Vascular involvement in the pathophysiology of acute audiovestibular loss

Oussoren, F.K.

VASCULAR INVOLVEMENT IN THE PATHOPHYSIOLOGY OF ACUTE AUDIOVESTIBULAR LOSS

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VASCULAR INVOLVEMENT IN THE PATHOPHYSIOLOGY OF ACUTE AUDIOVESTIBULAR LOSS

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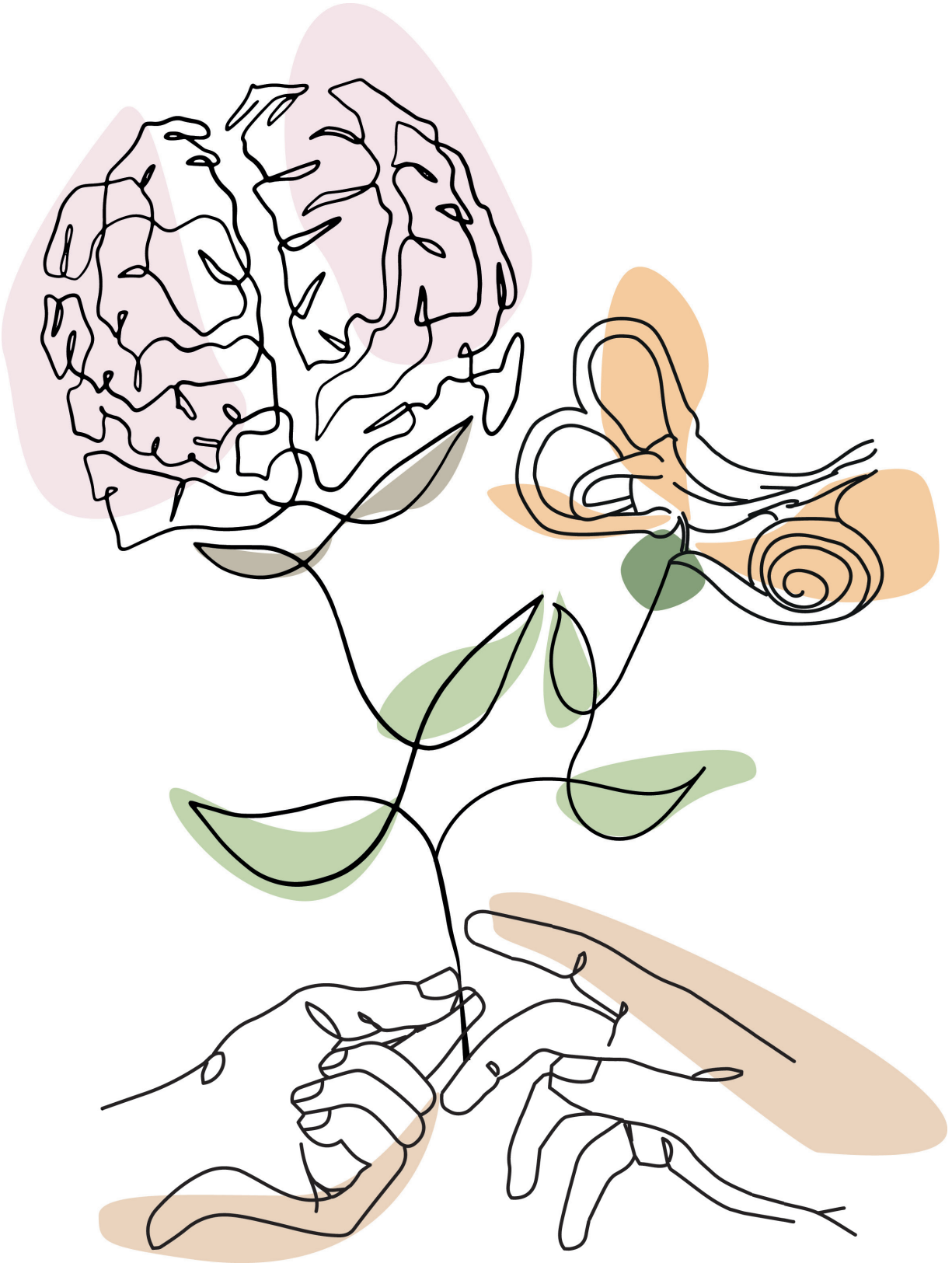


Chapter

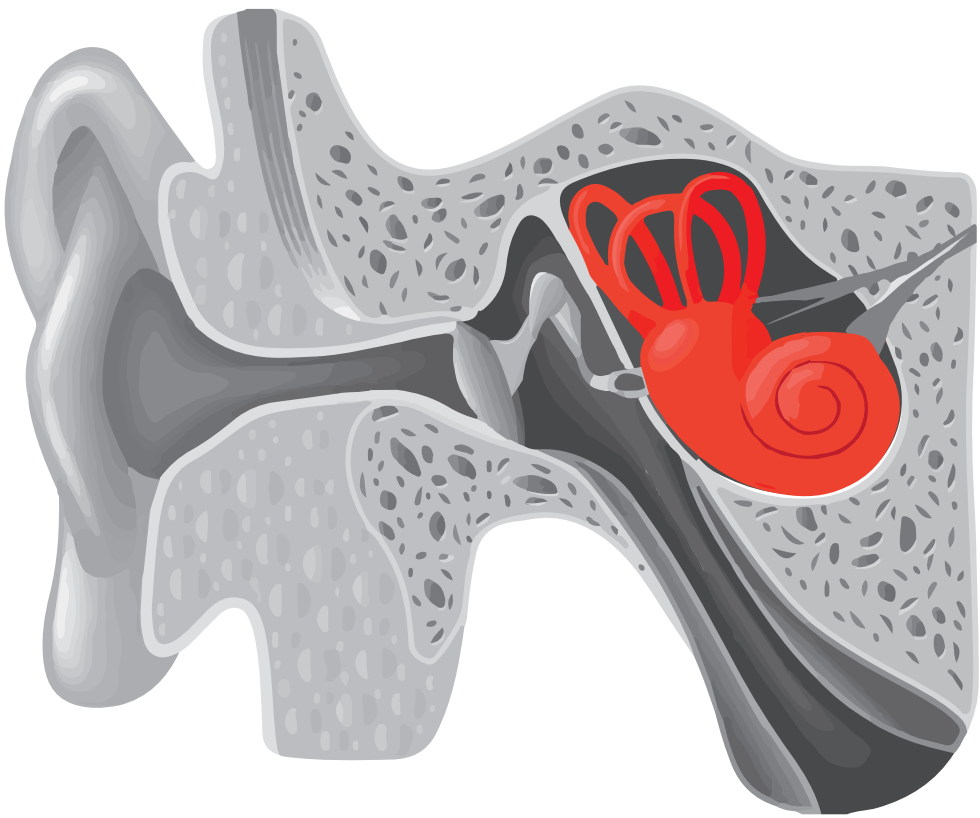
1

Introduction

The labyrinth, which consists of the cochlea, the vestibule and the semicircular canals is located in the petrous part of the temporal bone in the skull[1]. The anterior part of the labyrinth, the cochlea, is the organ responsible for hearing. The vestibule and semicircular canals are responsible for maintaining equilibrium by motion detection. Acute disruption in the function of the cochlea, the vestibule, the semicircular canals, or a combination thereof, can result in hearing loss, vestibulopathy or both. Vestibulopathy is characterized by an impaired or absent function of the vestibulo-ocular reflex (VOR) causing unsteadiness when walking or standing, nausea and oscillopsia. Patients presenting with acute hearing loss, vestibulopathy or both can be diagnosed with sudden sensorineural hearing loss (SSNHL), vestibular neuritis or labyrinthitis accordingly.

The exact pathogenesis of these three disorders remains unclear[3–5]. A subclinical viral infection of the inner ear is hypothesized to result in an immune response and thereby induce hearing loss, vertigo and vestibulopathy[6]. However, in randomized controlled trials the use of anti-inflammatory drugs like corticosteroids has not been proven to be superior to placebo, or the natural progression of the disease, in reducing complaints and restoration or hearing and balance function[7,8]. Furthermore, direct evidence of the

Figure 1.| Schematic representation of the right labyrinth within the temporal bone consisting of the spiral-shaped cochlea, the vestibule and the horizontal, posterior and anterior semicircular canals.



presence of viral agents such as isolation of the virus from the labyrinth or detection of viral particles by electron microscopy has, so far, not been established in humans[9]. Therefore the following questions arise. Is another pathophysiology of acute hearing loss and vertigo more likely? And consequently, would another therapy be more appropriate to establish recovery and prohibit decline of hearing and balance?

Vertigo, it was thought at the time, could only be caused by a disease of the cerebellum. He observed this kind of patient for years and saw absolutely no symptoms of brain disease[2].

Robert Barany on Prosper Meniere.

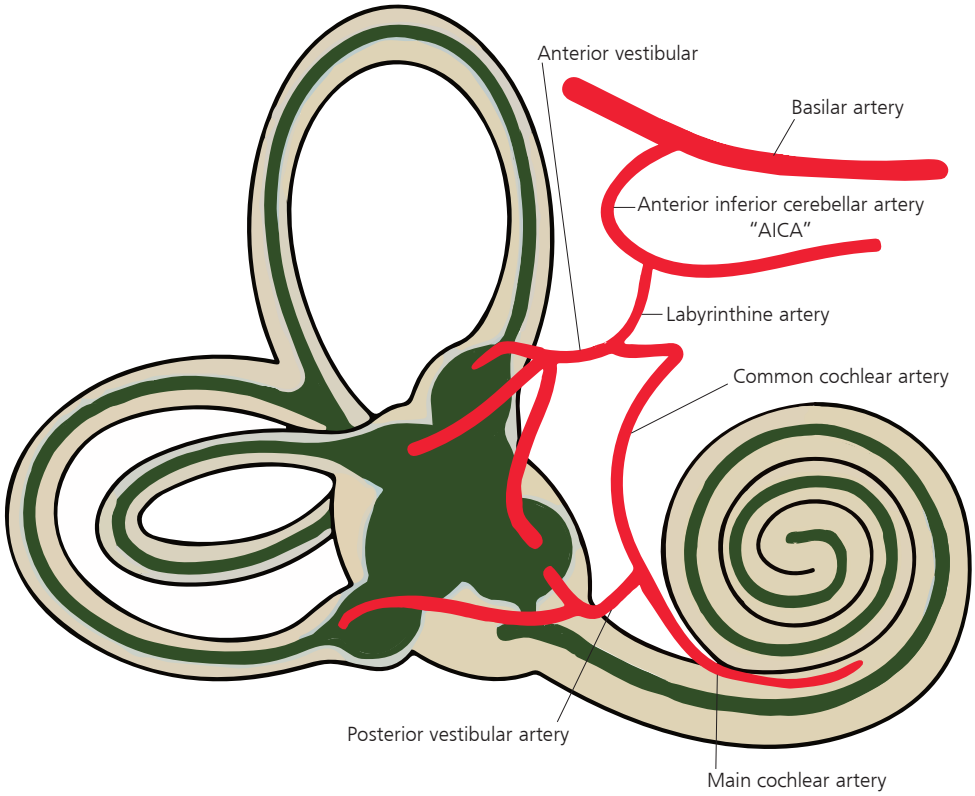
In his Nobel prize acceptance speech in 1916, Robert Barany described a fundamental dilemma that remains relevant even in the contemporary clinical situation. When is dizziness a symptom of cerebral disease and when can dizziness solely be attributed to an inner ear disorder?

The sudden onset and frequent unilateral presentation could indicate vascular involvement in SSNHL, VN and labyrinthitis. Similarly to the eye in amaurosis fugax, which causes temporary loss of sight due to transient ischemia of the retinal artery, the inner ear can be considered an end organ that is vulnerable to ischemia. The anterior inferior cerebellar artery (AICA) is a branch of the basilar artery that supplies the labyrinthine artery[10–12]. The labyrinthine artery later separates into the common cochlear and anterior vestibular artery that both have limited collateral blood supply[10–12], see figure 2. Patients experiencing amaurosis fugax are treated with anticoagulants to prevent a cerebrovascular accident from occurring. In a similar way, vascular involvement in the pathophysiology of acute hearing loss and vertigo could have serious consequences. This loss of hearing and vestibular function might be an early sign of cerebral vascular disease and warrant interventions like cardiovascular risk management and anticoagulant administration.

Since hearing loss and vestibulopathy by itself are not life-threatening conditions, histological research on the cochlea and vestibulum following the onset of disease is not possible in humans. Evidence for vascular involvement in the pathogenesis of SSNHL, VN or labyrinthitis can therefore either be obtained by studying histological specimens of rodents or indirectly, by investigating associations with cardiovascular disease.

Cardiovascular risk factors are known to increase the risk of generalized vascular disease[13,14]. As the term generalized indicates, this vascular disease can occur throughout the body. It can manifest itself as a myocardial infarction, peripheral arterial occlusive disease or a cerebral vascular accident, in case respectively, the heart, a leg or the brain is involved. In this thesis we focus on cerebral vascular disease because of the location of the cochlea and vestibulum inside the skull.

Figure 2.| Schematic representation of the blood supply to the cochlea and vestibule.



Cerebral small vessel disease is a disorder of the brain's perforating arterioles and capillaries that can be visualized on MRI[15,16]. Typical manifestations of small vessel disease are white matter hyperintensities, lacunes, microbleeds, superficial siderosis, and microinfarcts[16]. These lesions by itself do not often demonstrate noticeable neurological deficits, though substantial numbers of lesions, or combinations thereof, are associated with up to a quarter of ischemic strokes. They are in fact the most common cause of vascular dementia[16]. In the literature, arteriosclerosis, lipohyalinosis and fibrinoid necrosis are all disease mechanisms described to cause small vessel disease of the brain, so the exact pathogenesis might be more complex than blood vessel occlusion leading to infarction[16]. While the exact pathophysiology has not yet been unraveled, older age, hyperlipidemia and especially hypertension are cardiovascular risk factors that can contribute to cerebral small vessel disease[15–17].

Outline of the thesis

The objective of this thesis is to investigate associations between cardiovascular disease and acute hearing loss, acute vestibulopathy or both and thereby provide an indication of the plausibility of vascular involvement in the pathophysiology of SSNHL, VN or labyrinthitis.

In chapter two, we summarize the existing literature on associations between cardiovascular disease and SSNHL by performing a systematic review and meta-analyses of studies that either explored the cardiovascular risk factors, the degree of cerebral small vessel disease or the subsequent risk of stroke in patients with SSNHL.

In chapter 3 and chapter 4 we retrospectively investigate the presence of cerebral small vessel disease in elderly patients with vestibular neuritis and sudden sensorineural hearing loss. We hypothesize there to be more white matter hyperintensities in patients with VN and SSNHL compared to controls, since we expect them to have more cardiovascular comorbidity.

In chapter 5 we investigate the presence of white matter hyperintensities in patients diagnosed with Meniere's disease. Foster and Breeze were the first to launch the hypothesis of a vascular mechanism involved in the pathophysiology of Meniere's disease[18]. If this hypothesis proves to be correct, we would expect to see a significant difference in degree of white matter hyperintensities between patients with MD and controls.

In chapter 6 we use the primary care database of the Radboud University to assess the subsequent risk of stroke patients experience within 5 years after diagnosis with SSNHL. We hypothesize the relative risk of stroke to be increased in patients with SSNHL compared to healthy controls of the same age and from the same geographic area.

In chapter 7 we retrospectively review the characteristics of patients with concurrent sudden sensorineural hearing loss and vestibulopathy who are diagnosed with idiopathic labyrinthitis. Additionally, we assess their persistent limitations in terms of balance problems and activity-avoidance in a cross-sectional setting.

Chapter 8 describes the design of a prospective multicenter study in the Netherlands and Belgium, to assess the cardiovascular risk factors and cerebral small vessel disease in patients with SSNHL compared to controls.

A summary of the results and recommendations for future research follows in chapter 9.

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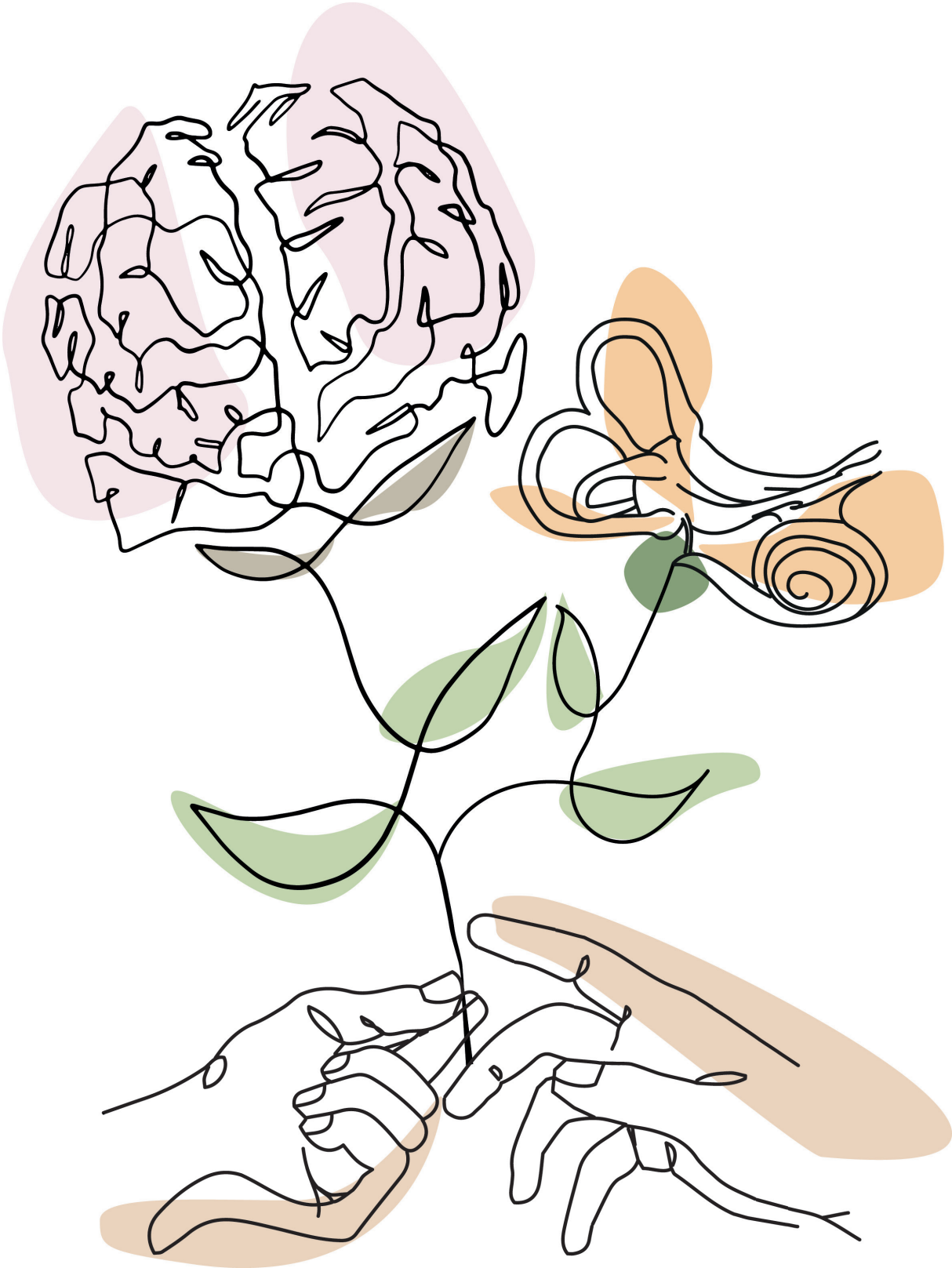

Chapter

2

Cardiovascular risk factors, cerebral small vessel disease and subsequent risk of stroke in patients with iSSNHL: Systematic review and meta-analyses of the current literature

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Introduction

Sudden hearing loss is an otologic emergency that is defined by acute hearing loss of at least 30 dB over 3 contiguous frequencies occurring within 72 hours[1]. The incidence of sudden deafness is described to be 11 up to 77 per 100,000 subjects[1]. Various theories on the underlying pathophysiology of sudden deafness have been suggested, including infectious, auto-immune or metabolic involvement, though the exact cause of sudden deafness remains unknown in the majority of cases[2]. Recently, a vascular hypothesis of origin has gained considerable attention. Since hearing loss is the sole manifestation in 0.6 up to 3% of patients with a posterior circulation cerebral infarction and in 8 up to 31% hearing loss is prodromal to neurological symptoms[3], Idiopathic Sudden Sensorineural Hearing Loss (iSSNHL) might be an indicator of future stroke and thus may warrant adequate cardiovascular risk management.

Literature in recent years has focused on correlations between iSSNHL and general cardiovascular disease. Lin et al. summarized articles investigating several risk factors for developing iSSNHL in 2011[4]. Several other case-controlled studies followed that either supported or contradicted their results[5–10].

Cardiovascular risk factors are known to cause arteriosclerosis, which could result in cerebral small vessel disease, visible on magnetic resonance imaging (MRI) as white matter hyperintensities (WMH). The presence of white matter hyperintensities alone increases the risk of future stroke[11]. With this systematic review and corresponding meta-analyses, we provide a comprehensive overview of the scientific evidence regarding the association between iSSNHL and generalized cardiovascular disease. We investigated cardiovascular risk factors for developing iSSNHL, the presence of white matter hyperintensities in patients with iSSNHL, and the subsequent risk of stroke after experiencing iSSNHL.

Method

These systematic reviews and meta-analyses were performed and reported according to the Preferred Reporting Item for Systematic Reviews and Meta-analyses (PRISMA) guideline.

Literature search

A literature search was performed using the medical databases Embase, Pubmed, and CINAHL, from inception up to 18-05-2022 to identify studies that address the following research questions. 1. Do the cardiovascular risk factors: increased BMI, diabetes, hyperlipidemia, hypertension and a medical history of cardiac disease raise the risk of developing iSSNHL? 2. Is there more cerebral small vessel disease visible on MRI in patients with iSSNHL compared to controls? 3. Do patients with iSSNHL have an increased risk to

develop a stroke compared to controls? The search was repeated on 08-11-2022, just before completion of the article in order to update the search results.

Article selection was performed using the online research tool Rayyan (Rayyan Systems Inc., Cambridge, MA, USA). After detection and deletion of duplicates, all articles were screened for eligibility based on title and abstract by two authors independently from each other, either F.O and T.B or F.O. and R.L. We included only clinical research papers that were published in English or Dutch. Case reports with less than 5 included cases and literature reviews were excluded.

Research question 1: Risk factors of iSSNHL

The search terms "risk factor" and "sudden sensorineural hearing loss", including their synonyms, were adapted according to the syntax of each specific database. Details of the search strategies used and their results are displayed in supplementary Table 1.

