss and measures of brain health for which scanning at a higher field strength would be preferred.

Unfortunately I have not (yet) used data on functional changes of the brain as a measure of brain health. Even though functional changes in brain health are a known marker of neurodegeneration. In normal ageing, neurodegeneration is characterized by grey- and white matter atrophy and the formation of white matter hyperintensities. Additionally, it is thought that these brain changes are preceded by changes in the functional organization of the brain.[65] The functional dynamics of the brain can be investigated by means of functional MRI (fMRI). fMRI indirectly reflects neural activity by measuring MRI signal fluctuations caused by variations in blood oxygenation and flow resulting from changes in neural metabolic demand.[66] Indeed, with increasing age the functional organization of the brain appears to decrease.[66] Whether hearing loss is potentially related to reduced functional connectivity of the brain may be an interesting research question in the search towards the underlying pathway in the association between hearing function and dementia. Some small studies did explore this relation and reported that higher levels of hearing loss were accompanied by decreased functionality of the auditory cortex,[67] and disrupted spontaneous activity in different brain regions amongst which the superior temporal gyrus and the parahippocampal gyrus.[68] Large population-based studies on hearing loss and functional connectivity do not exist yet, underlining the potential and the need to study this possible relation.

In none of the studies in the current thesis I specifically focused on the primary auditory cortex, an area in the brain involved in sound processing, which is located in the superior temporal gyrus. Possibilities were explored to obtain information for participants on auditory cortex volume. Unfortunately, the precise location of the primary auditory cortex remains controversial, due to highly differentiating sizes and shapes of the auditory cortex between individuals.[69] Especially in large population-based studies, identifying the auditory cortex for every participant would be highly time consuming and prone to erroneous classification. Instead, information on the superior temporal gyrus can be used as a proxy, as it is certain that the primary auditory cortex, in whatever size or shape, is located there.[69] Unexpectedly, I did not find that associations in the temporal lobe were predominantly driven by effects in the superior temporal gyrus in **chapter 4.2**. Rather, the effects were found for the entire temporal lobe. This may point towards effects of ageing in general rather than direct effects of hearing loss on neurodegeneration as it is known that the temporal lobe is one of the first structures to degenerate with older age.[40]

Cognitive function and dementia

As hearing assessment has been added into the Rotterdam Study protocol in 2011, just one follow-up measurement on cognitive function was available for the study I conducted, with a mean follow-up time of 4.4 years. The fact that I did not find a significant association between hearing loss and cognitive decline, may thus be explained by this relatively short follow-up time. Moreover, in this thesis I did not explore whether hearing loss was associated with an increased risk of dementia. So far, studies identifying hearing loss as a risk factor for dementia were mostly conducted in the United States and in a some other European countries, but not in the Netherlands so far. For purposes of generalizability and confirmation of previous results, it would add considerably to the current knowledge to assess this association in the Rotterdam Study. Unfortunately, incidence of dementia in participants with a baseline hearing assessment is limited (N = 15), precluding the possibility to infer on risk of developing dementia in participants with higher baseline levels of hearing loss.

CLINICAL IMPLICATIONS AND FUTURE RESEARCH

In the past decade, epidemiological studies have aided considerably to the current knowledge on hearing loss as a risk factor for dementia. Yet, we still have a long way ahead of us to truly elucidate how hearing loss is related to dementia and how we may potentially prevent accelerated degeneration of both hearing function and brain health. Worldwide, the number of persons developing hearing loss and dementia is still increasing, and will likely continue to do so, given the ageing of the population.[4, 57] Findings described in this thesis may first contribute to identifying potential modifiable risk factors for both hearing function and brain health. Second, our findings add to the current knowledge on a potential mechanism underlying the association between hearing loss and dementia. Yet, several aspects with regard to understanding the underlying mechanism between hearing function and dementia still remains unclear. In this final part of my thesis, I concentrate on the clinical implications of these findings and potential future directions.