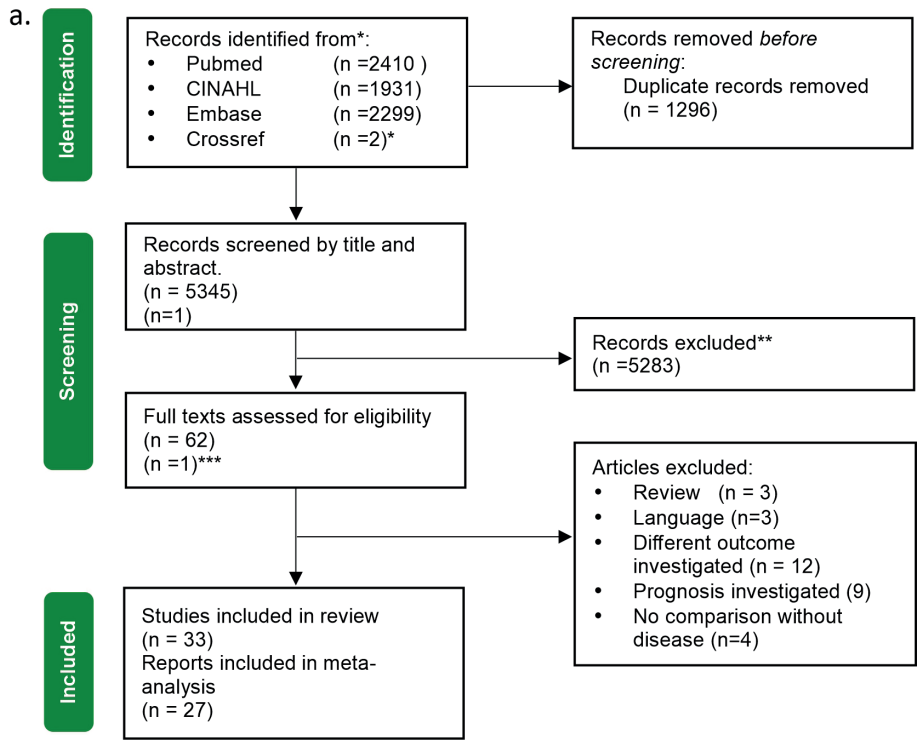
Articles that did not investigate the presence of any of the cardiovascular risk factors; Body mass index (BMI), diabetes mellitus (DM), hyperlipidemia, hypertension, medical history of cardiac disease or smoking were excluded. The remaining articles were then evaluated by full text. Articles that did not compare the prevalence of these risk factors with a control cohort or nationwide prevalence estimates were excluded (shown in Fig. 1a).

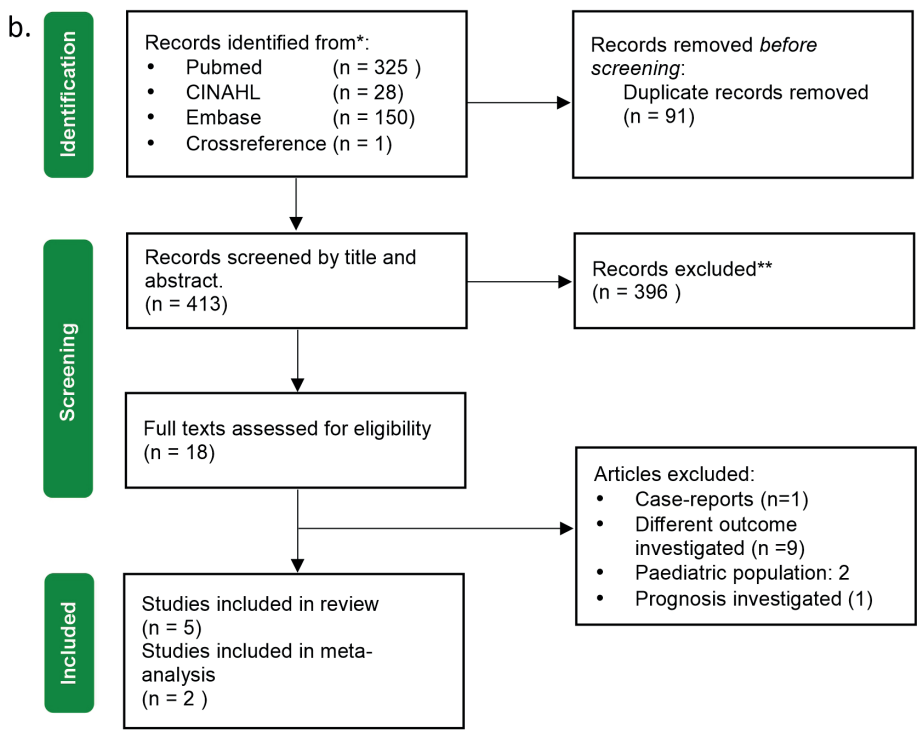
Research question 2: Cerebral small vessel disease in iSSNHL

The terms "white matter hyperintensities", "silent brain infarctions", and "idiopathic sudden sensorineural hearing loss", including their synonyms, were adapted according to the syntax of each database. Supplementary Table 1 shows the search strategy used for identification of articles in the three databases. Articles that did not study cerebral small vessel disease and sudden deafness were excluded based on title and abstract. The remaining articles were evaluated by full text reading. Articles that included non-idiopathic cases of sudden sensorineural hearing loss and articles describing a pediatric population were excluded.

Research question 3: Risk of stroke after iSSNHL

The search terms "sudden sensorineural hearing loss" and "cerebrovascular disease", including their synonyms, were adapted according to the syntax of each of the three databases used (see supplementary Table 1). Articles that did not investigate the association between hearing loss and stroke were excluded. The remaining articles were then evaluated by full text reading. Articles that investigated the risk of iSSNHL after experiencing stroke were excluded. Also, articles that investigated age-related hearing loss, as opposed to sudden sensorineural hearing loss, were excluded. The inclusion process is described in a PRISMA flow diagram (shown in Fig. 1c).


a.
Identification
Records identified from*:
• Pubmed (n =2410)
• CINAHL (n =1931)
• Embase (n =2299)
• Crossref (n =2)*
Records removed *before screening*:
Duplicate records removed (n = 1296)
Screening
Records screened by title and abstract.
(n = 5345)
(n=1)
Records excluded**
(n =5283)
Full texts assessed for eligibility
(n = 62)
(n =1)***
Articles excluded:
• Review (n = 3)
• Language (n=3)
• Different outcome investigated (n = 12)
• Prognosis investigated (9)
• No comparison without disease (n=4)
Included
Studies included in review
(n = 33)
Reports included in meta-analysis
(n = 27)


b.
Identification
Records identified from*:
• Pubmed (n = 325)
• CINAHL (n = 28)
• Embase (n = 150)
• Crossreference (n = 1)
Records removed *before screening*:
Duplicate records removed (n = 91)
Screening
Records screened by title and abstract.
(n = 413)
Records excluded**
(n = 396)
Full texts assessed for eligibility
(n = 18)
Articles excluded:
• Case-reports (n=1)
• Different outcome investigated (n =9)
• Paediatric population: 2
• Prognosis investigated (1)
Included
Studies included in review
(n = 5)
Studies included in meta-analysis
(n = 2)

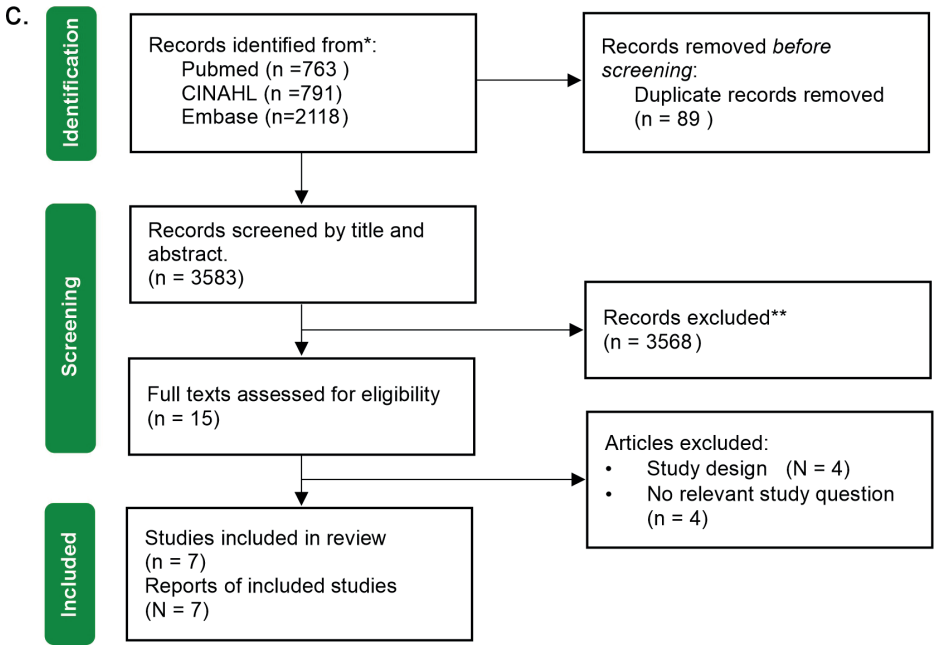


Figure 1.| The inclusion process for the systematic reviews following the PRISMA 2020 updated guideline for reporting systematic reviews. a. Flow diagram of the inclusion process or articles investigating the cardiovascular risk factors for SSNHL. b. Flow diagram of the inclusion process of articles investigating the degree of white matter hyperintensities in patients with SSNHL. c. Flow diagram of the inclusion process of articles investigating the risk of stroke following SSNHL. *Three databases were used to search for relevant articles for all research questions. ** Records were excluded based on title and abstract. n=number, *** Additional literatur search, prior to article submission resulted in one additional inclusion SSNHL=Sudden Sensorineural Hearing Loss.

Risk of bias assessment

Risk of bias assessment was performed using the Joanna Briggs Institute risk of bias assessment tool for either case-control studies or cohort studies, whichever was appropriate[12].

The risk of bias was assessed by evaluation of the equality of the study population and identification of cases, the confounding factors and handling thereof, the outcomes, the duration of follow-up, and the statistical analysis used. Two authors independently assessed the risk of bias, discrepancies were discussed until consensus was reached.

Statistical analysis

Meta-analyses were performed for each of the identified cardiovascular risk factors and the degree of WMH present on MRI using Review Manager version 5.4 (The Cochrane Collaboration, London, UK). Odds ratios for dichotomous values and the mean difference for continuous values including their confidence intervals were calculated using a fixed effects model. Proportional odds ratios for the ordinal outcome, the Fazekas score,

were analyzed using a dichotomous model, since establishing the clinical meaning of the summary statistic of an ordinal model would be challenging. We used a cut-off value in the dichotomous model of 3, since normal Fazekas scores would range from 0 to 2 with increasing age[13,14].

Heterogeneity is defined as a *proportion* of observed variance that reflects real differences in effect size. The common metric for measuring the magnitude of the between-study heterogeneity is I^2. In case of heterogeneous data, a sequential algorithm sensitivity analysis was performed, described in detail by Patsopoulos[15]. We accepted an analysis to be reliable in terms of heterogeneity when I^2<50%. Statistical significance was defined as a two-tailed p-value < 0.05.

Results

Research question 1: Risk factors of iSSNHL

Of the total of 6,641 articles, full text was assessed for 62. Repetition of the search strategy just before completion of the article resulted in another eligible study[16]. A total of 32 articles met the inclusion criteria, 21 of these investigated total cholesterol values, 18 HDL-cholesterol, 19 LDL-cholesterol, 13 hypertension, 12 DM, 14 smoking, 5 history of cardiac disease, and 9 BMI. An overview of the characteristics and results of each included study can be found in Table 1.

Risk of bias assessment

The risk of bias assessment of each article is shown in Table 2. Two cohort studies evaluated the incidence of sudden deafness in a cohort either with or without the cardiovascular risk factor hypercholesterolemia or diabetes[17,18]. Both studies were of good quality. In both articles, the cohorts were matched for age and gender. Also, other cardiovascular risk factors (CVRFs) were identified and corrected for in a Cox proportional hazard model. The identification of cases was based on the national health insurance databases of Taiwan and Korea using the ICD-9 classification which might have resulted in some wrongful inclusion of patients who did not meet the standardized criteria for iSSNHL.

The quality of the remaining case-control studies ranged from poor (3/31 articles) to good (12/31 articles). In most studies, controls were matched for age and gender, in some also for CVRFs like DM, renal insufficiency, or coronary artery disease. However, in 9 articles no matching was performed[19–27]. Two of these studies did not recruit a control cohort, but instead compared the CVRF incidence in their study cohort to the reported prevalence estimates nationwide[26,27].

Eleven articles presented unadjusted results[16,19,32,22,24,26–31]. Two studies adjusted for several CVRFs together, without a separate analysis per risk factor[25,33]. Another two studies did perform a regression analysis with multiple outcomes, but did not include possible

confounders in these analyses[34,35]. All studies with adjusted results used a logistic regression model.

Two studies presented data from a secondary analysis of Lee et al[36,37]. These articles did differ in terms of CVRFs analyzed and were therefore selectively included in the meta-analyses. Two other studies used the same database and had overlapping inclusion periods, but the studied CVRFs differed between the studies[18,38].

Table 1.| Study characteristics of the articles in the cardiovascular risk factor analysis.

Author	Year	Population	Age (mean, ± SD)	Risk factor	Definition	Results	OR (p-value)
Aimoni	2010	SSNHL: 141 Controls: 271	SSNHL: 54.6 ± 15.8 Controls: 55.0 ± 15.8	TC	Absolute serum total cholesterol value	SSNHL 227.2 mg/dl (SD 40.0) Controls 214.4 mg/dl (SD 40.8)	2.17 (0.006)
				Diabetes	1. History of physician diagnosed DM 2. Taking antidiabetic medication Fasting blood glucose > 126mg/dl.	SSNHL: 15.6% Controls: 8.5%	2.07 (0.039)
				Hypertension	1. History of physician diagnosed HTN Taking antihypertensive drugs	SSNHL: 33.3% Controls: 33.2%	1.02 (0.945)
				Smoking	Former or current cigarette smoking	SSNHL: 55.8% (26 former, 46 current) Controls: 52.0% (former 67, current 77)	1.10 (0.709)
Ballesteros	2009	SSNHL: 99 Controls: 150	SSNHL: 51.7 ± 16.4 Controls: 49.9 ±13.6	BMI	Weight/height^2 = kg/m^2	SSNHL: 26.2 (SD 4.02) Controls: n.d.	n.d.
				TC	Absolute serum total cholesterol value	SSNHL: 208.73 mg/dl (SD 48.92) Controls: n.d.	n.d.
				HDL -C	Serum HDL- cholesterol	SSNHL: 57.24 mg/dl (SD 19.06) Controls: n.d.	n.d.
				LDL -C	Serum LDL-cholesterol	SSNHL: 131.29 mg/dl (SD 34.23) Controls: n.d.	n.d.
				Diabetes	n.d.	SSNHL: 7% Controls: 3%	n.d.
				Hypertension	n.d.	SSNHL: 21.1% Controls: 12.%	n.d.
				MI	Myocardial infarction and other acute coronary syndromes	SSNHL: 8.8% Controls: 2.5%	n.d.
				Smoking	n.d.	SSNHL: 30.5% Controls: 22%	n.d.

Author	Year	Population	Age (mean, ± SD)	Risk factor	Definition	Results	OR (p-value)
Cadoni	2007	SSNHL: 30 Controls: 34	SSNHL: 45.6 (range 23-72) Controls: 49.3 (range 23-77)	TC	Absolute serum total cholesterol Hypercholesterolemia: total cholesterol > 200mg/dl	SSNHL: 200mg/dl (SD38.95) Controls: 175 mg/dl (SD 26.51)	6.88 (0.0007)
				LDL-C	Serum LDL-cholesterol Hypercholesterolemia: LDL-cholesterol >130mg/dl	SSNHL: 128 mg/dl (SD 35.89) Controls: 110.7 mg/dl (SD 31.34)	3.25 (0.0298)
Cadoni	2010	SSNHL: 43 Controls: 43	SSNHL: 50±14 Controls: 43 ±11	TC	Absolute serum total cholesterol Hypercholesterolemia: total cholesterol > 200mg/dl	SSNHL: 213 mg/dl (SD 44) Controls: 175 mg/dl (SD21.4)	5.17 (p<0.001)
				LDL-C	Serum LDL-cholesterol LDL-cholesterol > 130mg/dl	SSNHL: 131 mg/dl (SD 32.30) Controls: 110 mg/dl (SD 22.66)	5.20 (0.024)
Capaccio	2007	SSNHL: 100 Controls: 200	SSNHL: 48.1 ± 14.6 Controls: n.d.	TC	Absolute serum total cholesterol value	SSNHL: 224 mg/dl (SD 32.6) Controls: 185.8 mg/dl (SD 18.5)	1.06 (p=n.d.)
Chang	2014	SSNHL + Hch: 73957 SSNHL – Hch: 73957	N.d.	TC	HCh: ICD 9 code 272.0-272.1 (pure hypercholesterolemia, pure hypertriglycerimia).	SSNHL in + HCh cohort: 503 SSNHL in – HCh cohort: 308	1.62 (p<0.01)*
Chien	2015	SSNHL: 181 Controls: 181	SSNHL: 48.7 ± 14.1 Controls: 46.4± 11.0	HDL-C	Serum HDL cholesterol	SSNHL: 49 mg/dl (84-136)[∞] Controls: 53 mg/dl (46-63)	n.d.
				Diabetes	Taking antidiabetic medication	SSNHL: 20 (11.0%) Controls: 13 (7.2%)	n.d.
				Hypertension	Taking antihypertensive drugs	SSNHL: 71 (39.2%)[#] Controls: 43 (23.8%)	n.d.

				Smoking	n.d.	SSNHL: 28 (15.5%) Controls: 26 (14.4%)	n.d.
Ciccone	2012	SSNHL: 29 Controls: 29	SSNHL: 54 ± 15 Controls: 46 ± 16	BMI	Weight/height^2 = kg/m^2	SSNHL:.28 (SD 5) Controls: 26 (SD 6)	n.d.
				TC	Absolute serum total cholesterol	SSNHL: 188 mg/dl (SD 33) Controls: 171 mg/dl (SD 29)	0.977 (0.317)
				HDL-C	Serum HDL- cholesterol	SSNHL: 48 mg/dl (SD10) Controls: 49 mg/dl (SD 10)	1.013 (0.759)
				LDL-C	Serum LDL-cholesterol	SSNHL: 118 mg/dl (SD 27) Controls: 101 mg/dl (SD 28)	1.046 (0.098)
				Diabetes	Fasting blood glucose level > 126 mg/dl or taking antidiabetic medication	SSNHL: 3 (10%) Controls: 5 (17%)	n.d.
				Hypertension	Systolic blood pressure> 140mmHg and/or diastolic pressure >90mmHg or taking antihypertensive drugs	SSNHL: 17 (58%) Controls: 12 (41%)	n.d.
				Smoking	Regularly smoked at least 5 cigarettes/day during the previous 3 months or had stopped smoking less than 1 year before start study	SSNHL: 7 (24) Controls: 4 (14)	n.d.

Author	Year	Population	Age (mean, ± SD)	Risk factor	Definition	Results	OR (p-value)
Elden	2012	SSNHL: 52 Contros: 50	SSNHL: 50.0 ± 23.50 Controls: 42.50 ± 16.25	BMI	Weight/height^2 = kg/m^2	SSNHL: 26.48 ± 4.71 Controls: 27.46 ± 4.31	n.d.
				TC	n.d.	SSNHL: 187 mg/dl (51)$^{\infty}$ Controls: 192.50 (29,50)	n.d.
				HDL-C	n.d.	SSNHL: 43.56 mg/dl (SD 6.59)# Controls: 46.58 mg/dl (SD 4.63)	n.d.
				LDL-C	n.d.	SSNHL: 123.17 mg/dl (SD 29.40) Controls: 129 mg/dl (SD 27.49)	n.d.
				Hypertension	Systolic and diastolic blood pressure in mmHg.	Syst: SSNHL: 127.60 mmHg (SD 18.46)# Controls: 111.6 mmHg (SD 15.95) Diast: SSNHL: 78.46 mmHg (SD 12.30) Controls: 72 mmHg (SD 12.45)	n.d.
				Smoking	n.d	SSNHL: 19 (36.5%) Controls: 18 (36%)	n.d.
Fasano	2017	SSNHL: 131 Controls: 77	SSNHL: 54 Controls: 52.5	TC	Absolute serum total cholesterol	SSNHL: 186.9 mg/dl (SD43.2) Controls: 194.4 mg/dl (SD 28.9)	n.d.
				HDL-C	Serum HDL- cholesterol	SSNHL: 55.7 mg/dl (SD1.27) Controls: 58.4 mg/dl (SD 12.0)	n.d.

				LDL-C	Serum LDL-cholesterol	SSNHL: 112.5 mg/dl (SD 36.3)[#] Controls: 123.2 mg/dl (SD 27.8)	n.d.
Jalali	2020	SSNHL:81 Controls: 243	SSNHL: 45.2 ±14.6 Controls: 44.9 ± 14.3	TC	Absolute serum total cholesterol	SSNHL: 176 mg/dl (SD 33) Controls: 178.4 mg/dl (SD26.4)	n.d.
				HDL-C	Serum HDL- cholesterol	SSNHL: 43.0 mg/dl (SD 7.7)[#] Controls: 46.5 mg/dl (SD 8.0)	2.99 (<0.001)
				LDL-C	Serum LDL-cholesterol	SSNHL:99.0 mg/dl (SD 24.7) Controls: 103.3 mg/dl (SD 22.0)	n.d.
				Diabetes	1. History of physician diagnosed DM 2. Taking antidiabetic medication Fasting blood glucose > 126mg/dl.	SSNHL: 9 (11.1%) Controls: 13 (5.3%)	n.d.
				Hypertension	1. History of physician-diagnosed HTN 2. Taking antihypertensive drugs	SSNHL: 12 (14.8%)[#] Controls: 17 (7.0%)	2.64 (0.029)
				Smoking	n.d.	SSNHL: 13 (16.0%) Controls: 40 (16.5%)	0.96 (0.917)
Kaneva	2019	SSNHL: 27 Controls: 24	SSNHL: 37.7 (27-51) Controls: 32.3 (25-47)	TC	Absolute serum total cholesterol	SSNHL: 4.26 mmol/l (3.84-,5.00)[∞] Controls: 4.09 mmol/l (3.61, 4.63)	n.d.
				HDL-C	Serum HDL-cholesterol	SSNHL: 1.36 mmol/l (0.93, 1.51)[∞] Controls: 1.39 mmol/l(91.12, 1.80)	n.d.
				LDL-C	Serum LDL-cholesterol	SSNHL: 2.55 mmol/l (1.87, 3.18) [∞] Controls: 1.92 mmol/l (1.34, 2.91)	n.d.

Author	Year	Population	Age (mean, ± SD)	Risk factor	Definition	Results	OR (p-value)
Lee	2015	SSNHL: 324 Control: 972	SSNHL: 49.6 ± 16.5 Controls: 48.8 ± 14.7	BMI	Weight/height^2 = kg/m^2 BMI > 27.5kg/m^2	SSNHL: 23.91 kg/m^2 (SD 3.29) Controls: 23.30 kg/m^2 (SD 3.21)	n.d.
				TC	Absolute serum total cholesterol	SSNHL: 192.92 mg/dl (SD 37.9) Controls: 183.46 mg/dl (SD 34.89)	n.d.
				HDL-C	Serum HDL- cholesterol	SSNHL: 57.62 mg/dl (SD 15.3)# Controls: 54.34 mg/dl (SD 13.05)	n.d.
				LDL-C	Serum LDL-cholesterol	SSNHL: 110.64 mg/dl (SD 35.61) Controls: 107.21 mg/dl (SD 31.25)	n.d.
Li	2021	SSNHL: 2288 Controls: 2288	SSNHL: 49.7 ± 15.3 Controls: 51.0 ± 13.4	TC	Absolute serum total cholesterol	SSNHL: 5.24 mmol/l (SD 1.16) Controls: 5.29 mmol/l (SD1.04)#	0.96 (0.107)
				HDL-C	Serum HDL- cholesterol	SSNHL: 1.35 mmol/l (SD 0.34) Controls: 1.40 mmol/l (SD 0.35)#	0.67 (<0.001)
				LDL-	Serum LDL-cholesterol	SSHNL: 2.96 mmol/l (SD 0.93) Controls: 2.90 mmol/l (SD 0.81)	1.10 (0.006)
Lin	2012	Diabetes: 26556 No diabetes: 26556	n.d.	Diabetes	ICD-9 code 250.xx and A-181	Diabetes: 245 SSNHL (0.92%) No diabetes: 153 SSNHL (0.58%)	1.54 (<0.0001)*

Marcucci	2005	SSNHL: 155 Controls: 155	SSNHL: 55 (range 19-79) Controls: 54 (range 19-78)	TC	Total cholesterol > 200mg/dl	SSNHL: 52 (33.5 %) Controls: 11 (7.0%)	19 (<0.0001)
				Hypertension	Systolic blood pressure > 140mmHg and/or diastolic pressure >90mmHg.	SSNHL: 25 (16.1%) Controls: 18 (11.6%)	0.7
				Smoking	n.d	SSNHL: 21 (13.5%) Controls: 23 (14.8%)	0.9
Mohammed	2014	SSNHL: 22 Controls: 55	SSNHL: 44.7±11.3 Controls: 41.7± 11.1	TC	Absolute serum total cholesterol	SSNHL: 190.5mg/dl (SD 43.2)# Controls: 145.1 mg/dl (SD 31.5)	n.d
				HDL-C	Serum HDL- cholesterol	SSNHL: 48.3mg/dl (SD 8.75) Controls: 49.7 mg/dl (SD 8.77)	n.d
				LDL-C	Serum LDL-cholesterol	SSNHL: 118.6mg/dl (SD 36.0)# Controls: 81.8 mg/dl (SD 34.2)	n.d.
Mosnier	2011	SSNHL: 96 Controls: 179	SSNHL: 50.0 Controls: n.d.	BMI	Weight/height2 = kg/m^2	SSNHL: 25.2 kg/m^2 (SD 2.6) Controls: 24.7 kg/m^2 (SD 0.4)	n.d.
				Hypertension	Systolic and diastolic blood pressure in mmHg.	Syst: SSNHL: 130 mmHg (SD 1.7)# Controls: 124 mmHg (SD 1.1) Diast: SSNHL: 74 mmHg (SD 1.2) Controls: 76 mmHg (SD 0.9)	Syst. 1.04 Diast. N.d.
				MI	Coronary artery insufficiency OR Myocardial infarction OR Stroke OR TIA OR intermittent claudication	SSNHL 10.8%# Controls: 3.4%	3.94

Author	Year	Population	Age (mean, ± SD)	Risk factor	Definition	Results	OR (p-value)
Nakamura	2001	SSNHL: 154 Controls: 16043	SSNHL: 49.7 ± 14.1 Controls: 52.5 ± 10.1	Smoking	Current cigarette smoking	SSNHL: 49 (31.8) Controls: 5261 (32.8)	n.d.
Nakashima	1997	SSNHL: 109 Controls: 109	SSNHL: 44.2 ± 16.2 Controls: 43.8 ± 15.9	Diabetes	n.d.	SSNHL: 6 (5.5%) Controls: 5 (4.6%)	1.25
				Hypertension	n.d.	SSNHL: 23 (21.1) Controls: 13 (11.9)	2.00 (0.07)
				Smoking	Current cigarette smoking	SSNHL: 29 (26.9%) Controls: 31 (29.0)	1.12
Oiticica	2010	SSNHL: 166 Controls: Brazilian population n.d.	SSNHL: 46.5 ± 16.2 Controls: 44.7 ± 15.7	TC	Total cholesterol > 200mg/dl	SSNHL: 79 (50.3%) Controls: 40 %	n.d.
				LDL-C	LDL-cholesterol > 160mg/dl	SSNHL: 32 (20.5) Controls: 30 (20.3)	n.d.
Oreskovic	2010	SSNHL: 54 Controls: 55	SSNHL: 55 ± 14 Controls: 40 ± 15	TC	Absolute serum total cholesterol	SSNHL: 5.9 mmol/l (SD 1.1)# Controls: 5 mmol/l (SD 1.0)	n.d.
				HDL-C	Serum HDL- cholesterol	SSNHL: 1.3 mmol/l (0.6-3.5)∞ Controls: 1.3 mmol/l (0.8-2.4)	n.d.
				LDL-C	Serum LDL-cholesterol	SSNHL: 3.7 mmol/l (SD 0.9)# Controls: 2.9 mmol/l (SD 0.8)	n.d.
Park	2022	SSNHL: 239 Controls: 239	SSNHL: 52.3 ± 16.3 Controls: 54.5 ± 15.0	Diabetes	≥100 mg/dL high blood sugar-fasting glucose	SSNHL: 42 (17.6%)# Controls: 27 (11.3)	n.d.
				Hypertension	Systolic blood pressure ≥130mmHg or diastolic blood pressure ≥85mmhg	SSNHL: 64 (26.9%) Controls: 47 (19.7%)	n.d.

				HDL-C	Serum HDL-cholesterol	SSNHL: 52.2 (SD 11.5) Controls: 50.4 (SD 12.1)	n.d.
Passamonti	2015	SSNHL: 118 Controls: 415	SSNHL: 48 (range 34-57) Controls 41 (32-52)	Diabetes	Fasting plasma glucose levels > 126 mg/dl	SSNHL: 2 (2%) Controls: 4 (1%)	n.d.
				Hypertension	Systolic blood pressure >140mmHg or diastolic blood pressure >90mmhg	SSNHL: 29 (24%) Controls: 42 (10%)	n.d.
				Smoking	Current cigarette smoking	SSNHL: 37 (31%) Controls: 91 (22%)	n.d.
Quaranta	2008	SSNHL: 37 Controls: 47	SSNHL: 46.3 (range 13-79) Controls: 44.8 (range 16-70)	TC	Absolute serum total cholesterol	SSNHL: 183.94mg/dl (SD 50.22) Controls: 186.8 mg/dl (SD 42.06)	n.d.
				HDL-C	Serum HDL- cholesterol	SSNHL: 52.37 mg/dl (SD 17.61) Controls: 43.73 mg/dl (SD 548.19)	n.d.
				LDL-C	Serum LDL-cholesterol	SSNHL: 119.06 mg/dl (SD 39.74) Controls: 112.46 mg/dl (SD 36.32)	n.d.
Rajati	2016	SSNHL: 30 Controls: 30	SSNHL: 45 ± 12.7 Controls: 45 ± 11.8	BMI	n.d.	SSNHL: 25.32 (SD 4.4) Controls: 26.49 (SD 4.9)	n.d.
				TC	Absolute serum total cholesterol	SSNHL: 207.8 mg/dl (SD 50.8) Controls: 196.6 mg/dl (SD 46.7)	n.d.
				HDL-C	Serum HDL- cholesterol	SSNHL: 51.9 mg/dl (SD 9.6) Controls: 47.5 mg/dl (SD 13.5)	n.d.
				LDL-C	Serum LDL-cholesterol	SSNHL: 135.4 mg/dl (SD 37.3) Controls: 124.6 mg/dl (SD 38.6)	n.d.

Author	Year	Population	Age (mean, ± SD)	Risk factor	Definition	Results	OR (p-value)
Rinaldi	2020	SSNHL: 39 Controls: 44	SSNHL: 53.70 ± 13.73 Controls: 48.43 ± 11.13	BMI	Weight/height^2 = kg/m^2	SSNHL:26.80 kg/m^2 (SD 3.44) # Controls: 25.23 kg/m^2 (SD 3.52)	n.d.
				TC	Absolute serum total cholesterol	SSNHL: 193.69 mg/dl (SD 37.27) Controls: 188.89 mg/dl (SD 38.44)	n.d.
				HDL-C	Serum HDL- cholesterol	SSNHL: 56.08 mg/dl (13.19) Controls: 54.61 mg/dl (SD 13.33)	n.d.
				LDL-C	Serum LDL-cholesterol	SSNHL: 118 mg/dl (SD 33.80) Controls: 113.87 mg/dl (SD 32.28)	n.d.
				Smoking	Regularly smoked at least 5 cigarettes/day during the previous 3 months or had stopped smoking less than 1 year before start study	SSNHL: 11 (18.21%) Controls: 17 (38.64%)	n.d.
Rudack	2006	SSNHL: 142 Controls: 84	SSNHL: 51.2 ± 17.2 Controls: 49.8 ± 13.6	TC	Absolute serum total cholesterol	SSNHL: 215 mg/dl (SD 32) Controls: 227 mg/dl (SD 38)	n.d.
				HDL-C	Serum HDL- cholesterol	SSNHL: 61 mg/dl (SD 16) Controls: 54 mg/dl (SD 14)	n.d.
				LDL-C	Serum LDL-cholesterol	SSNHL: 114 mg/dl (SD 29) Controls: 124 mg/dl (SD 29)	n.d.

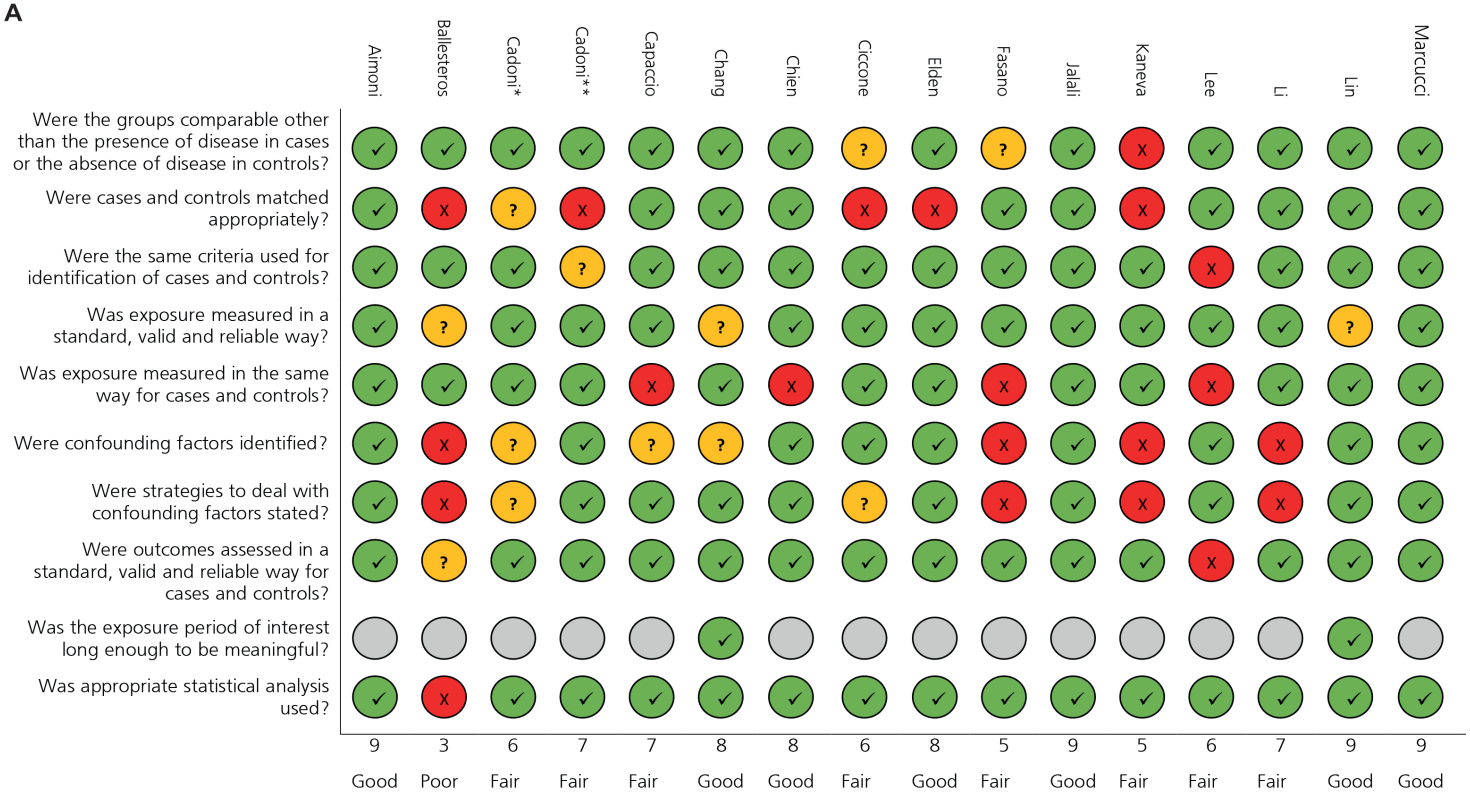
				Diabetes	History of physician diagnosed DM	SSNHL: 8 (5.6%) Controls: 2 (2.4%)	n.d.
				Hypertension	Systolic blood pressure >140mmHg or diastolic blood pressure >90mmhg at blood withdrawal	SSNHL: 20 (14.1%) Controls: 20 (23.8%)	n.d.
				MI	History of physician diagnosed MI	SSNHL: 5 (3.5%) Controls: 2 (2.4%)	n.d.
				Smoking	Current cigarette smoking at blood withdrawal	SSNHL: 80 (56.3%)# Controls: 16 (19.0%)	n.d.
Schulz	2014	SSNHL: 23 Controls: 10	SSNHL: 64 (30-78) Controls: 58.5 (19-75)	BMI	Weight/height2 = kg/m2	SSNHL: 27.1 (21.3, 34.6)∞ Controls: 26.1 (22.8, 37.6)	n.d
				Diabetes	Taking antidiabetic medication OR fasting blood glucose > 126mg/dl.	SSNHL 2 (8.7%) Controls: 3 (30%)	n.d.
				Smoking	n.d.	SSNHL: 0 (0%) Controls: 2 (20%	n.d.
Suckfull	2002	SSNHL: 53 Controls: 53	SSNHL: 53.7 ± 17.9 Controls: 53.5 ± 17.7	TC	Absolute serum total cholesterol	SSNHL: 217 mg/dl (SD 52) Controls: 214 mg/dl (SD 33)	n.d.
				HDL-C	Serum HDL- cholesterol	SSNHL: 56 mg/dl (SD 16) Controls: 57 mg/dl (SD 33)	n.d.
				LDL-C	Serum LDL-cholesterol	SSNHL: 139 mg/dl (SD 40) Controls: 132 mg/dl (SD 30)	n.d.
Umesawa	2017	SSNHL: 3073 Controls: 7641	SSNHL men: 55.9±15.1 SSSNHL women: 55.7± 15.3	BMI	Weight/height^2 = kg/m^2 BMI >25 kg/m^2,	SSNHL men: 23.9 kg/m^2 Control men: n.d. SSNHL women: 23.0 kg/m^2 Control women: n.d.	n.d.

Author	Year	Population	Age (mean, ± SD)	Risk factor	Definition	Results	OR (p-value)
				Diabetes	1. History of physician diagnosed DM 2. Taking antidiabetic medication	SSNHL men: 21.9 % Control men: n.d. SSNHL women: 13.0% Control women: n.d.	n.d.
				MI	History of heart disease assessed by questionnaire	SSNHL men: 15.1% Control men: n.d. SSNHL women: 8.8% Control women: n.d.	n.d.
				Smoking	Consuming cigarettes daily	SSNHL men: 38.0% Control men: n.d. SSNHL women: 12.2% Control women: n.d.	n.d.
Wang	2020	SSNHL: 324 Controls: 972	SSNHL: 49.6 ± 16.5 Controls: 48.8 ± 14.7	Hypertension	n.d.	SSNHL: 71 (21.91%) Controls: 175 (18%)	1.28 (0.1208)
				MI	History of coronary heart disease (n.f.s)	SSNHL: 6 (1.85%) Controls: 17 (1.75%)	1.06 (0.9033)
Weng	2013	SSNHL: 250 Controls: 250	SSNHL: 56.4 (range 15-84) Controls: n.d.	TC	Absolute serum total cholesterol	SSNHL: 4.738 mmol/L(SD 1.021) Controls: 4.378 mmol/L (SD 0.937)	1.459 (<0.01)
				HDL-C	Serum HDL- cholesterol	SSNHL: 1.432 mmol/L (SD 0.401) Controls: 1.459 mmol/L (SD 0.420)	0.849 (0.448)
				LDL-C	Serum LDL-cholesterol	SSNHL: 2.679 mmol/L (SD 0.856) Controls: 2.380 mmol/L (SD 0.723)	1.628 (<0.01)

A description of all 32 included studies is provided including the definition used for the identification of cardiovascular risk factors, the main results and the odds ratio. #significant difference at p<0.005. ∞=median and interquartile ranges are displayed due to non-normally distributed data. BMI=Body Mass Index, HDL-C= High-Density Lipoprotein Cholesterol, HTN= Hypertension, LDL-C=Low-Density Lipoprotein Cholesterol, MI= Myocardial infarction, N.d.=not determined, n.f.s. = not further specified, OR=Odds Ratio, SD=Standard Deviation, SSNHL=sudden sensorineural hearing loss, TIA=Transient Ischemic Attack, TC=Total Cholesterol.

Table 2.| Risk of bias assessments sheets.

A

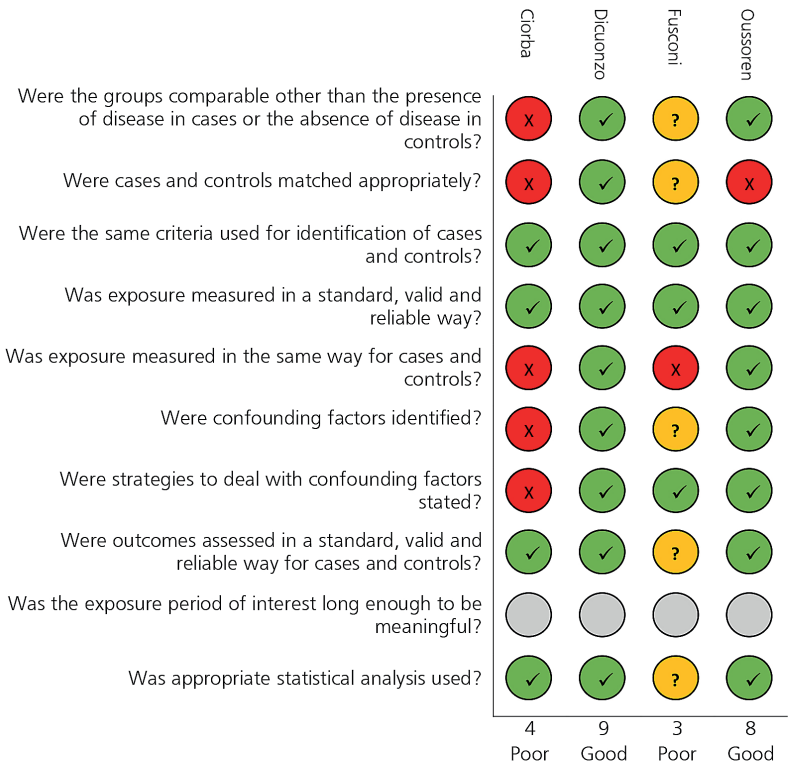


*Cadoni 2007

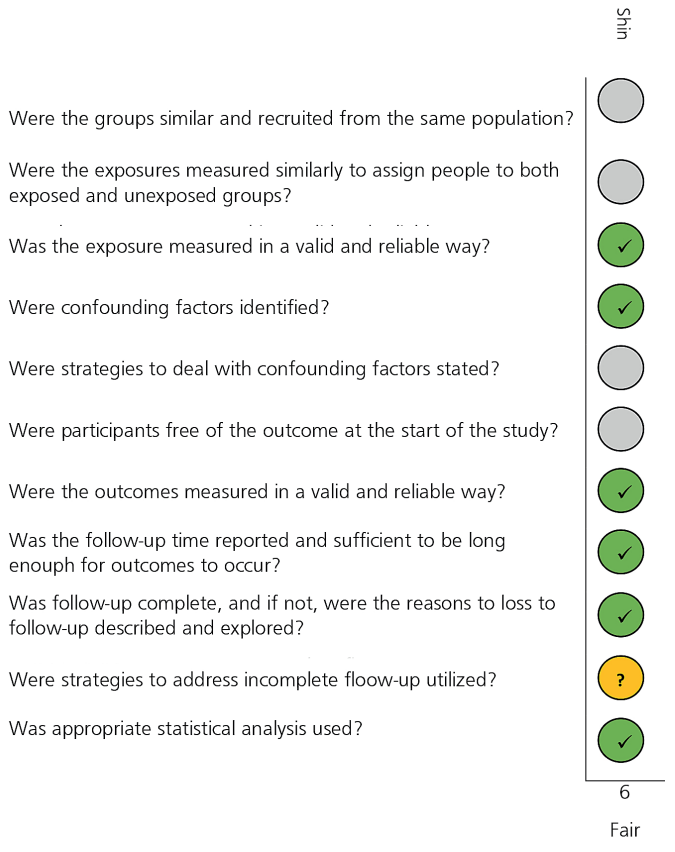
**Cadoni 2010


A
Were the groups comparable other than the presence of disease in cases or the absence of disease in controls?
Were cases and controls matched appropriately?
Were the same criteria used for identification of cases and controls?
Was exposure measured in a standard, valid and reliable way?
Was exposure measured in the same way for cases and controls?
Were confounding factors identified?
Were strategies to deal with confounding factors stated?
Were outcomes assessed in a standard, valid and reliable way for cases and controls?
Was the exposure period of interest long enough to be meaningful?
Was appropriate statistical analysis used?
Mohammed
Mosnier
Nakamura
Nakashima
Oiticica
Oreskovic
Park
Passamont
Quaranta i
Rajati
Rinaldi
Rudack
Schulz
Suckfull
Umasawa
Wang
Weng
6 8 5 7 1 5 9 6 9 8 6 6 5 5 3 6 9
Fair Good Fair Fair Poor Fair Good Fair Good Good Fair Fair Fair Fair Poor Fair Good

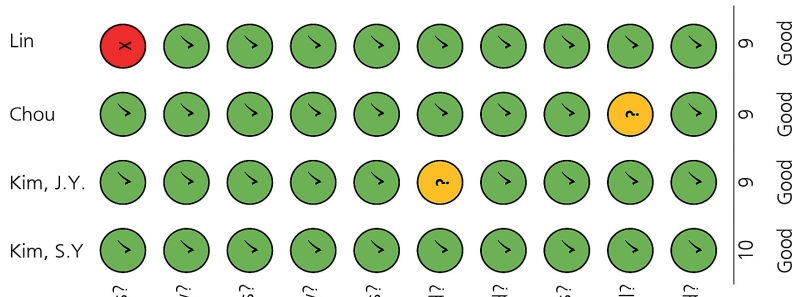
B1


Ciorba
Dicuonzo
Fusconi
Oussoren
Were the groups comparable other than the presence of disease in cases or the absence of disease in controls?
Were cases and controls matched appropriately?
Were the same criteria used for identification of cases and controls?
Was exposure measured in a standard, valid and reliable way?
Was exposure measured in the same way for cases and controls?
Were confounding factors identified?
Were strategies to deal with confounding factors stated?
Were outcomes assessed in a standard, valid and reliable way for cases and controls?
Was the exposure period of interest long enough to be meaningful?
Was appropriate statistical analysis used?
4
Poor
9
Good
3
Poor
8
Good

B2


Shin
Were the groups similar and recruited from the same population?
Were the exposures measured similarly to assign people to both exposed and unexposed groups?
Was the exposure measured in a valid and reliable way?
Were confounding factors identified?
Were strategies to deal with confounding factors stated?
Were participants free of the outcome at the start of the study?
Were the outcomes measured in a valid and reliable way?
Was the follow-up time reported and sufficient to be long enouph for outcomes to occur?
Was follow-up complete, and if not, were the reasons to loss to follow-up described and explored?
Were strategies to address incomplete floow-up utilized?
Was appropriate statistical analysis used?
6
Fair

C1


Kim, S.Y
Kim, J.Y.
Chou
Lin
Were the groups comparable other than the presence of disease in cases or the absence of disease in controls?
Were cases and controls matched appropriately?
Were the same criteria used for identification of cases and controls?
Was exposure measured in a standard, valid and reliable way?
Was exposure measured in the same way for cases and controls?
Were confounding factors identified?
Were strategies to deal with confounding factors stated?
Were outcomes assessed in a standard, valid and reliable way for cases and controls?
Was the exposure period of interest long enough to be meaningful?
Was appropriate statistical analysis used?
10 9 9 9
Good Good Good Good

C2

Risk of bias assessment using the Johanna Briggs institute critical appraisal tools of a. 33 case-control studies investigating the prevalence of cardiovascular risk factors between patients diagnosed with iSSNHL and controls b.1. four case-control studies and investigating the degree of white matter hyperintensities in patients diagnosed with iSSNHL and controls b.2 a cohort study investigating the degree of white matter hyperintensities in patients with iSSNHL c.1. four case-control studies investigating the risk of stroke following iSSNHL and c.2. three cohort studies investigating the risk of stroke following iSSNHL. Below the line the overall quality of the articles is described as poor fair of good.