Risk factors for hearing function and brain health

Taking together all the results in the current thesis it can be argued that adhering to a healthy lifestyle is key in healthy ageing. Preventing overweight, atherosclerosis and vitamin D deficiency may prove beneficial for both hearing function and brain health. This can be accomplished, as indicated in my results, by adhering to an overall healthy dietary pattern which may have either direct effects on hearing function and brain health, or indirect effects by promoting general cardiovascular health. Moreover, it will

likely maintain sufficient vitamin D levels, prevent overweight and obesity and through this lower the risk of cardiovascular disease. Other risk factors that are well-known to have a negative impact on brain health, such as sedentary behaviour, smoking, and consuming (too much) alcohol, are relatively unexplored in regard to hearing function. As such, it may be of interest to explore these lifestyle factors in relation to hearing function in future population-based studies. This could also provide information on which subgroups are more susceptible for lifestyle factors influencing hearing function and brain health. Such specific information could then be used to develop targeted interventions. On top of this, promoting adherence to a healthy lifestyle not only caries the promise to support hearing function and brain health, it will also have a beneficial effect on other (chronic) diseases associated with an unfavourable lifestyle. To put it differently, it will improve public health in general. For future studies, in the Rotterdam Study or in any other population-based sample, it is essential to have longitudinal data with multiple repeated measurements of both the determinant and outcome of interest. Only then it can be derived whether for example an unhealthy diet accelerates neurodegeneration besides normal age-related changes or that atherosclerosis increases the incidence of hearing impairment. Moreover, as lifestyle factors and cardiovascular risk factors are highly intertwined it could be of interest to explore both lifestyle factors and/or cardiovascular risk factors together in regard to hearing function and brain health instead of assessing them separately. This might shed more light on the interaction between these factors and the overall effect on hearing abilities and neurodegeneration.

On a completely different note, due to the globally changing climate, interest in vegetarian and plant-based diets has increased across the general population. Not consuming any meat and fish or eating no animal products at all is proven to protect the environment, but preliminary evidence also has shown health benefits on an individual level. For example, in the early 1990s it was reported that participants whom consumed large amounts of meat as compared to participants who had not eaten meat in 30 years, were twice as likely to develop dementia.[70] Unfortunately, of the 5,690 participants in the Rotterdam Study who underwent dietary assessment, only few adhere to a vegetarian or plant-based diet (N = 133 [2.3%], N = 79 [1.4%], respectively), limiting power and thus possibilities to research effects of these diets on general health, cognitive function and dementia risk. Nevertheless, results in the Rotterdam Study imply a beneficial effect of adherence to a diet higher in plant-based foods and lower in animal-based foods on the development of diabetes type 2 and obesity.[71, 72] Thus, eating vegetarian and plant-based might be a promising strategy in healthy ageing.

Hearing loss as a risk factor for dementia in population-based studies

Whilst considerable effort has been made to investigate the direct association between hearing loss, brain health and cognitive function, more evidence is still needed to en-

sure that hearing loss is indeed a risk factor for dementia. This can be accomplished by collecting data on hearing- and cognitive function and incident dementia over sufficient follow-up time with multiple repeated measurements of both hearing thresholds and cognitive function in varying populations with wide age ranges. Moreover, researchers should take careful notice of concurring ageing effects, possibly confounding previously found results. Additionally, other potential common-causes such as lifestyle- and cardiovascular risk factors should also be taken into account in statistical models to avoid potential false positive results. If hearing loss is indeed directly and independently related to accelerated structural and functional neurodegeneration, it is of great importance to collect detailed information on hearing aid use, and study whether this can slow down or modify the cognitive decline associated with hearing loss. Only then we might be able to say more about the clinical relevance of hearing loss as a (modifiable) risk factor for dementia. Whenever this data on hearing aids is available, we could conduct a so-called target trial emulation in population-based samples.[73] Unfortunately, data on when participants first started using a hearing aid is missing in the Rotterdam Study. Moreover, using data from a Dutch population likely introduces selection bias, as hearing aids are refunded at hearing thresholds from 35 dB or greater. On top of this, even though the benefits of hearing aid use among older adults with hearing loss have been well documented, actual hearing aid use is poor.[74] For example, in a survey conducted in 2011 in Germany, France and the United Kingdom showed that between 4.7% and 12.4% of people never used the hearing aid that they own.[75] Furthermore, actual hearing aid purchase and/or use appears to be highly dependent on several audiological and non-audiological determinants such as degree of hearing loss (the higher the degree of hearing loss, the better the compliance to hearing aid use), perception of hearing handicap, sex (females use it more than males), education (higher education associated with better compliance) and income (those with higher incomes used hearing aids more regularly).[75] Thus, we should keep in mind that we might be dealing with a selected population and results from studies might not be generalizable towards the entire population that has a hearing impairment great enough to be eligible for a hearing device. Nevertheless, it might also be of interest to investigate the effect of hearing aid use in groups of populations with all degrees of hearing loss (and not restrict research to for example individuals with moderate hearing loss), individuals with mild cognitive impairment (MCI) or even in individuals with full-blown cognitive impairment/dementia. To do so, we would need clinical trials offering hearing aids at different degrees of hearing loss and/or cognitive status.