Study outcomes

BMI

Nine articles measured the BMI in patients with iSSNHL. One article did not describe the BMI in controls and was therefore excluded[19,21]. Another study compared the BMI between women and men with iSSNHL and could therefore not be included in the analysis[26].

The remaining six articles found a 0.55 kg/m^2 higher mean BMI in patients with iSSNHL (95% CI 0.24 – 0.86)[22,30,39–41] (shown in Fig. 2). No sensitivity analysis was required.

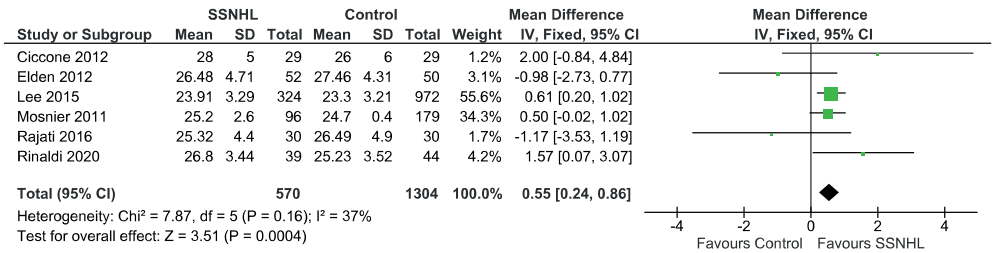


Figure 2.| Results of the meta-analysis including 570 patients with SSNHL from 6 articles that investigate the average BMI of patients with SSNHL compared to controls. A fixed effects model was used. CI=Confidence interval.

Total cholesterol

Total cholesterol was assessed in 21 articles[20,21,40–45,24,28–32,35,37]. Of these articles, 3 articles did not provide absolute values of cholesterol but only described the number of patients with elevated total cholesterol and another article did not provide control data[18,19,46]. These articles were therefore not included in the meta-analysis. The mean total cholesterol was higher in patients with SSNHL, the difference was 4.89 mg/dl (95%CI 3.11 – 6.68) (shown in Fig. 3a). A sensitivity analysis was performed where we excluded 7 articles until the I^2 dropped below 50%, indicating modest heterogeneity. In this analysis patients with iSSNHL had on average 8.44 mg/dl higher mean total cholesterol values than controls (95%CI 5.21 – 11.68, p<0.00001) (shown in Fig. 3b).

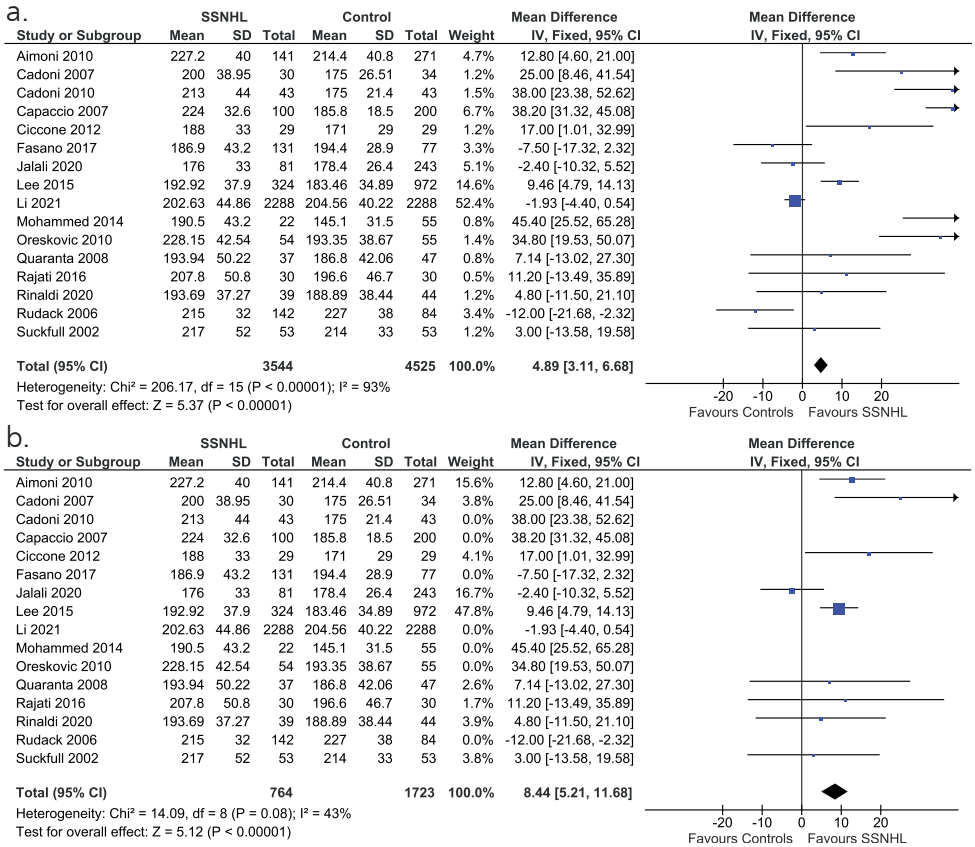


Figure 3.1 a. Results from the meta-analysis including 3544 patients with SSNHL from 16 articles investigating the total cholesterol value of patients with SSNHL versus controls. **b.** results from the sensitivity analysis after exclusion of 7 articles due to large heterogeneity in data. CI= confidence interval, SSNHL= sudden sensorineural hearing loss.

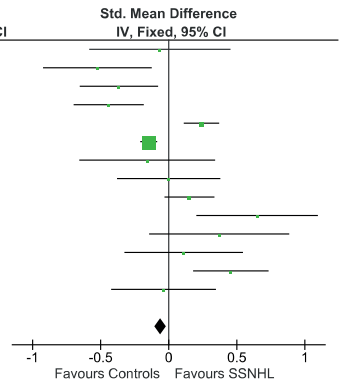
HDL-cholesterol

HDL-cholesterol values were assessed in 18 articles[16,19,32,33,37,40,41,44,45,47,21–24,28–31]. However, one article did not describe the absolute value of HDL in the control cohort and could therefore not be included in the meta-analysis[19]. Two other studies only reported the median and interquartile ranges of the HDL-values and were excluded from the analysis[23,33]. The article by Weng *et al.* used previously published data by Lee *et al.* and was therefore excluded[37]. On average HDL cholesterol was 0.06 mg/dl (95%CI -0.11 – 0.01, p=0.01) lower in patients with iSSNHL compared to controls (shown in Fig. 4a). After subsequent sensitivity analysis including 10 articles, the mean HDL value was 0.16 mg/dl lower in patients with iSSNHL compared to controls (95%CI -0.21 – -0.11, p<0.00001) (shown in Fig. 4b).

a.

Study or Subgroup	SSNHL Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Ciccone 2012	48	10	29	49	19	29	0.8%	-0.06 [-0.58, 0.45]
Elden 2012	43.56	6.59	52	46.58	4.63	50	1.3%	-0.52 [-0.92, -0.13]
Fasano 2017	55.7	1.27	131	58.4	12	77	2.6%	-0.37 [-0.65, -0.08]
Jalali 2020	43	7.7	81	46.5	8	243	3.3%	-0.44 [-0.69, -0.19]
Lee 2015	57.62	15.3	324	54.34	13.05	972	13.2%	0.24 [0.11, 0.37]
Li 2021	52.2	13.148	2288	54.14	13.148	2288	62.5%	-0.15 [-0.21, -0.09]
Mohammed 2014	48.3	8.75	22	49.7	8.77	55	0.9%	-0.16 [-0.65, 0.34]
Oreskovic 2010	51.14	19.3	54	51.14	15.5	55	1.5%	0.00 [-0.38, 0.38]
Park 2022	52.2	11.5	239	50.4	12.1	239	6.5%	0.15 [-0.03, 0.33]
Quaranta 2008	52.37	17.61	37	43.73	8.19	47	1.1%	0.65 [0.21, 1.09]
Rajati 2016	51.9	9.6	30	47.5	13.5	30	0.8%	0.37 [-0.14, 0.88]
Rinaldi 2020	56.08	13.19	39	54.61	13.33	44	1.1%	0.11 [-0.32, 0.54]
Rudack 2006	61	16	142	54	14	84	2.8%	0.46 [0.18, 0.73]
Suckfull 2002	56	16	53	57	33	53	1.5%	-0.04 [-0.42, 0.34]
Total (95% CI)			**3521**			**4266**	**100.0%**	**-0.06 [-0.11, -0.01]**

Heterogeneity: Chi² = 81.50, df = 13 (P < 0.00001); I² = 84%
Test for overall effect: Z = 2.56 (P = 0.01)



b.

Study or Subgroup	SSNHL Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Ciccone 2012	48	10	29	49	19	29	1.0%	-0.06 [-0.58, 0.45]
Elden 2012	43.56	6.59	52	46.58	4.63	50	1.8%	-0.52 [-0.92, -0.13]
Fasano 2017	55.7	1.27	131	58.4	12	77	3.4%	-0.37 [-0.65, -0.08]
Jalali 2020	43	7.7	81	46.5	8	243	4.3%	-0.44 [-0.69, -0.19]
Lee 2015	57.62	15.3	324	54.34	13.05	972		Not estimable
Li 2021	52.2	13.148	2288	54.14	13.148	2288	82.0%	-0.15 [-0.21, -0.09]
Mohammed 2014	48.3	8.75	22	49.7	8.77	55	1.1%	-0.16 [-0.65, 0.34]
Oreskovic 2010	51.14	19.3	54	51.14	15.5	55	2.0%	0.00 [-0.38, 0.38]
Park 2022	52.2	11.5	239	50.4	12.1	239		Not estimable
Quaranta 2008	52.37	17.61	37	43.73	8.19	47		Not estimable
Rajati 2016	51.9	9.6	30	47.5	13.5	30	1.1%	0.37 [-0.14, 0.88]
Rinaldi 2020	56.08	13.19	39	54.61	13.33	44	1.5%	0.11 [-0.32, 0.54]
Rudack 2006	61	16	142	54	14	84		Not estimable
Suckfull 2002	56	16	53	57	33	53	1.9%	-0.04 [-0.42, 0.34]
Total (95% CI)			**2779**			**2924**	**100.0%**	**-0.16 [-0.21, -0.11]**

Heterogeneity: Chi² = 17.03, df = 9 (P = 0.05); I² = 47%
Test for overall effect: Z = 5.94 (P < 0.00001)

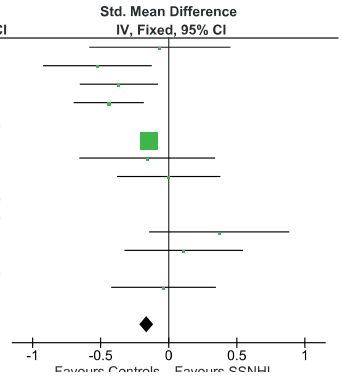


Figure 4.| a. Results from the meta-analysis including 3421 patients with SSNHL from 14 articles investigating the HDL cholesterol value of patients with SSNHL versus controls. **b.** results from the sensitivity analysis after exclusion of 4 articles due to large heterogeneity in data. CI= Confidence Interval, HDL=High-Density Lipoprotein, SSNHL=Sudden Sensorineural Hearing Loss.

LDL cholesterol

Nineteen articles investigated LDL cholesterol values in patients with iSSNHL[19,20,35,37,40,41,44,45,47,21–24,28–31]. Of these, one article did not report the values in control patients and another did not provide absolute LDL-cholesterol values[19,23].

In the remaining articles LDL-cholesterol was on average 0.08 mg/dl higher in patients with iSSNHL than in controls (95% CI -0.04 – 0.13) (shown in Fig. 5a). After sensitivity analysis with 10 articles, this mean difference remained 0.08 mg/dl (95% CI 0.03 – 0.13, p=0.002) (shown in Fig. 5b).

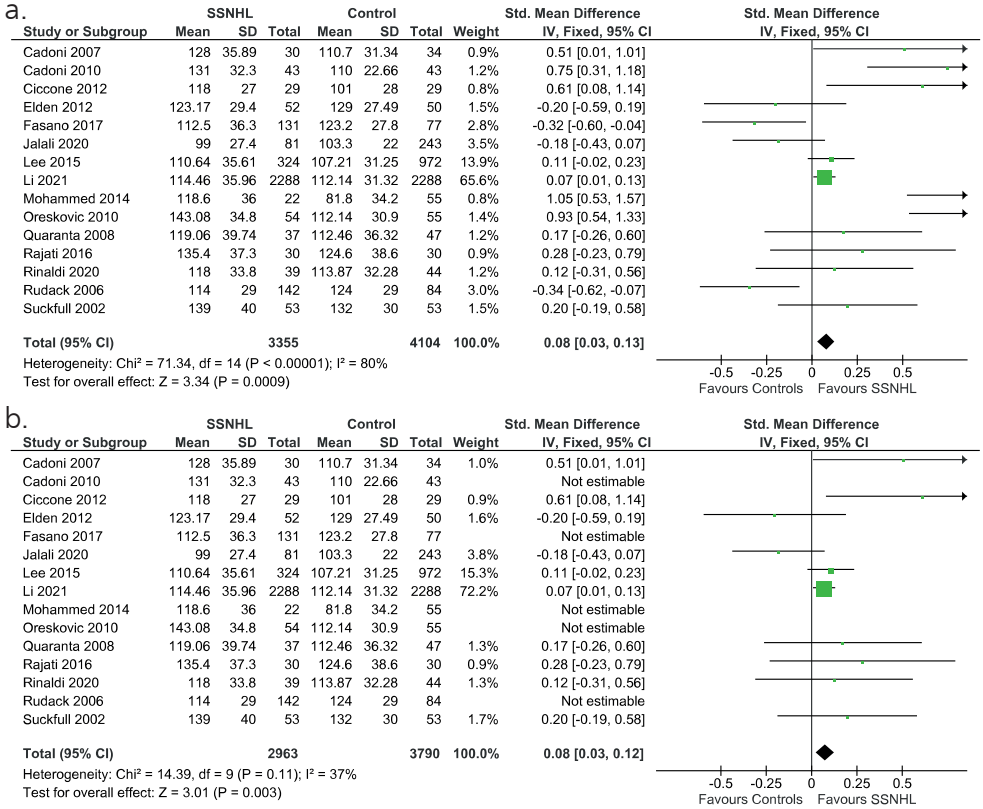


Figure 5.1 a. Results from the meta-analysis including 3355 patients with SSNHL from 15 articles investigating the LDL cholesterol value of patients with SSNHL versus controls. **b.** Results from the sensitivity analysis after exclusion of 5 articles based on large heterogeneity. CI=Confidence Interval, LDL=Low-Density Lipoprotein, SSNHL= Sudden Sensorineural Hearing Loss.

Diabetes

Twelve articles described the correlation between DM and iSSNHL[16,19,48,49,21,25,26,34,38,42,44,45]. One article compared the incidence of iSSNHL in patients with and without DM[38]. Another article compared the incidence of diabetes between women and men with iSSNHL[26]. Both articles were excluded from the meta-analysis. On average, patients with iSSNHL had an odds ratio of 1.64 of having diabetes compared to controls (95% CI 1.24 – 2.19, p=0.0006) (shown in Fig. 6). The in-between study heterogeneity was 0%, so no sensitivity analysis was applied.

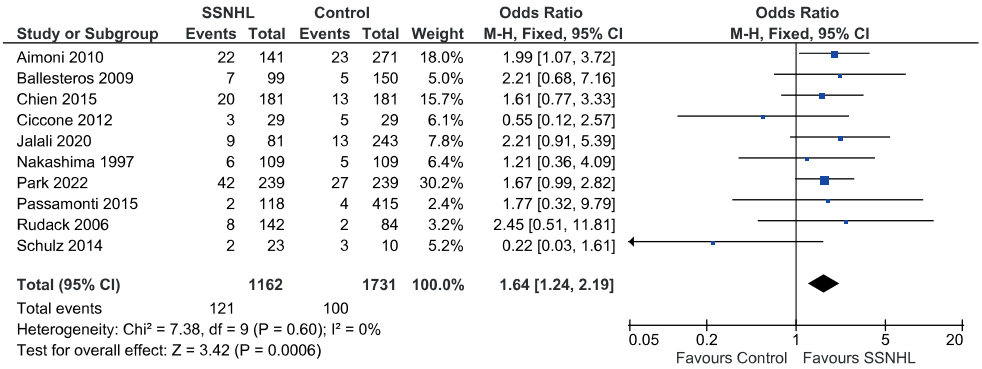


Figure 6.| Results from the meta-analysis including 1162 patients with SSNHL from 10 articles investigating the prevalence of diabetes amongst patients with SSNHL versus controls. CI= Confidence Interval, SSNHL= Sudden Sensorineural Hearing Loss.

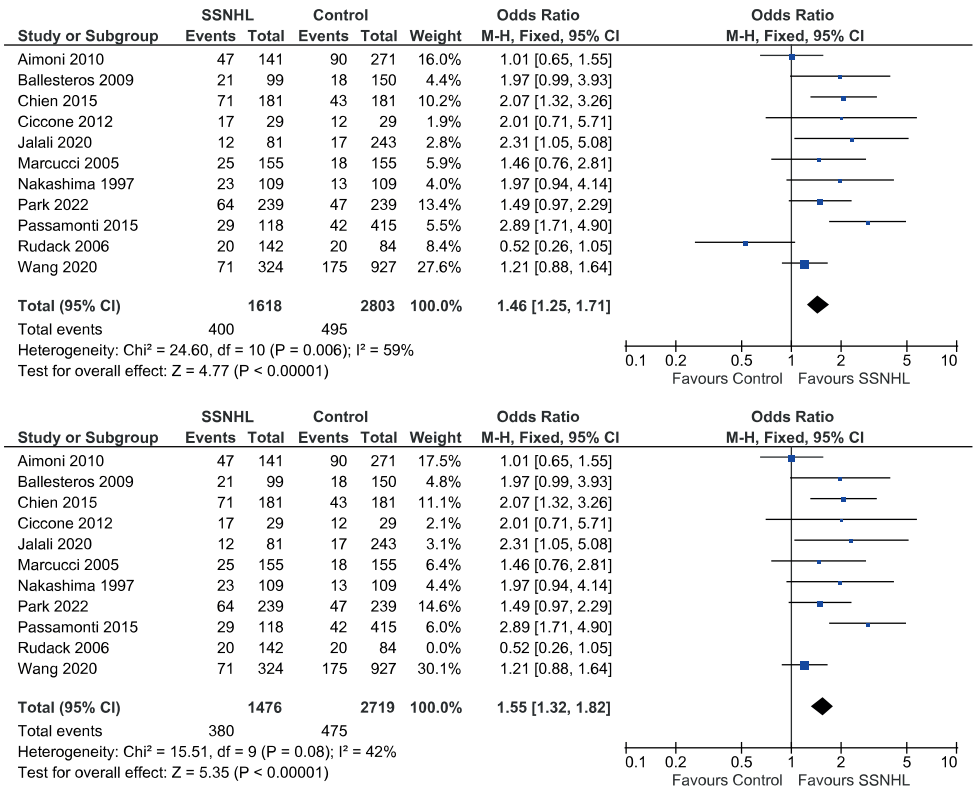


Figure 7.| a. Results from the meta-analysis including 1618 patients with SSNHL from 11 articles investigating the prevalence of hypertension amongst patients with SSNHL versus controls. **b.** Results of the sensitivity analysis after exclusion of one article due to the large heterogeneity in the data. CI=confidence interval, SSNHL= sudden sensorineural hearing loss.

Hypertension

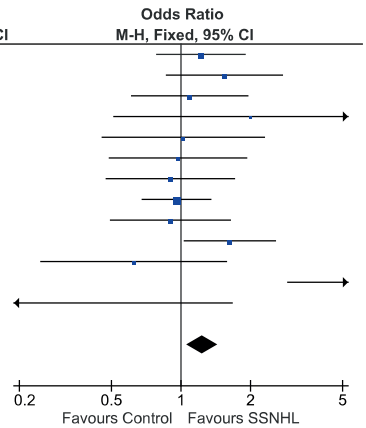
Thirteen articles were included in the systematic review[16,19,45,46,49,21,22,25,33,36,39,42,44]. Two articles did not describe the incidence of hypertension, but measured the average systolic and diastolic blood pressure and compared this to a control cohort; these studies were therefore excluded from further analysis[22,39].

Patients with iSSNHL had an odds ratio of 1.46 of having hypertension compared to controls (95% CI 1.25 – 1.71, p<0.00001) (shown in Fig. 7a). After sensitivity analysis including 10 articles, the odds ratio of having hypertension was 1.55 (95%CI 1.32 – 1.82, p<0.00001) for patients with iSSNHL (shown in Fig. 7b).

a.

Study or Subgroup	SSNHL Events	SSNHL Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Aimoni 2010	46	141	77	271	13.2%	1.22 [0.79, 1.89]
Ballesteros 2009	30	99	33	150	6.8%	1.54 [0.87, 2.75]
Chien 2015	28	181	26	181	8.2%	1.09 [0.61, 1.95]
Ciccone 2012	7	29	4	29	1.1%	1.99 [0.51, 7.71]
Elden 2012	19	52	18	50	4.3%	1.02 [0.46, 2.30]
Jalali 2020	13	81	40	243	6.2%	0.97 [0.49, 1.92]
Marcucci 2005	21	155	23	155	7.4%	0.90 [0.47, 1.70]
Nakamura 2001	49	154	5261	16043	25.3%	0.96 [0.68, 1.34]
Nakashima 1997	29	108	31	107	8.5%	0.90 [0.50, 1.63]
Passamonti 2015	37	118	91	415	10.3%	1.63 [1.03, 2.56]
Rinaldi 2020	11	39	17	44	4.3%	0.62 [0.25, 1.57]
Rudack 2006	80	142	16	84	3.3%	5.48 [2.90, 10.38]
Schulz 2014	0	23	2	10	1.2%	0.07 [0.00, 1.66]
Total (95% CI)		**1322**		**17782**	**100.0%**	**1.24 [1.06, 1.45]**
Total events	370		5639			

Heterogeneity: Chi² = 33.76, df = 12 (P = 0.0007); I² = 64%
Test for overall effect: Z = 2.65 (P = 0.008)



b.

Study or Subgroup	SSNHL Events	SSNHL Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Aimoni 2010	46	141	77	271	13.6%	1.22 [0.79, 1.89]
Ballesteros 2009	30	99	33	150	7.0%	1.54 [0.87, 2.75]
Chien 2015	28	181	26	181	8.4%	1.09 [0.61, 1.95]
Ciccone 2012	7	29	4	29	1.2%	1.99 [0.51, 7.71]
Elden 2012	19	52	18	50	4.5%	1.02 [0.46, 2.30]
Jalali 2020	13	81	40	243	6.4%	0.97 [0.49, 1.92]
Marcucci 2005	21	155	23	155	7.6%	0.90 [0.47, 1.70]
Nakamura 2001	49	154	5261	16043	26.2%	0.96 [0.68, 1.34]
Nakashima 1997	29	108	31	107	8.7%	0.90 [0.50, 1.63]
Passamonti 2015	37	118	91	415	10.6%	1.63 [1.03, 2.56]
Rinaldi 2020	11	39	17	44	4.4%	0.62 [0.25, 1.57]
Rudack 2006	80	142	16	84		Not estimable
Schulz 2014	0	23	2	10	1.3%	0.07 [0.00, 1.66]
Total (95% CI)		**1180**		**17698**	**100.0%**	**1.10 [0.93, 1.30]**
Total events	290		5623			

Heterogeneity: Chi² = 11.09, df = 11 (P = 0.44); I² = 1%
Test for overall effect: Z = 1.08 (P = 0.28)

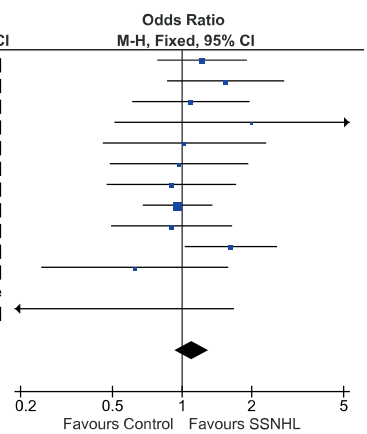


Figure 8.| a. Results from the meta-analysis including 1322 patients with SSNHL from 13 articles investigating the prevalence of smoking amongst patients with SSNHL versus controls. **b.** Results from the sensitivity analysis after exclusion of one article due to the large heterogeneity in data. CI=confidence interval, SSNHL=sudden sensorineural hearing loss.

Smoking

Fourteen articles investigated the incidence of smoking among patients with iSSNHL [19,21,45,46,49,50,22,25,26,30,33,34,42,44]. Of these, one article was excluded from the analysis since it did not describe the incidence of smoking in the total control cohort, but subdivided the control cohort in men and women[26].

The odds ratio of smoking was 1.24 in patients with iSSNHL (95% CI 1.06 – 1.45) (shown in Fig. 8a). After sensitivity analysis including 12 articles the odds ratio for smoking was non-significantly higher in patients with iSSNHL, OR 1.10 (95%CI 0.93 – 1.30, p=0.28) (shown in Fig. 8b).

Cardiac disease

Five articles reported the prevalence of a medical history of cardiac disease in patients with iSSNHL[19,26,36,39,45]. In one article, the difference was calculated in women and men separately and did not include the primary data[26]. This article was therefore not included in the analysis.

The remaining four articles resulted in a mean odds ratio of 2.05 for having a medical history of cardiac disease in patients with iSSNHL (95% CI 1.19 – 3.52, p=0.010) (shown in Fig. 9).

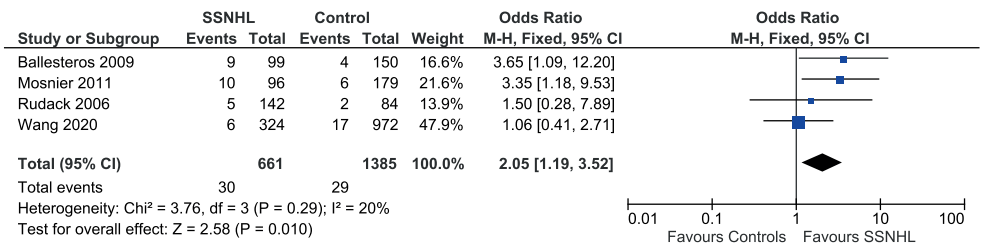


Figure 9. | Results from the meta-analysis including 661 patients with SSNHL from 4 articles investigating the prevalence of cardiac disease amongst patients with SSNHL versus controls.

Research question 2: Cerebral small vessel disease and iSSNHL

A total of 413 original articles were identified. Only five articles reported the presence of cerebral small vessel disease, in particular white matter hyperintensities, in patients with iSSNHL[51–54]. One of these articles was a cohort study that compared the prognosis of hearing loss between iSSNHL patients with and without white matter hyperintensities. This article reported the prevalence of each Fazekas score in the studied cohort and was therefore included in the systematic review, but excluded from the meta-analysis[51].

All four case-control articles compared the presence of white matter hyperintensities in patients with and without iSSNHL[52–54]. Table 3 displays the study characteristics of the included studies.

Risk of bias assessment

The quality of the four case-control studies ranged from poor to good. Three studies had a retrospective study design and one study included patients with sudden deafness prospectively[53]. In three studies the control cohort was matched for sociodemographic characteristics, such as age and gender[52,53], though Fusconi *et al*. did not further specify the matching characteristics[54]. In the study by Ciorba *et al.*, the control cohort was significantly younger than the study cohort[52].

In only one study both cohorts underwent pure-tone audiometry (PTA) assessment[52]. MRI assessment was performed using T2-weighted or FLAIR sequences in all studies. The number of raters was only described in two articles and the reliability of the MRI assessments was only tested in one study.

All four articles used the Fazekas score as measurement for the degree of white matter hyperintensities. Ciorba *et al*. additionally reported the Wahlund scale for white matter hyperintensities[52]. Oussoren *et al*. also identified silent brain infarctions, though the incidence thereof was low in both cohorts[55]. Three articles provided the total Fazekas scores, the sum of the white matter hyperintensities both periventricular and in the deep white matter, while Dicuonzo *et al*. compared the incidence of hyperintensities in the periventricular white matter (PVWM) and deep white matter (DWM) separately[53]. Three studies used a (ordinal) logistic regression model to adjust for potential confounders like age, gender and MRI sequence[53–55].

The only cohort study was of fair quality, but did not compare the Fazekas scores in patients with and without iSSNHL[51]. The data was retrospectively retrieved from hospital records, however, missing data was not reported. Non-idiopathic cases of SSNHL were excluded. The authors clearly described the radiological assessment and PTA tests. Binary logistic regression was performed to adjust the average hearing thresholds for age and other possible confounders[51].

Table 3.| Study characteristics of articles in the cerebral small vessel disease analysis.

Author	Year	Study design	Population	Age	Outcome	Results
Ciorba	2019	Retrospective case-control	SSNHL: 64 Controls: 32 SSNHL <55y: 23	SSNHL: 58.25 ± 14.91 Controls: 40.28 ± 13.64	WML: Fazekas scale Wahlunds scale	SSNHL: Fazekas: 0: 15; 1: 6; 2: 2; >2: 0 Warlund: 0-3: 21; 4-8: 2; ≥ 9: 0 Controls: n.d.
Dicuonzo	2019	Prospective case-control	SSNHL: 36 Controls: 36	SSNHL: 54.4 ± 15.6 Controls: 53.0 ± 12.5	WML: Fazekas scale	SSNHL: PVWM: 0: 12; 1: 11; 2: 10; 3: 3 — DWM: 0: 18; 1: 9; 2: 8; 3: 1 Controls: PVWM: 0: 23; 1: 12; 2: 1; 3: 0 — DWM: 0: 26; 1: 9; 2: 1; 3: 0
Fusconi	2019	Retrospective case-control	SSNHL: 113 Controls: 107	SSNHL: 44.54 Controls: 44.75	WML: Fazekas scale	SSNHL: 0: 58.82 %; 1: 17.65 %; 2: 17.65 %; 3: 3.92 %; 4: 1.96%; 5: 0%; 6: 0% Controls: 0: 58.33 %; 1: 18.33 %; 2: 10.00 %; 3: 11.67 %; 4: 1.67%; 5: 0%; 6: 0%

<table>
<tr><td>Oussoren</td><td>2022</td><td>Retrospective case-control</td><td>SSNHL:
Controls:</td><td>SSNHL: 65.9 ± 9.3
Controls: 65.1 ± 9.0</td><td>WML:
Fazekas scale</td><td><table><tr><th>SSNHL:</th><th>Controls:</th></tr><tr><td>0: 8.5 %
1: 22.9 %
2: 35.6 %
3: 17.8 %
4: 10.2%
5: 2.5%
6: 2.5%</td><td>0: 5.9 %
1: 29.7 %
2: 28.0 %
3: 19.5 %
4: 9.3%
5: 6.8%
6: 0.8%</td></tr></table></td></tr>
<tr><td>Shin</td><td>2022</td><td>Retrospective cohort</td><td>SSNHL: 107</td><td>SSNHL: 54.6 ± 13.4</td><td>Hearing outcomes compared between the Fazekas scores</td><td>SSNHL:
0: 78
1: 17
2: 12

Significant hearing difference between Fazekas score 1 and 2. (p=0.009)</td></tr>
</table>

A description of all 5 included articles is provided including the study design, the mean age of the subjects, the effect size of the outcome and the main results. F= Fazekas scale, n.d.= not determined, SSNHL=sudden sensorineural hearing loss, W= Wahlunds scale, WML=white matter leukoaraiosis.

Outcomes

Since the cohort study did not describe a control cohort without iSSNHL, we could not include their results in the meta-analysis. The article by Dicuonzo *et al.* did not provide the total Fazekas scores and was consequently excluded from the meta-analysis. Data on the total Fazekas score of each included patient could not be distilled from the article by Ciorba *et al.* and therefore it was also excluded from the meta-analysis. We included two articles with a total study population of 456 patients, of whom 231 were diagnosed with iSSNHL[53,55].

Forty-five patients with iSSNHL had a Fazekas score higher than three, compared to 57 patients in the control cohort. Patients with iSSNHL did not have a higher odds of a higher Fazekas (OR 0.70, 95%CI 0.44-1.12, p=0.14) score (shown in Fig. 10).

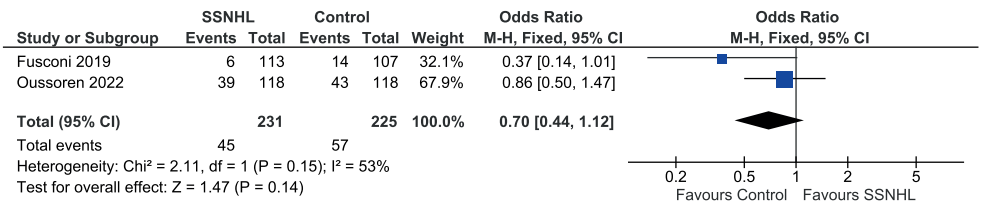


Figure 10.| Results from the meta-analysis including 231 patients with SSNHL from 2 articles investigating the degree of white matter hyperintensities amongst patients with SSNHL versus controls. Events display the number of patients who had a Fazekas score of 3 or higher on MRI. CI= Confidence Interval, SSNHL= Sudden Sensorineural Hearing Loss.

Research question 3: Risk of stroke after iSSNHL

Of the 3,583 articles screened for eligibility, 7 articles met the inclusion criteria. Table 4 displays the study characteristics and outcomes.

Risk of bias assessment

The risk of bias assessment is shown in table 2. Two cohort studies described the incidence of stroke in a iSSNHL cohort and compared this to the general population of Taiwan and of Emilia Romagna region, respectively, but the studies did not include a control cohort[5,7]. Another article compared the incidence of stroke between patients with iSSNHL alone, iSSNHL with vertigo and vertigo alone, but no healthy control cohort was compiled[56]. In the remaining articles with a control cohort, this cohort was matched for age and gender and, in most cases, also for cardiovascular comorbidities like diabetes and hypertension. One of the case-control studies described the incidence of stroke after iSSNHL in a cohort of hemodialysis patients[9].

Table 4.| Study characteristics of articles included in the risk of stroke analysis.

Author, year	Study design	Database	Study population	Inclusion period	Definition SSNHL	Definition Stroke	Effect size	Follow-up (years)	Results
Lin et al, 2008	Retrospective case control	TNHIRD	SSNHL: 1423 Appendectomy: 5692	1998-2003	ICD-9-CM code 388.2	ICD-9-CM code 430 up to 438.	Hazard rates	10	HR Stroke in SSNHL 1.64 (1.31-2.07)
Chang, C.F. et al, 2013	Retrospective cohort	Hospital records	SSNHL: 349	2000-2004	SSNHL: Hearing loss 30dB over 3 contiguous frequencies within 72 hours.	Acute neurological deficits and/ or infarction or hemorrhage on imaging.	Incidence rates	6.8	IR stroke in SSNHL cohort: 4.6% IR in population: 0.3-0.6%
Ciorba et al, 2015	Retrospective cohort	Hospital discharge data and regional statistics office.	SSNHL: 484 and 8188 Stroke: 9985 and 103004	2001-2012	SSNHL: ICD-9-CM 388.2	ICD-9-CM 43301,43311, 43321,43331, 43381,43391, 43401,43411,436	Annual crude incidence rates Expected vs observed number of strokes.	6	IR stroke in SSNHL: 1.9% Expected: 6 Observed: 9
Chang, T.P. et al, 2017	Retrospective cohort	TNHIRD	SSNHL alone: 1998 SSNHL with vertigo: 678 Vertigo alone: 215980	2002-2009	SSNHL alone: ICD-9-CM code 388.2 SSNHL with vertigo: ICD-9-CM code 388.2 and 386.x or 780.4 (within 30 days) Vertigo alone: ICD-9-CM code 386.x or 780.4	ICD-9-CM codes 430 upto 438.	Hazard rates	7*	HR stroke in SSNHL with vertigo 1.75 vs SSNHL alone. HR SSNHL with vertigo 1.23 vs vertigo alone. (latter non-sig).
Kim, J.Y. et al, 2018	Retrospective case-control	KNHIS	SSNHL: 154 Control: 616	2002-2005	SSNHL: ICD-10-CM codes H9120, H9121, H9129, H810. Received a PTA and steroid treatment.	ICD-10-CM codes I60 up to I63.	Hazard rates	11*	Stroke in SSNHL: Adjusted HR 2.02 95% CI (1.16-3.51)

Author, year	Study design	Database	Study population	Inclusion period	Definition SSNHL	Definition Stroke	Effect size	Follow-up (years)	Results
Kim, S.Y. et al, 2018	Retrospective case-control	KNHIS	SSNHL: 4944 Control: 19776	2002-2013	SSNHL: ICD-10-CM code 91.2 Received a PTA and steroid treatment.	ICD-10-CM codes I60 up to I63	Hazard rates	5*	HR stroke in SSNHL: 1.22 95% CI (1.05-1.43)
Chou et al, 2018	Retrospective case-control	TNHIRD	SSNHL with HD: 288 HD alone: 1728	1997-2008	ICD-9-CM code 388.2 and ICD-9-CM code 585, 3 months of HD or PD.	ICD-9-CM codes 430 up to 438.	Hazard rates	11*	HR 2.34, 95% CI 1.45–3.78

Description of the seven included studies in the systematic review including the study design, definition used for iSSNHL, the effect sizes and the main

Two studies used hospital discharge data[5,57], the other studies were performed using data gathered from the national health insurance databases of Korea and Taiwan, respectively. Health insurance claims of almost all inhabitants in these countries can be retrieved from these databases, enabling large scale cohort or case-controlled studies. The diagnosis codes used for inclusion were broad, hence patients might not have met the standardized criteria for iSSNHL, which could have resulted in inclusion bias. The different codes used from the international classification system are summarized in supplementary table 2.

The total inclusion period ranged from 1998 until 2015. The inclusion periods of the two Taiwanese studies overlapped in inclusion period, as did two Korean studies. This might have resulted in inclusion of identical cases. All studies had a retrospective study design, although the follow-up duration varied. The Italian cohort study did not control for potential confounders[5]. All remaining studies used a Cox proportional hazard model to adjust for potential confounders. Overall, the case-controlled studies were performed accurately with limited chance of bias, while the cohort studies were performed without a control group and consequently their results are more difficult to interpret and extrapolate to the general population. No data on prophylactic therapy for stroke or other cardiovascular disease, after sudden sensorineural hearing loss had occurred, could be retrieved.

Study outcomes

All four case-control studies described higher incidences of stroke in the iSSNHL cohort compared to controls, with hazard ratios ranging from 1.22 up to 4.08. The upper limit of the hazard ratio is based on a study that compared hemodialysis patients with and without iSSNHL.

In a European cohort study, Ciorba *et al.* compared the incidence of stroke after iSSNHL with the general population. They found a stroke incidence of 1.9%, nine cases of stroke were found, while according to the annual incidence of stroke in the Italian region, one would have expected to find 6 cases of stroke[5]. This difference was, however, not statistically significant. In another study, patients with iSSNHL were divided into two cohorts, patients who experienced stroke and patients who did not experience stroke. The incidence of stroke after iSSNHL was compared to the overall incidence of stroke in the Taiwanese population. The incidence rate in the study cohort was 0.6% versus an incidence of 0.3-0.6% in the entire population[7]. In the cohort study by Chang *et al.*, incidence rates of stroke were compared between three study groups; iSSNHL with vertigo, iSSNHL without vertigo and vertigo alone[56]. The hazard ratio of stroke in patients with iSSNHL with vertigo was 1.75 and 1.23 compared to iSSNHL without vertigo and vertigo alone, respectively.

Discussion

With this systematic review and meta-analyses we systematically assessed the association between sudden deafness and systemic cardiovascular disease. We compared the presence of cardiovascular risk factors, the degree of white matter hyperintensities and the risk of subsequent stroke after experiencing idiopathic sudden deafness. Patients with iSSNHL had on average a higher BMI, a higher total and LDL cholesterol and higher odds of having diabetes, hypertension and a medical history with cardiac disease compared to healthy controls. HDL-cholesterol was significantly lower in the iSSNHL cohorts, while smoking was non-significantly higher in patients with iSSNHL. In contrast, patients with iSSNHL did not have a higher degree of white matter hyperintensities measured with the Fazekas scale compared to healthy controls. Patients with iSSNHL did have a higher odds of developing stroke in the years following their sudden deafness.

The acute onset of hearing loss resembles the presentation of acute cardiovascular disease. With limited collateral blood supply to the cochlea and vestibule, the organ is vulnerable to ischemia and a vascular origin of sudden deafness seems therefore plausible. The hypothesized mechanism of vascular involvement in the etiology of iSSNHL is that atherosclerosis causes hypoperfusion of the cochlea, resulting in a reduction of the number of inner and outer hair cells and stiffening of the basilar membrane. This, in conjunction with increased plasma viscosity leads to degeneration of the stria vascularis, without complete artery occlusion[58]. Identification of thrombotic events and localized damage is difficult due to the microscopical size, complex anatomy and location of the cochlea in the temporal bone. Therefore, assessment of the vascular involvement in the pathophysiology of iSSNHL is primarily based on associations with generalized cardiovascular disease.

The association between iSSNHL and cardiovascular risk factors has been investigated intensively over the last decade but this has resulted in conflicting results from heterogeneous study populations. While Lin *et al*. identified smoking as a risk factor of iSSNHL in a meta-analysis from 2012[4], more recent case-control studies could not confirm this association[30,34,44]. Not surprisingly, the odds for smoking favored patients with iSSNHL compared to controls, though non-significantly. A more recent meta-analysis by Simões *et al*. identified hypertriglyceridemia and hypercholesterolemia as independent risk factors for iSSNHL, while no increased risk was found for diabetes and hypertension, which are known risk factors for stroke[59]. Simões *et al*., however, excluded many articles from their meta-analysis based on heterogeneous outcomes. Whilst Simões and colleagues only included dichotomous outcomes for all CVRFs, we compared the average total cholesterol, HDL-cholesterol, and LDL-cholesterol in order to increase the number of included articles. We additionally analyzed other cardiovascular risk factors (i.e., BMI, smoking and medical history of cardiac disease) to complete the CVRF panel. In doing so, we included a total of 33 articles. Since we included articles that described mean

cholesterol values, we also included some articles of which the mean cholesterol value was below the threshold to define hypercholesterolemia. After exclusion of these articles, we still found a significantly higher mean cholesterol value in patients with iSSNHL compared to controls. We performed an additional analysis where we removed articles with skewed weight. We defined skewed weight to be articles that contributed over 50% of the total included number of subjects, since their result would strongly influences the outcome of the meta-analysis. Exclusion of the articles responsible for skewed weight did not alter the outcome, though the heterogeneity between the included articles remained high.

The main limitations of the included studies are the small study populations. Eleven studies included less than 60 cases of iSSNHL, compared to only three articles with over 150 cases. Most studies did not perform a power analysis, so type I and II errors remain possible. The reliability of a regression analysis declines significantly with small study populations, especially in non-stratified cohorts, while in some articles the mean age differed significantly between the iSSNHL and control cohorts. Additionally, three studies used national health insurance databases to compile their cohorts. Without hospital data to verify the diagnosis, this could result in wrongful inclusion of subjects who did not meet the generally accepted criteria for sudden deafness.

To our knowledge we are the first to review articles investigating the degree of white matter hyperintensities in patients with iSSNHL. If cardiovascular risk factors are more frequently present in patients with iSSNHL, these are likely to result in cerebral small vessel disease (CSVD) such as WMH, since the presence thereof is associated with CVRFs like hypertension and increased age. Contrary to this hypothesis, we did not find an increased degree of white matter hyperintensities in patients with iSSNHL when compared with controls. This result is, however, based on only two articles. Several articles that also investigated the association between WMH and iSSNHL were excluded since their primary data could not be retrieved from the article or otherwise. The main limitation of the included studies is the retrospective study design and absence of proper power analyses. The chances of a type II error are small, however, due to the adequate matching for age and gender and regression analysis for possible confounders. The mean age of both articles did differ. While Fusconi *et al*. did not apply age restrictions, Oussoren *et al*. only included patients aged 50 or older. Fusconi *et al*. found a positive association between iSSNHL and Fazekas score in patients aged 48 up to 60 but Oussoren *et al*. could not confirm this association.