Hearing loss as a risk factor for dementia in clinical trials

A recent study showed that in individuals with hearing loss and without any form of a hearing device, cortical brain reorganization takes place. This is reflected by increased

cortical activation of the auditory cortex next to activity in the somatosensory regions of the brain when presented with a somatosensory stimuli.[76] This reorganization can be explained by increased reliance on other sensory modalities to speech perception in those with hearing loss.[76] Interestingly, some preliminary, but promising evidence is already showing the benefits of hearing aid use or cochlear implantation on brain health both in humans and in animals.[77, 78] In congenital deaf cats it was recorded that the primary auditory cortex develops significantly different as compared to their normal hearing counterparts. After the congenital deaf cats received cochlear implantation, functional organization of the auditory cortex was significantly changed by the new hearing experience. The largest difference that was recorded in these cats was a substantial larger activated cortical area.[78] Moreover, in a case report of a 9-year old girl with unilateral sudden-sensorineural hearing loss, who was eligible for cochlear implantation, researchers examined potential cortical changes before and after cochlear implantation.[79] Pre-cochlear implantation, auditory stimulation of the patient's normal hearing ear resulted in temporal and frontal activation. However, this frontal activation appeared to be absent after the cochlear implantation, suggesting a decrease in listening effort with the hearing device.[79] Even though above mentioned results should be interpreted with caution as it concerns just a single case and animal research which may not apply to humans, results might point towards a reversible effect of cortical reorganization when hearing devices are implemented. Nevertheless, we are mostly interested in the effects of such devices in the elderly. To achieve benefits of cochlear implants in older adults, some cortical plasticity is needed to restore a level of speech understanding. Therefore it is encouraging that cochlear implants seem to catch on well in elderly patients with the highest degrees of hearing loss.[80] In a French study with 9 participants, aged 48-66 years with single-sided deafness, three measurements were obtained before cochlear implantation, and 6 and 12 months post cochlear implantation. Even though it is a small sample size, cortical modification occurred rapidly at 6 and 12 months post implantation in response to cortical auditory evoked potentials. On top of this, in a small randomized trial with elderly veterans participants (aged 66 – 80 years) who received a hearing aid reported improved social and emotional functioning and better cognitive functioning as compared to those who did not receive a hearing aid after 4 months of hearing aid use.[77] So, even in elderly groups of participants, preliminary evidence is available pointing towards favourable cortical reorganization and improvements in social- and cognitive functioning after the implementation of hearing devices.[80]

To further elucidate this effect, (larger) randomized clinical trials, applying both in-depth auditory function testing, extensive cognitive testing and detailed non-invasive brain imaging studies in an elderly population are needed. In the United States of America researchers have initiated the Ageing and Cognitive Health Evaluation in Elders (ACHIEVE) study and the Hearing Equity through Accessible Research and Solutions

(HEARS) study, two randomized controlled trials aiming to determine efficacy of hearing treatment in reducing cognitive decline in older adults.[81] As both studies are still ongoing, results are not available yet. Whenever these studies show that hearing devices do delay or slow down cognitive decline in at-risk older adults, this could have a very promising clinical, social, and public health impact as use of hearing devices is a relatively easy and inexpensive intervention. Moreover, exploring potential beneficial effects may not only be of interest in participants without cognitive decline and mild degrees of hearing loss, it could also prove useful to offer hearing aids at higher degrees of hearing loss or when individuals are already diagnosed with MCI or dementia. Implementing hearing aids at a MCI stage might show whether such an intervention would lead to a slower cognitive decline and/or a potential later onset of cognitive impairment. Applying hearing aids in the dementia phase may feel counterintuitive, yet it might reduce caregiver burden due to improved communication between the patient and the caregiver. The same goes for individuals with severe degrees of hearing loss. Restored/better communication as a result of hearing devices could lead to improved general health, as individuals better understand instructions given by for example doctors about medical prescriptions and/or treatments. Which again possibly results in lower rates of rehospitalisation and reduced health care costs.

In conclusion, hearing loss and neurodegeneration impacts the public health enormously on the level of physical- and psychological well-being but also by increasing the risk of adverse (neurological) outcomes. Given the ageing of the population and the accompanying rise of age-related diseases such as hearing impairment and dementia, huge amounts of work are still needed to promote and support healthier ageing. This thesis has highlighted some interesting avenues to explore further in this regard.

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