The final association between cardiovascular disease and iSSNHL is the risk of subsequent stroke. In 2008, Lin *et al*. were the first to report an increased risk of stroke following sudden deafness. In the past years multiple retrospective cohort studies analyzed the same association. A recent meta-analysis by Lammers *et al*. summarized these articles and found an overall increased adjusted risk of stroke of 1.21 to 1.63 following iSSNHL, compared to controls. However, their overall result was based on only 3 articles, all from Asian populations with solely positive outcomes. The articles describing negative associations

were not included due to their heterogeneous outcomes. To provide a thorough review of all available literature we decided to include all articles in our systematic review without quantitative analysis. While Lammers *et al*. found an adjusted risk of stroke of 1.21 to 1.63 in an all-Asian population, the only European article by Ciorba *et al*. did not find a higher risk of stroke than in the general Italian population. Yet, in terms of numbers this article included only a fraction of the study population size used in the Asian studies. Nonetheless, it does bring to mind the possibility of ethnical differences in the risk of stroke. It is known that stroke is more common in Asian populations than in the non-Hispanic white population[60], therefore it might be possible that the risk of stroke after sudden deafness is also higher in among Asians. As mentioned before, the most significant limitation of the Korean and Taiwanese studies included is the lack of hospital data.

Conclusion

Hypertension, diabetes, a medical history with cardiac disease, elevated total cholesterol and LDL-cholesterol appear to be independent risk factors for iSSNHL. Also, patients with iSSNHL have a higher risk of stroke compared to controls. These outcomes are in favor of vascular involvement in the pathogenesis of iSSNHL. In contrast, patients with iSSNHL do not show more CSVD on MRI. These conclusions should be interpreted with care due to the significant risk of bias and large heterogeneity in study data and study outcomes. Prospective cohort studies with hospital-derived clinical data are needed to establish the accuracy of the investigated associations and whether or not cardiovascular risk management in case of sudden hearing loss is appropriate.

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Supplementary Table 1. Table Search strategies: risk factors of SSNHL

Pubmed:

Date: 03-12-2021

("risk factor"[Title/Abstract] OR "risk"[Title/Abstract] OR "cardiovascular risk factors"[Title/Abstract] OR "cardiovascular risk"[Title/Abstract] OR "hypertension"[Title/Abstract] OR "hyperlipedaemia"[Title/Abstract] OR "smoking"[Title/Abstract] OR "myocardial infarction"[Title/Abstract] OR "diabetes mellitus, type 2"[MeSH Terms] OR "risk factors"[MeSH Terms] OR "BMI" [MeSH Terms] OR "weight" [Title/Abstract]) Number of articles: 3,331,274

AND

((("hearing loss"[Title/Abstract] OR "sudden deafness"[Title/Abstract] OR "sudden sensorineural hearing loss"[Title/Abstract] OR "sudden hearing loss"[Title/Abstract] OR "deafness"[Title/Abstract] OR "ISSNHL"[Title/Abstract] OR "SSNHL"[Title/Abstract] OR "SNHL"[Title/Abstract] OR "ISNHL"[Title/Abstract] OR "hearing loss, sudden"[MeSH Terms]) Number of articles: 69,379
fha[Filter]: hasabstract humans[Filter]: humans[MH] english[Filter]: english [LA]
Combined search: number of articles 2410

Embase:

Date: 03-12-2021

exp sudden deafness/ or hearing impairment/ or ("Hearing Loss" or sudden hearing loss or sudden deafness or sudden sensorineural hearing loss or SSNHL or SSHL or ISSNHL or ISSHL or SHL or ISNHL or ISHL).ti,ab,kw. Number of articles: 94024

AND

(cardiovascular risk factor or hypertension or diabetes or smoking or myocardial infarction or coronary heart disease or cholesterol or hyperlipidemia or BMI or weight).ti,ab,kw. Number or articles: 707250
(exp animal/ or nonhuman/) not exp human/ limit to english language
Combined search: number of articles: 2299

CINAHL

Date: 03-12-2021

risk factors OR TX risk OR AB risk factors OR TX cardiovascular risk OR cardiovascular risk factors OR TX hypertension OR TX myocardial infarction OR TX diabetes OR TX (hyperlipidemia or dyslipidemia or hypercholesterolemia or high cholesterol) OR TX(smoking or tobacco or cigarette or nicotine) OR TX (BMI or weight) Number of articles: 1,460,226

AND

TX sudden deafness OR TX ssnhl OR TX hearing loss OR TX sensorineural hearing loss OR TX sudden hearing loss OR TX (deafness or hearing impairment or deaf or hard of hearing) Number of articles: 41,295

Limiters - Abstract Available; Published Date: 19700101-; Human; Publication Type: Journal Article
Expanders - Apply equivalent subjects
Narrow by Language: - english
Search modes - Boolean/Phrase

Combined search: number of articles 1931

Search strategies: CSVD in SSNHL

Pubmed

Date 18-05-2020

"hearing loss, sudden"[MeSH Terms] OR ("hearing"[All Fields] AND "loss"[All Fields] AND "sudden"[All Fields]) OR "sudden hearing loss"[All Fields] OR ("sudden"[All Fields] AND "deafness"[All Fields]) OR "sudden deafness"[All Fields] OR "hearing loss"[Title/Abstract] OR "SSNHL"[All Fields] OR "iSSNHL"[All Fields] OR "SNHL"[Title/Abstract] OR "deafness"[Title/Abstract] OR ("hearing loss, sudden"[MeSH Terms] OR ("hearing"[All Fields] AND "loss"[All Fields] AND "sudden"[All Fields]) OR "sudden hearing loss"[All Fields] OR ("sudden"[All Fields] AND "deafness"[All Fields]) OR "sudden deafness"[All Fields])
Number of articles: 70857

AND

"cerebral vascular damage"[Title/Abstract] OR "CSVD"[All Fields] OR ("cerebral small vessel diseases"[MeSH Terms] OR ("cerebral"[All Fields] AND "small"[All Fields] AND "vessel"[All Fields] AND "diseases"[All Fields]) OR "cerebral small vessel diseases"[All Fields] OR ("cerebral"[All Fields] AND "small"[All Fields] AND "vessel"[All Fields] AND "disease"[All Fields]) OR "cerebral small vessel disease"[All Fields]) OR (("white matter"[MeSH Terms] OR ("white"[All Fields] AND "matter"[All Fields]) OR "white matter"[All Fields]) AND ("hyperintense"[All Fields] OR "hyperintensities"[All Fields] OR "hyperintensity"[All Fields] OR "hyperintensive"[All Fields])) OR "WMH"[All Fields] OR "brain infarctions"[Title/Abstract] OR "silent brain infarctions"[Title/Abstract] OR ("leukoaraiosis"[MeSH Terms] OR "leukoaraiosis"[All Fields]) OR "white matter abnormalities"[Title/Abstract] OR "white matter lesions"[Title/Abstract]
Number of articles: 24387

Combined search: number of articles: 325

Embase

Date: 18-05-2022

sudden deafness.ab. or SSNHL.af. or SNHL.ab. or deafness.ab. or hearing loss.ab. or sudden sensorineural hearing loss.ab. or sudden hearing loss.af.
Number of articles: 73453

AND

cerebral vascular damage.ab. or CSVD.af. or cerebral small vessel disease.ab. or white matter hyperintensities.ab. or WMH.af. or leukoaraiosis.ab. or white matter abnormalities.ab. or white matter lesions.ab. or silent brain infarctions.ab. or brain infarctions.ab.
Number of articles: 19832

Combined search: number of articles: 150

CINAHL

Date: 18-05-2022

AB sudden deafness OR TX ssnhl OR AB SNHL OR AB (hearing loss or deafness or hearing impairment or deaf or hard of hearing) OR TX sudden hearing loss OR AB sudden sensorineural hearing loss Number of articles: 22904

AND

cerebral vascular damage OR TX CSVD OR AB cerebral small vessel disease OR AB white matter hyperintensities OR AB white matter abnormalities OR AB white matter lesions OR AB white matter disease OR AB brain infarction OR AB silent brain infarctions OR AB leukoaraiosis OR TX WMH Number of articles: 4578
Combined search: number of articles: 28

Search strategies: Risk of stroke

Pubmed

Date: 17-03-2021

"Risk"[Mesh] OR "Risk Factors" OR Risk OR "Epidemiologic Studies"[Mesh] OR cohort[tiab] OR (case[tiab] AND (control[tiab] OR controll*[tiab] OR comparison[tiab] OR referent[tiab])) OR causation[tiab] OR causal[tiab] OR "odds ratio"[tiab] OR etiol*[tiab] OR aetiol*[tiab] OR "natural history"[tiab] OR predict*[tiab] OR prognos*[tiab] OR outcome[tiab] OR course[tiab] OR retrospect*[tiab] Number of articles: 7,637,217

AND

"Hearing Loss, Sudden"[Mesh] OR "Deafness"[Mesh] OR "Hearing Loss"[Mesh] OR "Hearing Loss"[tiab]OR sudden hearing loss[tiab]OR sudden deafness[tiab]OR sudden sensorineural hearing loss[tiab]OR SSNHL[tiab] OR SSHL[tiab] OR ISSNHL[tiab] OR ISSHL[tiab] OR SHL[tiab] OR ISNHL [tiab] OR ISHL [tiab] Number of articles: 93,276

AND

"Cerebrovascular Disorders"[Mesh] OR "Stroke"[Mesh] OR Strokes[tiab]OR Cerebrovascular Accident* [tiab]OR CVA[tiab] OR Cerebrovascular Stroke*[tiab]OR Cerebral Stroke*[tiab]OR Acute Stroke*[tiab]OR transient ischemic attack[tiab]OR cerebrovascular[tiab]OR cerebrovascular infarc*[tiab]OR haemorrhage[tiab]OR hemorrhage[tiab]OR cerebral infarc* [tiab]OR AICA infarction[tiab]OR AICA infarc*[tiab]OR PICA infarc*[tiab]OR cerebellar infarc* Number of articles 578,958
humans[Filter]: humans[MH] english[Filter]: english [LA]
Total articles combined search: 763

Embase

Date: 17-03-2021

exp risk factor/ or exp risk/ or exp epidemiology/ or ("Risk Factor*" or Risk cohort).ti,ab,kw. or (case and (control or controll* or comparison or referent)).ti,ab,kw. or (causation or causal or "odds ratio" or etiol* or aetiol* or "natural history" or predict* or prognos* or outcome or course or retrospect*).ti,ab,kw. Number of articles: 9847996

AND
exp sudden deafness/ or hearing impairment/ or ("Hearing Loss" or sudden hearing loss or sudden deafness or sudden sensorineural hearing loss or SSNHL or SSHL or ISSNHL or ISSHL or SHL or ISNHL or ISHL).ti,ab,kw. Number of articles: 102052
AND
exp cerebrovascular disease/ or exp cerebrovascular accident/ or (Stroke* or Cerebrovascular Accident* or CVA or Cerebrovascular Stroke* or Cerebral Stroke* or Acute Stroke* or transient ischemic attack or cerebrovascular or cerebrovascular infarc* or haemorrhage or hemorrhage or cerebral infarc* or AICA infarction or AICA infarc* or PICA infarc* or cerebellar infarc*).ti,ab,kw. Number of articles: 997950
(exp animal/ or nonhuman/) not exp human/ limit to english language
Combined search: number of articles: 2118

CINAHL

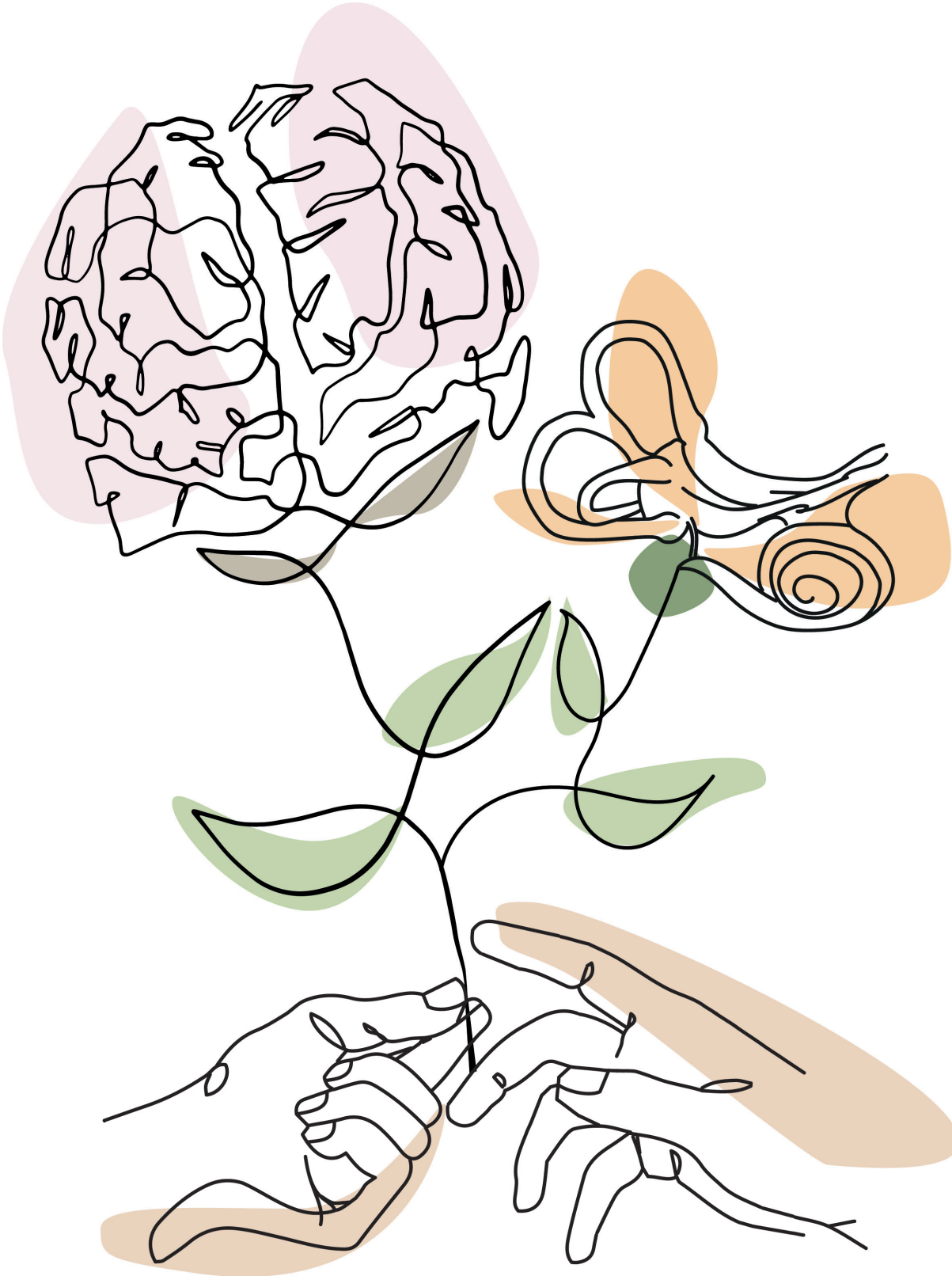
Date: 08-09-2021

cerebrovascular disorders OR TX (stroke or cerebrovascular accident or cva) OR (transient ischemic attack or tia) OR (haemorrhage or hemorrhage) OR cerebral infarction OR AICA infarction OR PICA infarction OR cerebellar infarct
AND
hearing loss OR sudden hearing loss OR (sudden sensorineural hearing loss or idiopathic sudden sensorineural hearing loss or issnhl or isnhl or ssnhl or snhl) OR sudden deafness OR (deafness or hearing impairment or deaf or hard of hearing)
AND
risk factors OR (cohort study or case control study) OR etiology OR (odds ratio or relative risk) OR MW epidemiologic study OR course OR (causation or aetiology or factor or cause)
Limiters - Abstract Available Expanders - Apply equivalent subjects Narrow by Language: - english Search modes - Boolean/Phrase
Combined search: number of articles: 791

ICD code	Definition
ICD-9	
388.2	Sudden hearing loss, unspecified
386	Vertiginous syndromes and other disorders of vestibular system
386.0	Meniere's disease
386.1	Other and unspecified peripheral vertigo
386.2	Vertigo of central origin
386.3	Labyrinthitis
386.4	Labyrinthine fistula
386.5	Labyrinthine dysfunction
386.8	Other disorders of labyrinth
386.9	Unspecified vertiginous syndromes and labyrinthine disorders
780.4	Dizziness and giddiness
430	Subarachnoid hemorrhage
431	Intracerebral hemorrhage
432	Other and unspecified intracranial hemorrhage
433	Occlusion and stenosis of precerebral arteries
433.01	Occlusion and stenosis of basilar artery with cerebral infarction
433.11	Occlusion and stenosis of carotid artery with cerebral infarction
433.21	Occlusion and stenosis of vertebral artery with cerebral infarction
433.31	Occlusion and stenosis of multiple and bilateral precerebral arteries with cerebral infarction
433.81	Occlusion and stenosis of other specified precerebral artery with cerebral infarction
433.91	Occlusion and stenosis of unspecified precerebral artery with cerebral infarction
434	Occlusion of cerebral arteries
434.01	Cerebral thrombosis with cerebral infarction
434.11	Cerebral embolism with cerebral infarction
435	Transient cerebral ischemia
436	Acute, but ill-defined, cerebrovascular disease
437	Other and ill-defined cerebrovascular disease
438	Late effects of cerebrovascular disease
ICD-OP 47	Operations on appendix

ICD-10	
H810	Menière's disease
H9120	Sudden idiopathic hearing loss, unspecified ear
H9121	Sudden idiopathic hearing loss, right ear
H9122	Sudden idiopathic hearing loss, left ear
I60	Nontraumatic subarachnoid hemorrhage
I61	Nontraumatic intracerebral hemorrhage
I62	Other and unspecified nontraumatic intracranial hemorrhage
I63	Cerebral infarction

Supplementary Table 2. ICD 9 and ICD 10 codes. The different definitions for SSNHL and stroke used for patient selection and outcomes. ICD=International classification of disease, ICD-OP=International classification of disease operation, H=Diseases of the ear and mastoid process, I=Diseases of the circulatory system.



Chapter

3

Cerebral small vessel disease in elderly patients with vestibular neuritis

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Introduction

Acute audiovestibular loss is a neurotologic emergency. The cause of vestibular neuritis (VN), sudden sensorineural hearing loss (SSNHL) or labyrinthitis is unknown in a significant number of cases1,2.

Recently, research has focused on a possible vascular origin of hearing and vestibular loss[3–6]. An acute onset of symptoms and frequently unilateral presentation resemble acute cardiovascular diseases.

Very little information is available on vascular involvement in VN. It is believed to be an inflammatory disorder of viral origin[7]. However, patients do not show clinical benefit from antiviral therapy or corticosteroid use[8,9]. The question is whether VN might have a different etiology and, consequently, a different therapy should be applied.

Because of its relatively high incidence, SSNHL has been studied frequently. Compared to the general population, cardiovascular risk factors are more frequently present in patients with SSNHL[3,10,11]. Subsequently, several authors have investigated the chance of developing a stroke in patients with SSNHL. These studies show that, after correction for age and other cardiovascular risk factors, patients with sudden hearing loss have a 1.26-2.02 higher chance of developing a stroke than the general population[12–15].

A vascular compromised brain raises the chance of developing a stroke. On magnetic resonance imaging (MRI) imaging, cerebral small vessel disease(CSVD), visible as white matter hyperintensities, (silent) brain infarctions and microbleeds have shown to be indicative of developing stroke[16–19].

With this study we investigated whether patients with VN have more CSVD on MRI compared suggesting a vascular involvement in the pathophysiology of VN.

Materials and Methods

Setting

This retrospective case-controlled study was based upon hospital records from patients either visiting the emergency departments of Gelre Hospital Apeldoorn and Zutphen, the outpatient neurology clinic or the Apeldoorns Dizziness Centre (ADC), located in Gelre hospital. The ADC serves as a tertiary referral center that specializes in the diagnostic and therapeutic workup of dizziness. It is a multidisciplinary center involving the Neurology, Clinical neurophysiology and Otorhinolaryngology departments of the Gelre Hospital Apeldoorn. This retrospective cohort study gained ethical approval from the local ethics committee at Gelre Hospital Apeldoorn.

Cohorts

A study cohort was compiled of patients diagnosed with vestibular neuritis between January 2010 and March 2021 who received an MRI cerebrum. Patients either presented at the emergency departments of both Gelre hospitals or at the outpatient Apeldoorn dizziness centre.

Vestibular neuritis was defined as a single episode of acute, severe vertigo lasting for at least 24 hours in the absence of auditory symptoms or neurological symptoms, with or without loss of vestibular function measured with caloric testing. VN was distinguished from acute stroke by a positive head impulse test, by the presence of unidirectional horizontal nystagmus, by the absence of skew deviation (HINTS) and by the absence of an infarction on MRI. At the emergency departments patients the diagnostic tests were performed by different physicians.

The control cohort was compiled of patients who either visited the outpatient neurological department with facial pain, suspected for trigeminal neuralgia, or patients who visited the ADC with recurrent episodes of spontaneous vertigo lasting several seconds, suggestive of vestibular paroxysmia. All patients received an MRI cerebrum to rule out the presence of an intracranial neoplasm.

Exclusion criteria were age 49 years or younger and a history of cerebrovascular accident or transient ischemic attack. If during follow-up the type of dizziness changed and did not meet the aforementioned criteria of VN, these patients were excluded. Patients were also excluded if the MRI was performed more than a year after presentation at either the emergency department or the outpatient dizziness clinic.

MRI protocol

An MRI was suitable for radiological assessment of white matter hyperintensities and brain infarctions if at least one sequence of the entire brain, either FLAIR or T2, was available. The imaging was performed using a 1.5 Tesla MRI scanner. The cerebral sequence was depicted with a slice thickness of 5mm. Twenty-three MRI scans were performed elsewhere and uploaded in the Gelre Hospital database, two of these scans had a slice thickness of 4mm, and the remaining had a slice thickness of 5mm. The type of MRI scanner used for these external MRIs could not be retrieved.

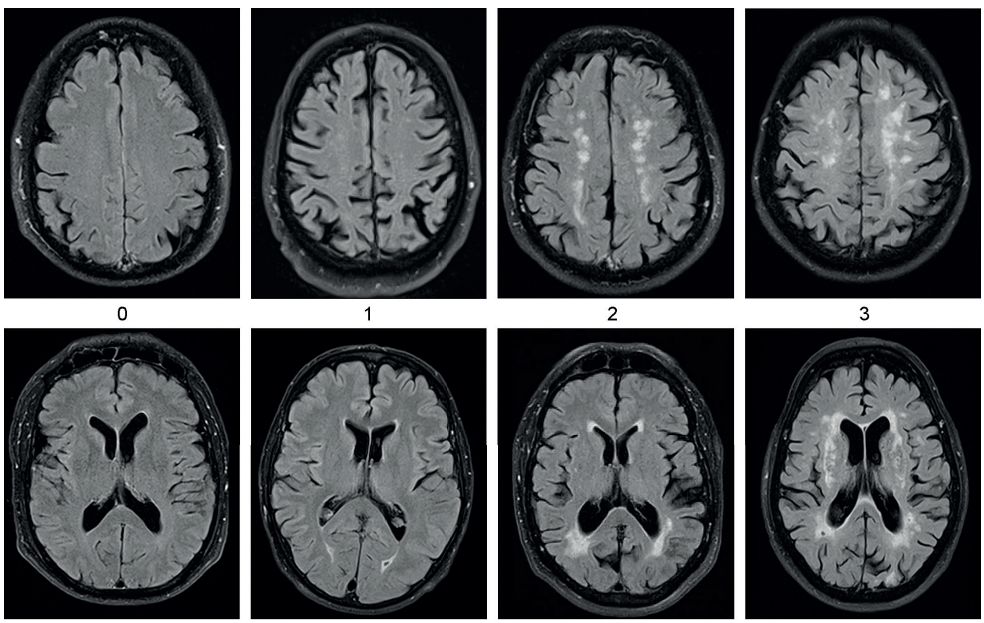
Outcomes

The primary outcome was the degree of cerebral vascular damage assessed on MRI imaging by measuring the Fazekas score. The Fazekas score is a validated diagnostic tool for assessing the severity of white matter hyper-intensities both periventricular and in the deep white matter with a possible score from 0 to 6, where 0 means no hyperintensities present, see figure 1.

A secondary outcome was the presence of brain infarctions on MRI imaging. Brain infarctions were defined by lesions of the brain of at least 3mm with a cerebrospinal fluid appearance on all MRI sequences, differentiable from leukoaraiosis and dilated Virchow-Robin spaces that did not result in prior neurological deficits[20].

Another secondary outcome was the difference in the presence of the cardiovascular risk factors; smoking, hypertension, hyperlipidemia, diabetes, a history of myocardial infarction and atrial fibrillation between the SSNHL and control cohort. The following assumptions were made in the identification of cardiovascular risk factors. Hypertension and diabetes were defined as being present either by having a positive medical history or if medication for these conditions were used. In case no complete medical history had been obtained, the variable was defined as missing. Hyperlipidemia was defined as being present when the patient had a positive medical history of dyslipidemia, used statins, or had an elevated total cholesterol level of >4.9 mmol/L within a month before or after presentation at our dizziness centre.

Figure 1.| Fazekas scale for MRI imaging.



Deep white matter (DWM)	Periventricular white matter (PVWM)
0 = absent	0 = absent
1 = punctate foci	1 = "caps" or pencil-thin lining
2 = beginning confluence	2 = smooth "halo"
3 = large confluent areas	3 = irregular periventricular signal extending into the deep white matter

The figure displays hyperintensities in the deep white matter (upper row) and periventricular (lower row).

Assessment

MRI imaging was assessed by two radiologists separately, LP and JK. The two radiologists involved in this study have multiple years of experience in examining MRI imaging of the head and neck. To limit observer bias, both radiologists were blinded for the patients' characteristics or study arm.

If there was a difference in Fazekas rating between the two raters, the following rules were applied. If the difference was 1 rank, the highest rank was then applied. If the difference was 2 ranks or more, the radiologists reviewed the case together until consensus was reached.

Baseline characteristics, data from diagnostic tests and MRI ratings were gathered and de-identified in a Castor electronic database (CastorECD, Amsterdam, The Netherlands).

Rater reliability testing

Inter- and intra-rater reliability for the two radiologists was assessed for the Fazekas rating scale using the present control cohort plus a cohort of patients who suffered from sudden sensorineural hearing loss. All patients were rated by the same raters involved in the present study. Sample size calculation showed that thirty patients had to be rated twice by both raters to evaluate the intra-rater reliability. A weighted Cohen's kappa coefficient was calculated using linear weighting, where the difference between low and high ratings is of equal importance.

Statistical analysis

Continuous variables were described using the following summary descriptive statistics: number of non-missing values, mean and standard deviation in case of normally distributed data or median and interquartile ranges in case of non-normally distributed data.

Categorical variables were described using frequencies and percentages. Percentages were calculated on the number of non-missing observations.

95% confidence intervals were calculated when applicable. Statistical testing was performed two-sided at a 0.05 significance level.

Differences in the ordinal ranking of the Fazekas scale between the two cohorts were calculated using the Mann-Whitney U test for ordinal non-paired data.

Because the presence of brain infarctions is a binary variable, the difference between the cohorts was compared using the Chi-square test.

Ordinal logistic regression analysis was performed to compare the outcomes between the cohorts while adjusting for the potential confounders: age, hypertension, hyperlipidemia, diabetes, a medical history of MI, smoking, gender, an outpatient or inpatient presentation, the presence of vestibular loss with an abnormal video head impulse testing or abnormal caloric testing and the type of MRI sequence used.

Results

Patient characteristics

A total of 101 patients with VN were included. The control cohort consisted of 203 patients, 149 suspected cases of trigeminal neuralgia and 54 suspected cases of vestibular paroxysmia. In the vestibular neuritis cohort, 50 patients were diagnosed upon presentation at the emergency department while 51 patients were diagnosed at the outpatient clinic of the Apeldoorn Dizziness Centre. None of the VN patients demonstrated bilateral vestibular dysfunction.

Baseline characteristics of both cohorts are displayed in table 1. The mean age did not differ significantly between both cohorts. Both study cohorts consisted of more women than men.

In patients with VN, hyperlipidemia and atrial fibrillation were significantly more common. Also a medical history of myocardial infarction, smoking and hypertension were more frequently present in the VN cohort, though not statistically significant. Diabetes was more frequently present in the control cohort, also not statistically significant.

Table 1.| Patient characteristics

	VN (N=101)	Control (N=203)	Missing	P-value
Age (mean, (SD))	64 (9.8)	63 (9.4)	0	0.423
*50-60	42 (41.6)	100 (49.3)	0	0.469
*71-80	28 (27.7)	56 (27.6)	0	
*61-70	28 (27.7)	41 (20.2)	0	
*>80	3 (3.0)	6 (3.0)	0	
Gender			0	0.460
Male	56 (55.4)	123 (60.6)		
Female	45 (44.6)	80 (39.4)		
Myocardial infarction	4 (4.0)	7 (3.4)	0	1.000
Anticoagulant use	12 (11.9)	21 (10.3)	0	0.700
Smoking			27	0.073
Former	21 (22.6)	25 (13.6)		
Yes	6 (6.5)	23 (12.5)		
Hypertension	35 (36)	67 (33.3)	6	0.700
Hyperlipidemia	52 (51.5.0)	63 (31.0)	0	0.001
Diabetes	7 (6.9)	20 (9.9)	0	0.522
Atrial Fibrillation	8 (7.9)	4 (2.0)	0	0.023

Patient characteristics of 101 patients with vestibular neuritis and a control cohort of 203 patients displayed in numbers and percentages. For age the mean and standard deviation are displayed.
N: number, SD: standard deviation, VN: Vestibular neuritis.

In case of presentation at the emergency department, the MRI was made after 24 hours in only 6 cases. All other patients received an MRI within 24hours up to several days after the onset of symptoms. The MRI of 31 (30.7%) patients in the VN cohort was assessed using a T2 sequence compared to 106 (52.2%) in the control cohort (p<0.001).

Rater-reliability

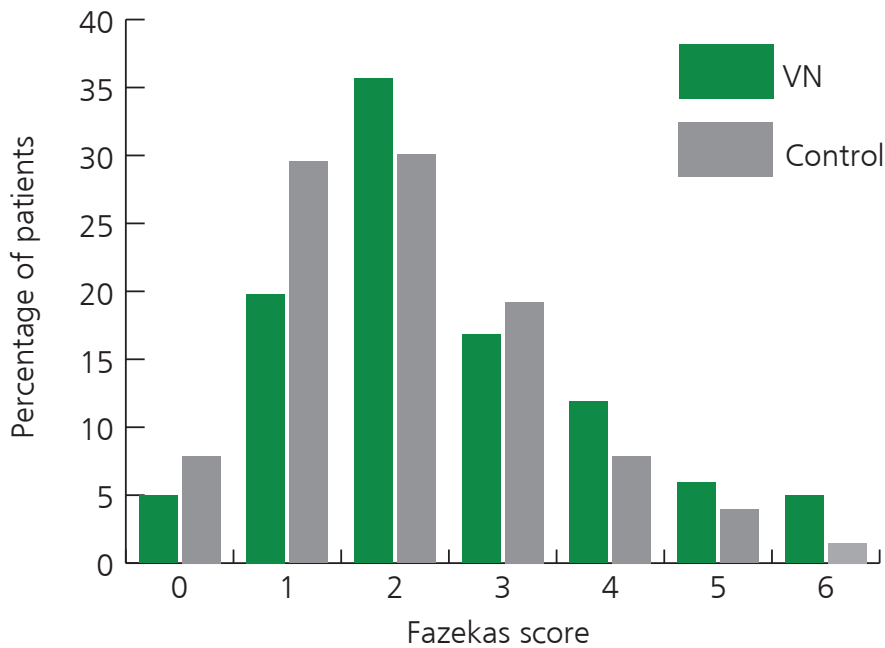
All 328 MRI scans were reviewed by both raters. In 201 cases both radiologists gave the same Fazekas score, in 103 cases they differed one point and in 24 cases the difference in score given was two points or more. This resulted in a kappa-coefficient of 0.74 for inter-rater reliability.

Thirty subjects were rated twice by each rater, which resulted in a weighted kappa-coefficient of 0.80 and 0.82 for rater 1 and 2 respectively, suggesting a near-perfect agreement for each rater.

Fazekas score

The distribution of Fazekas ratings in both cohorts is displayed in figure 2.

Figure 2.| Distribution of Fazekas scores.



The distribution of the Fazekas scale score 1 up to 6 over the both cohorts displayed in percentages. VN, vestibular neuritis.

The mode of the Fazekas score was 2 in both cohorts. The group that received Fazekas 5 and 6 form a larger proportion of cases in the VN cohort than in the control cohort. Therefore, the ordinal differed statistically significant (p=0.023).

Ordinal regression analysis

Table 2 displays the results of the ordinal regression analysis. In a univariate regression analysis only the variables neuritis, hypertension and age all significantly increased the risk of a higher Fazekas score. The remaining cardiovascular risk factors and diagnostic characteristics did not influence the Fazekas score.

After adding hypertension and age to the model, patients with vestibular neuritis had a 1.60 (95%CI 1.01-2.42, p=0.048) higher odds of having a higher Fazekas score. Age also significantly increased the odds of white matter hyperintensities on MRI.

Table 2.| Ordinal regression analysis

Variable	Univariate			Multivariate		
	Odds	Sig	95% CI	Odds	Sig	95% CI
Neuritis	2.10	0.012*	1.26-3.83	1.60	0.048*	1.01-2.42
Age	1.11	0.000*	1.08-1.13	1.10	0.000	1.07-1.13
Diabetes	0.96	0.909	0.47-1.94			
Gender	1.11	0.628	0.74-1.66			
History of MI	2.46	0.100	0.84-7.15			
Hyperlipidemia	1.22	0.358	0.81-1.85			
Hypertension	2.48	0.000*	1.60-3.84	1.52	0.067	0.97-2.39
Smoking	1.00	0.997	0.73-1.37			
Abnormal caloric testing	1.02	0.928	0.63-1.66			
Abnormal video-HIT	1.17	0.717	0.50-2.73			
Outpatient presentation	0.85	0.648	0.42-1.71			
MRI Sequence (FLAIR)	1.48	0.058	0.99-2.22			

Regression analysis for Fazekas score. FLAIR: Fluid Attenuated Inversion Recovery, HIT: head impulse test, CI: Confidence interval, MI: myocardial infarction, MRI: Magnetic Resonance Imaging, Sig: significance. *significant difference with an α level of 0.05.

Brain infarctions

Brain infarctions were present in 10 (9.9%) cases with VN and 21 (10.4%) cases in the control cohort. The difference between the two cohorts was not significant (p-value =1.0).

In both cohorts, most brain infarctions were located in the deep white matter, in 5 patients from the VN cohort and 7 from the control cohort. The cerebellum was affected in 3 patients with VN and 7 controls. In five control patients an infarction was located in

the basal ganglia, while none of the patients with VN had lesions in this region. In only one patient with vestibular neuritis a cortical infarction was seen, compared to 4 patients in the study cohort. In both cohorts the brainstem was not affected. Due to the limited number of cerebral infarctions, a regression analysis was not performed.

Discussion

We found a positive correlation between VN and CSVD on MRI imaging. Patients with VN had a 1.60 odds of receiving a higher Fazekas rating compared to the control cohort. Very few brain infarctions were seen in both groups resulting in no significant difference between the study cohorts. All cardiovascular risk factors, apart from diabetes, were more frequently present in the study cohort. However, the difference in prevalence was only statistically significant for hyperlipidemia and atrial fibrillation.

Literature on vascular involvement in the pathophysiology of VN is limited. We based our hypothesis upon the following train of thought. VN is generally expected to be the result of inflammation secondary to viral infection. VN often has a viral prodrome and latent herpes simplex virus type 1 has been detected in human vestibular ganglia with PCR[21]. Also, postmortem studies showed atrophy of the vestibular nerve and sensory epithelium, similar to pathological alterations seen in inner ear infections with measles[22–25]. Nevertheless, corticosteroid and antiviral therapy have failed to show clinical benefit in the treatment of VN[8,9].

The current treatment in the Netherlands is symptomatic with vestibular suppressants and anti-emetics. The question is whether VN can be solely contributed to a viral infection or if a different pathophysiology is probable. Since the ear and vestibular organ have limited collateral blood supply, it is particularly vulnerable to blood pressure dysregulation or acute occlusion.

Blood pressure dysregulation (BPD) in the vestibulocochlear blood circulation was first described by Fisch et al in 1972[26]. Cochlear atherosclerosis, related to cardiovascular risk factors as age, hypertension, diabetes, hyperlipidemia and smoking, results in a pathologic alteration in the composition of the arteries and arterioles. Hyalinosis causes thickening of the tunica adventitia, while the number of fibromuscular cells is reduced, which induces a decrease in adrenergic regulation[27]. Meanwhile, due to arteriosclerosis, the internal caliber of the arteriole is reduced. This combination of blood pressure dysregulation secondary to reduced adrenergic regulation and shrinking of the arterial lumen results in damage to the vestibular nerve fibers[28,29].

Acute onset vertigo or sudden sensorineural hearing loss, with or without vertigo, can also be caused by acute occlusion somewhere along the course of the anterior inferior cerebellar artery. After studying the vascular structure of the inner ear, Tange et al came up with a theoretical flowchart depicting obstruction lines and the expected symptoms caused by this obstruction[30]. In case of acute arterial occlusion, one would expect a

patient to present with combined audio-vestibulopathy, because of the common vascular supply to the cochlea and vestibule by the internal auditory artery.

A third argument supporting a vascular hypothesis of VN is based upon microvascular occlusion secondary to inflammation either due to viral infection or auto-immune response. Freedman et al found a significantly elevated expression of CD40 positive monocytes and macrophages in patients with VN[31]. These cells are known to cause platelet-monocytes aggregates that might cause thrombotic changes in the vascular system. A significantly increased expression of cyclooxygenase -2 (COX-2) was also found in patients with VN[32]. This enzyme is responsible for vasodilatation and is generally present in the peripheral blood mononuclear cells (PBMC's) of patients with cardiovascular comorbidity[32,33]. It is suggested that the proinflammatory activation of PBMC's and elevation of CD 40 expression reduces the microvascular perfusion of the vestibular organ by increased thrombotic events, resulting in loss of function of the vestibular organ.

Since the cochlea is supplied by the same vascular system as the vestibular organ, a similar hypothesis of vascular compromise in the origin SSNHL has gained considerable attention. Hypoperfusion due to arteriosclerosis and BPD is thought to result in damage of the stria vascularis and subsequent hearing loss.

Ciorba et al and Fusconi et al have investigated the presence of white matter hyperintensities as an indicator of cerebral small vessel disease in patients with SSNHL[34,35]. Ciorba et al found no difference in the incidence of WMH, they did, however, find a correlation between more WMH and a poorer hearing recovery[34]. Fusconi et al. found more WMH in individuals aged 40-60 in the SSNHL subset and also correlated this to a poorer rearing recovery[35]. Several other authors found a higher incidence of stroke following SSNHL than in the general population[12,14,15].

Oron et al investigated the presence of cardiovascular risk factors in patients with VN compared to the general population[36]. They found a significantly higher presence of dyslipidemia, hypertension, diabetes, ischemic heart disease, prior CVA/TIA, cigarettes smoking, and obesity when compared to healthy controls. Their study cohort consisted of 160 patients with VN with a mean age of 56 years old, which is a larger but also younger study populations than our cohort. Age was a significant contributor to the prevalence of cardiovascular risk factors. For this exact reason our study population consisted only of patients 50 years of age or older. Since age is known to be an important risk factor for both CSVD and the risk of developing stroke, we corrected for age in a multivariate regression analysis. After correction, patients in the VN cohort still had increased odds of having a higher degree of white matter hyperintensities.

Chung et al also investigated a possible vascular etiology in VN[37]. They compared metabolic syndrome scores and arterial stiffness, using brachial ankle pulse wave velocity, between patients with VN and controls[37]. They found an increased arterial stiffness and hypothesized that this increase might reflect endothelial dysfunction and microvascular

compromise in patients with VN. Since arterial stiffness can affect small vessels in the brain, it could lead to cerebral small vessel disease[38].

Adamec et al. previously demonstrated that white matter supratentorial lesions and older age reduced the odds of clinical recovery after VN[39]. They speculated that because of interaction with central compensatory mechanisms, white matter lesions can influence the clinical recovery after VN[39].

This is the first study to compare cerebral small vessel disease in elderly patients with VN to a control cohort. The positive association that was found could have significant clinical implications, since cerebral vascular damage increases the risk of developing cardiovascular disease. According to Fazekas et al., cerebral microbleeds, white matter hyperintensities, silent brain infarctions and lacunes are indicators of cognitive impairment and stroke[16–18]. The presence of these indicators in patients with VN should henceforth caution the physician for vascular involvement in VN.

We do need to address some limitations that are unavoidable as a consequence of the retrospective study design. As explained in the method section, several assumptions were made in the recording of cardiovascular risk factors. This could have resulted in some underestimation of the presence of these risk factors. However, there is no reason to suspect that this underestimation differed between both cohorts.

Also, we did not use a standardized sequence schedule for MRI assessment. In some patients, the Fazekas score and the presence of brain infarctions were evaluated on a FLAIR sequence, while in others a T2 sequence was used. White matter hyperintensities and brain infarctions can be seen on both sequences and the slice-thickness did not differ between patients. Furthermore, the type of MRI sequence used, did not correlate with the Fazekas score in the regression analysis.

As opposed to Menière's disease or vestibular migraine, there are no universally accepted criteria for the clinical diagnosis of vestibular neuritis. HINTS was proven to be superior to MRI in differentiating VN from a stroke in the acute phase[40]. The accuracy of diagnosing VN is determined predominantly by the physicians' experience in performing and interpreting these diagnostic tests. Since the patients presenting in the emergency departments were diagnosed by different physicians with different levels of competence in performing these diagnostic tests, this might have influenced the selected study cohort. In a univariate regression analysis, the outpatient presentation did not influence the degree of white matter hyperintensities in patients with vestibular neuritis.

Also, not all patients with VN receive an MRI. An MRI is usually performed to exclude a central cause of the dizziness. Patients who received an MRI might have had more severe dizziness than patients who did not receive imaging or had an unclear diagnosis at first. This might have resulted in some selection bias.

Finally, resilience, the capacity to cope with brain pathology is a factor that can be influenced by cerebral small vessel disease[28]. Patients with a high degree of cerebral

small vessel disease might develop more severe symptoms after vestibular neuritis than patients with limited small vessel disease, since they have limited brain reserve, i.e. white matter structural integrity, to compensate the loss of vestibular function. While high cognitive reserve, i.e. educational attainment and IQ, can attenuate the effect of cerebral small vessel disease on cognitive function[41]. In this study the premorbid cognitive ability was not tested and could therefore be a confounder. Future prospective studies should implement a baseline cognitive function test.

Regardless of these limitations, patients with vestibular neuritis presented more often with CSVD than the control cohort, supporting the hypothesis of vascular involvement in the pathophysiology of VN in a subset of elderly patients. These results, however, cannot be extrapolated to younger patients.

The next step would be to confirm a positive correlation of VN with cardiovascular risk factors and CSVD in a prospective setting, without the limitations of a retrospective study design. The time course of vertigo should be determined in prospective work, since a sudden onset would favor a vascular hypothesis whereas acute onset with evolution to peak intensity over 1 up to 3 days would better support a post-infectious or inflammatory mechanism. Further research should then focus on whether elderly patients with vestibular neuritis have a higher chance of developing cardiovascular disease and should receive cardiovascular risk management or anticoagulant therapy.

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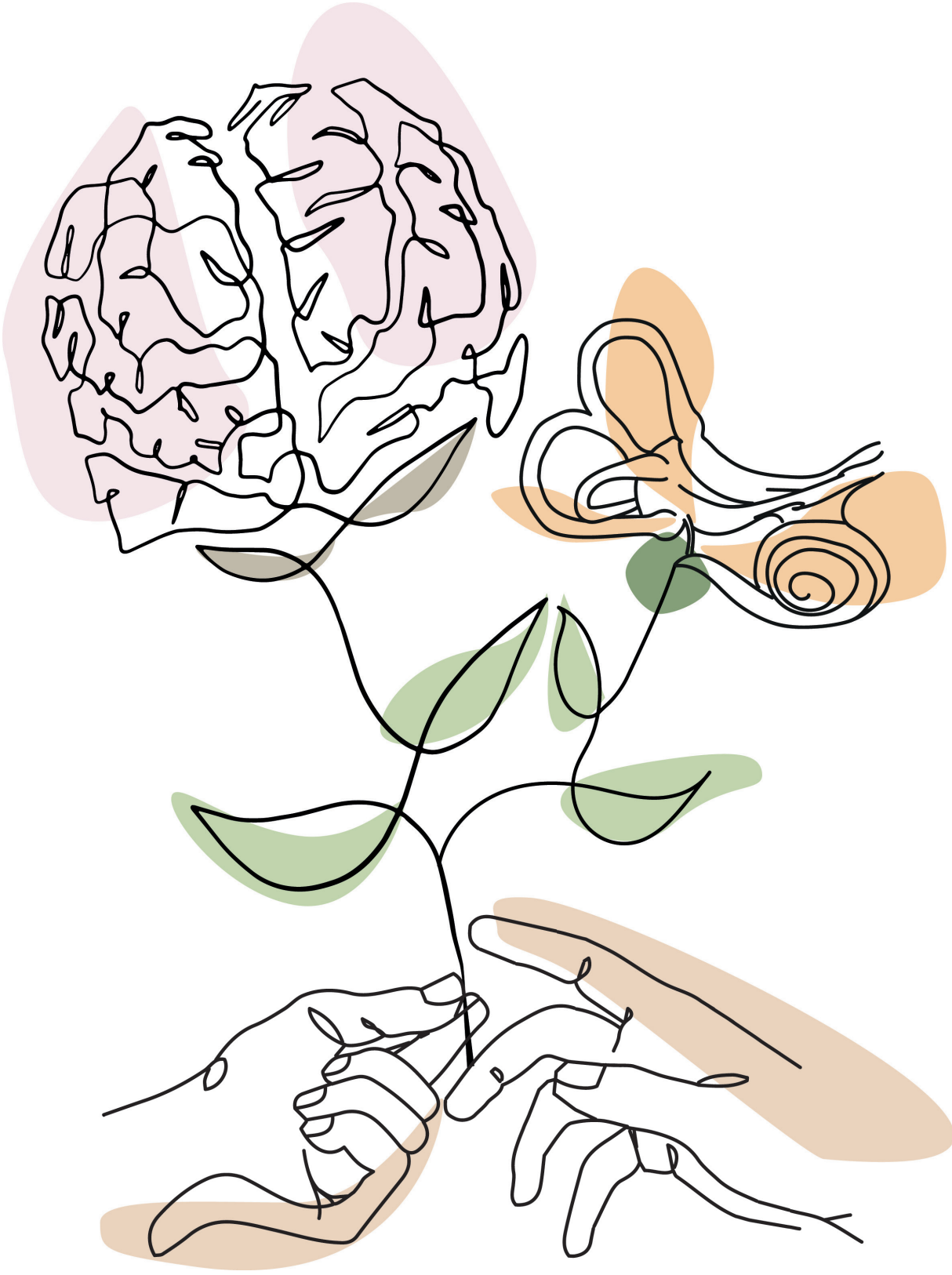

Chapter

4

Cerebral small vessel disease in elderly patients with sudden sensorineural hearing loss

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Introduction

Sudden sensorineural hearing loss (SSNHL) is an otological emergency in which an evident cause can be identified in 7-47% percent of the cases[1–3]. Reported incidence rates range from 11 up to 77 per 100.000 people each year[4]. The current treatment, which is mainly based upon a viral genesis with high-dose corticosteroid therapy, appears to be insufficient in 39 up to 75% of patients[5]. For these two reasons, a different etiology and subsequent treatment of SSNHL should be considered in several patients. Besides viral cochleitis, the following entities have been proposed to cause SSNHL: ototoxic drugs, neoplasms, auto-immune disorders and microvascular disease[6].

Especially in the last two decades, research has focused on the hypothesis of a vascular origin[7–10]. Hearing loss or vestibular loss is the sole manifestation in 0.6 up to 3% of patients with infarction of the posterior cerebral circulation[11], while in 8 up to 31% hearing or vestibular loss was succeeded by neurological symptoms[11]. A recent meta-analysis demonstrated a 1.46 higher risk of stroke in patients with iSSNHL[12]. Sudden deafness might therefore be an indicator of cerebral vascular disease and not merely a local condition.

Cerebral small vessel disease (CSVD) is a chronic progressive disorder of the arterioles, capillaries and small veins supplying the cerebral white matter. Some uncommon genetic or infectious forms aside, CSVD is mainly associated with cardiovascular risk factors, in particular increasing age and hypertension and, therefore, a major cause of stroke and vascular dementia[13–16]. Characteristics of CSVD are white matter hyperintensities (WMH), lacunes of presumed vascular origin, cerebral microbleeds and brain infarctions[17–20]. The presence of WMH alone results in a three-fold risk of stroke[21]. Fusconi et al investigated the presence of WMH on MRI imaging in patients with iSSNHL. Overall, the difference in WMH was not significant compared to the general population[22]. However, individuals with iSSNHL between 48 and 60 years old did have a 26% higher probability of WMH on MRI[22].

Research on the vascular involvement of iSSNHL in elderly patients is limited. This retrospective case-controlled study aimed at ascertaining whether, compared to a control cohort of patients without hearing loss, more white matter hyperintensities and infarctions are seen on MRI imaging in elderly patients with iSSNHL, aged 50 years or older.

Method

Setting

This retrospective case-controlled study was based upon hospital records from patients either visiting the outpatient otorhinolaryngology or neurology departments of Gelre Hospital Apeldoorn and Zutphen or the Apeldoorn Dizziness Centre (ADC), located in Gelre hospital. The ADC serves as a tertiary referral center that specializes in the diagnostic and therapeutic workup of dizziness. It is a multidisciplinary center involving the

Neurology, Clinical neurophysiology and Otorhinolaryngology departments of the Gelre Hospital Apeldoorn. This retrospective cohort study was approved by the institutional review board at Gelre Hospital Apeldoorn.

Inclusion

All records of patients seen by an otolaryngologist with acute hearing loss from January 2010 until May 2022 were retrieved. The definition of iSSNHL used in this study is a rapidly developing sensorineural hearing loss with a minimum of 30 dB over at least 3 contiguous frequencies on tone audiometry that occurs within a period of 72hours[5,23–25], in the absence of an identifiable cause for the hearing loss, like Meniere's disease, ototoxic drugs etcetera. Patients with iSSNHL were included in the study cohort if they had received an MRI to exclude a cerebellopontine neoplasm.

A control cohort was compiled of patients who either visited the outpatient neurological department with facial pain, suspected for trigeminal neuralgia, or patients who visited the ADC with recurrent episodes of spontaneous vertigo lasting several seconds, suggestive of vestibular paroxysmia. All patients received an MRI cerebrum to rule out the presence of an intracranial neoplasm or to detect a neurovascular conflict. No association between these diseases and CSVD has been described. Subjects in the study and control cohorts were matched for age and gender, with a maximum age difference of 1 year.

Exclusion criteria were age 49 years or younger and a history of cerebrovascular accident or transient ischemic attack.

MRI protocol

An MRI was suitable for radiological assessment of white matter hyperintensities and brain infarctions if at least one sequence of the entire brain, either FLAIR or T2, was available. Data on the MRI sequences used is displayed in table 1. All imaging was performed using a 1.5 Tesla MRI scanner. The cerebral sequence was depicted with a slice thickness of 5mm in the axial plane, with the exception of one case with a slice thickness of 4mm.

Outcomes

The primary outcome was the degree of cerebral vascular damage assessed on MRI imaging by measuring the Fazekas score. The Fazekas score is a validated diagnostic tool for assessing the severity of white matter hyperintensities in both the periventricular and the deep white matter with a possible score from 0 to 6, where 0 means no hyperintensities present, see figure 1.

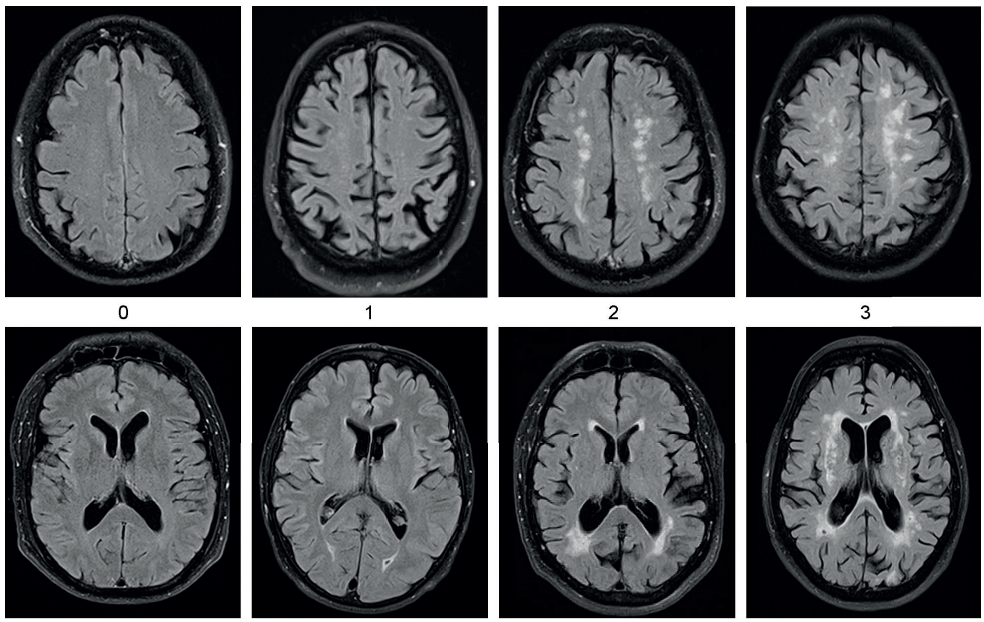
The secondary outcome was the presence of brain infarctions on MRI imaging. Brain infarctions were defined by lesions of the brain of at least 3mm with a cerebrospinal fluid appearance in grey intensity on both a FLAIR and T2 MRI sequence, differentiable from leukoaraiosis and dilated Virchow-Robin spaces[26].

Table 1.| MRI scanning protocol

Sequence	TR (ms)	TE (ms)	Slice thickness (mm)
FLAIR	8000	86	5
T2	4620	89	5

The mode (min, max repetition time and echo time) per scanning protocol characteristic of 88 FLAIR MRI scans and 148 T2 scans. Ms= millisecond, TE=echo time, TR= repetition time.

Figure 1.| Fazekas scale for MRI imaging.



Deep white matter (DWM)	Periventricular white matter (PVWM)
0 = absent	0 = absent
1 = punctate foci	1 = "caps" or pencil-thin lining
2 = beginning confluence	2 = smooth "halo"
3 = large confluent areas	3 = irregular periventricular signal extending into the deep white matter

The figure displays hyperintensities in the deep white matter (upper row) and periventricular white matter (lower row)[45].

The following cardiovascular risk factors were identified; smoking, hypertension, hyperlipidemia, diabetes, a history of myocardial infarction and atrial fibrillation. Hypertension and diabetes were defined as being present either by having a positive medical history or if medication for these conditions were used. In case no complete medical history had been obtained, the variable was defined as missing. Hyperlipidemia was defined as being present when the patient had a positive medical history of dyslipidemia, used statins, or had an elevated total cholesterol level of >4.9 mmol/L within a month before or after presentation at the outpatient dizziness centre, neurology or otorhinolaryngology department.

Assessment

MRI imaging was assessed by two neuroradiologists separately, LP and JK. The two radiologists involved in this study have multiple years of experience in examining MRI imaging of the head and neck. To limit observer bias, both radiologists were blinded for the patients' characteristics or study arm.

If there was a difference in Fazekas rating between the two raters, the following rules were applied. If the difference was 1 point, the highest score was then used. If the difference was 2 points or more, the radiologists reviewed the case together until consensus was reached.

Baseline characteristics, data from diagnostic tests and MRI ratings were gathered and de-identified in a Castor electronic database (CastorECD, Amsterdam, The Netherlands).

Rater reliability testing

Inter- and intra-rater reliability for the two radiologists was assessed for the Fazekas rating scale. All retrieved MRI scans were rated by both raters independently. Sample size calculation showed that thirty patients had to be rated twice by both raters to evaluate the intra-rater reliability. A weighted Cohen's kappa coefficient was calculated using linear weighting, where the difference between low and high ratings is of equal importance.

Statistical analysis

Continuous variables were described using the following summary descriptive statistics: number of non-missing values, mean and standard deviation in case of normally distributed data or median and interquartile ranges in case of non-normally distributed data.

Categorical variables were described using frequencies and percentages. Percentages were calculated on the number of non-missing observations.

95% confidence intervals were calculated when applicable. Statistical testing was performed two-sided at a 0.05 significance level.

Differences in the ordinal ranking of the Fazekas scale between the two cohorts were calculated using the Mann-Whitney U test for ordinal non-paired data. The presence of brain infarctions was compared between the cohorts using the Chi-square test.

A nonparametric independent ordered samples analysis, the Jonckheere Terpstra test, was performed to compare the mean hearing thresholds at presentation between the different Fazekas scores for each of the following frequencies; 500, 1000, 2000, 4000 and 8000Hz.

Ordinal logistic regression analysis was performed to compare the outcomes between the cohorts while adjusting for the potential confounders: the study cohort, age, gender, the MRI sequence used for assessment, the repetition time, the echo time, the Fletcher index

at presentation; the average hearing loss in the frequencies 1000, 2000 and 4000Hz, corticosteroid therapy and hearing improvement.

Results

A total of 118 patients with iSSNHL were included. The age and gender matched control cohort consisted of 79 (66.9%) patients suspected of trigeminal neuralgia and 39 (33.1%) patients suspected of vestibular paroxysmia.

Baseline characteristics of all patients are displayed in table 2. Both cohorts consisted of more men than women.

In the iSSNHL cohort, the high fletcher index, the average hearing loss in patients with iSSNHL over the frequencies 1000, 2000 and 4000Hz, was 70dB (±24dB). Hundred patients (84.7%) received corticosteroid therapy. The other patients either presented at the ENT department outside the therapeutic window for corticosteroid use or declined this therapy of their own accord. Hearing loss improved with at least 20% in 52 patients (44.1%) whereas in 66 patients (55.9%) the hearing threshold did not improve or even worsened over time.

Table 2.| Patient characteristics

	SSNHL (N=118)	Control (N=118)	Missing	P-value
Age (mean, (SD))	65 (9.3)	65 (9.0)	0	0.491
Gender		0	1.000	
Female	52	52		
Male	66	66		
History of myocardial infarction	13 (11.0)	7 (5.9)	0	0.242
Anticoagulant use	21 (17.8)	13 (11.0)	0	0.097
Smoking		34	0.850	
Yes	13 (13.7)	12 (11.2)		
Former	13 (13.7)	14 (13.1)		
No	69 (72.6)	81 (75.7)		
Hypertension	43 (38.4)	45 (38.5)	7	1.000
Hyperlipidemia	35 (33.3)	34 (29.1)	14	0.562
Diabetes	9 (7.8)	13 (11.0)	1	0.695
Atrial Fibrillation	8 (7.0)	2 (1.7)	3	0.057

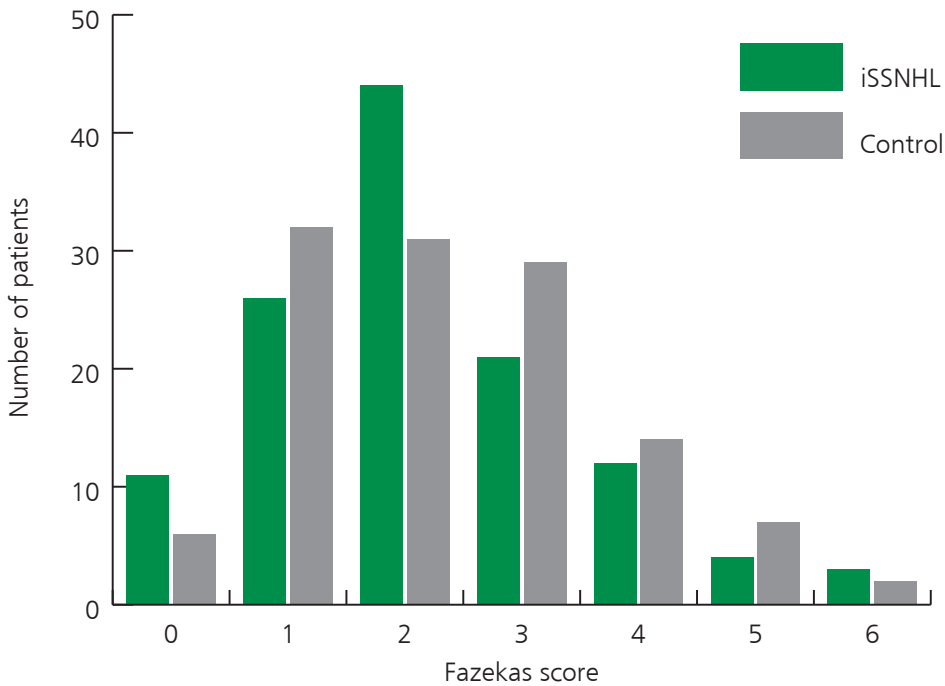
Patient characteristics of 118 patients experiencing SSNHL and a control cohort of 118 patients displayed in numbers and percentages. Percentages are calculated based on the number of non-missing values. For age, the mean and standard deviation are displayed. N: number, SD: standard deviation, SSNHL: sudden sensorineural hearing loss.

Rater-reliability

All retrieved MRI scans, before age and gender matching, were used for the rater-reliability testing. Three hundred and twenty-eight MRI scans were reviewed by both raters. In 201 cases both radiologists gave the same Fazekas score, in 103 cases they differed one point and in 24 cases the difference in score given was two points or more. This resulted in a kappa-coefficient of 0.74 for inter-rater reliability.

Thirty subjects were rated twice by each rater, which resulted in a weighted kappa-coefficient of 0.80 and 0.82 for rater 1 and 2 respectively, suggesting a near-perfect agreement for each rater.

Figure 2.| Distribution of Fazekas scores.



Fazekas score two was most frequently seen in the iSSNHL cohort compared to Fazekas score 1 in the control cohort. A Mann-Whitney U test resulted in a p-value of 0.968, demonstrating a nonsignificant difference in Fazekas score distribution.

Fazekas Score

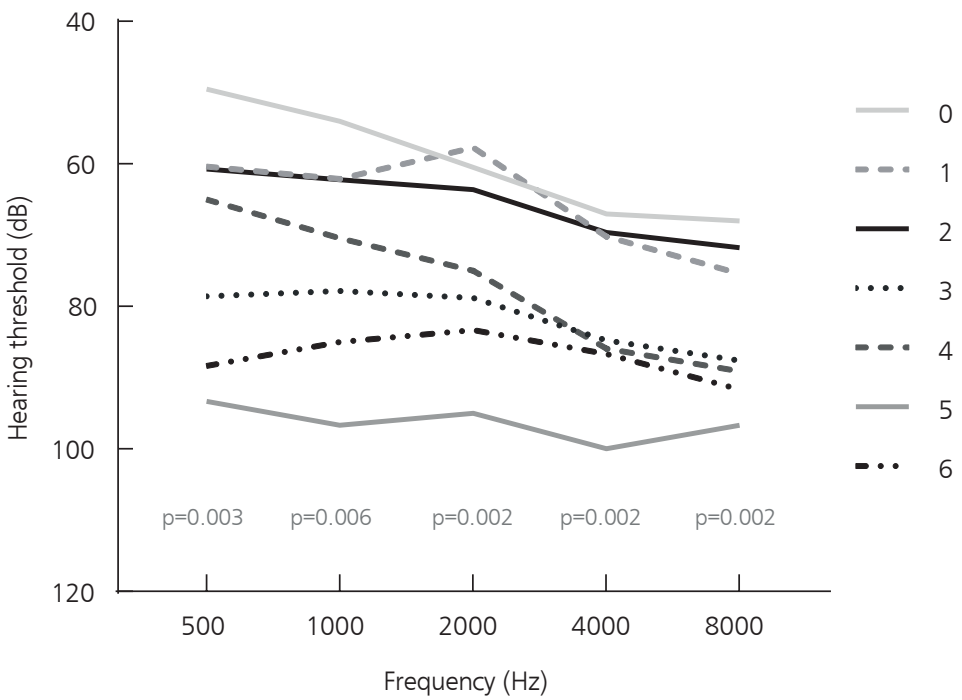
In the SSNHL cohort, Fazekas score 2 was most frequently seen on MRI compared to Fazekas score 1 in the control cohort, see figure 2. The distribution of the ordinal scale across both cohorts did not differ significantly. The sum of the Fazekas scores were 13925 and 14042, for iSSNHL and controls respectively (p=0.908).

Table 3.| Ordinal regression analysis

	Univariate			Multivariate		
	Odds	**Sig**	**95 %CI**	**Odds**	**Sig**	**95 %CI**
SSNHL	1.009	0.908	0.867-1,174			
Age	1.138	0.000	1.105-1.172	1.123	0.000	1.081-1.166
Gender	1.688	0.027	1.063-2.681	1.858	0.040	1.028-3.360
FLAIR Sequence	1.221	0.406	0.762-1.956			
Repetition time	1.000	0.776	1.000-1.000			
Echo time	0.996	0.670	0.976-1.016			
Fletcher_index	1.017	0.002	1.006-1.028	1.009	0.121	0.998-1.021
Corticosteroid use	1.849	0.184	0.746-4.584			
Hearing improvement	1.227	0.538	0.640-2.355			

Outcomes of the ordinal regression analysis. Estimated odds, its significance incl. lower and upper bound, of receiving a higher Fazekas score when having a one year older age, female gender, FLAIR sequence used in MRI assessment, a one point higher Repetition time, a one point higher echo time, the high Fletcher index at presentation, receiving corticosteroid use, hearing improvement compared to remaining hearing loss and the study arm. Sig: significance, FLAIR: Fluid Attenuated Inversion Recovery, SSNHL: Sudden Sensorineural Hearing Loss.

Figure 3.| Fazekas scores and mean hearing threshold in dB for each frequency



dB: decibel, Hz: Hertz. Outcomes of the Jonckheere Terpstra test for each frequency are displayed after p in the graft.

Brain infarctions

Brain infarctions were present in 8 (6.8%) patients with iSSNHL and in 13 (11.0%) patients from the control cohort. The difference between the two cohorts was not statistically significant (p=0.361). In both cohorts, the brain infarctions were most frequently located in the deep white matter.

Ordinal regression analysis

Table 3 displays the estimates of the odds ratio from the ordinal logistic regression analysis. The variables age, gender and the average hearing loss at presentation significantly increased the risk of receiving a higher Fazekas score. In the multivariate regression analysis, the variables age and female gender increased the risk of cerebral small vessel disease significantly.

When the hearing threshold was analysed within the iSSNHL cohort, we found a correlation of an increasing Fazekas score and a higher hearing threshold, measured in dB, see figure 3. A Jonckheere Terpstra test estimated this correlation to be statistically significant on all frequencies. This correlation is likely explained by the differences in age, since the significant correlation disappeared in the multivariate regression analysis. No correlation was found between the Fazekas score and hearing improvement.

Discussion

To investigate a possible correlation between cerebral small vessel disease and iSSNHL that could indicate a vascular involvement in the pathogenesis of acute hearing loss in elderly, we compared the degree of white matter hyperintensities and the presence of brain infarctions between two cohorts. We did not find a significant difference in Fazekas score or presence of brain infarctions in elderly patients with iSSNHL compared to controls.

The outcomes in this study are in contrast with previous literature that demonstrated an increased Fazekas score in elderly patients with iSSNHL[22,27]. So far, three studies investigated the association between iSSNHL and cerebral small vessel disease. Ciorba et al studied the presence of leukoaraiosis in 64 patients with iSSNHL using the Fazekas and Wahlund scale[28]. They did not find a difference in the degree of leukoaraiosis when compared to a control cohort[28]. However, patients with a higher Fazekas score did have a lower probability of complete hearing recovery. In contrast, Dicuonzo et al found significantly more white matter hyperintensities both in the deep white matter and periventricular white matter in patients with iSSNHL compared to controls. However, with only 36 subjects in the study sample, a reliable regression analysis could not be performed[27]. Fusconi et al found a significant correlation between iSSNHL and the Fazekas score among patients aged 48 up to 60 years old, this group only comprised 22% of the study population[29].

In the elderly population, the prevalence of CSVD ranges from 56% in patients aged 60 to 70 years, to 74% in 80 years and older[30]. This likely explains the relatively high median Fazekas score of 2 in our cohort compared to previous literature. We did not find a difference in distribution of Fazekas scores between both cohorts, nor did we find a correlation between the Fazekas score and the probability of hearing recovery. We did find a correlation between the Fazekas score and the hearing threshold at presentation, as did Ciorba et al, though this difference was caused by increasing age of the subjects[28].

Several authors have investigated the presence of cardiovascular risk factors in patients with iSSNHL. The association between iSSNHL and cardiovascular risk factors, however, remains controversial. In some studies elevated triglycerides and total cholesterol levels, as well as overweight, diabetes and a history of cardiovascular events have been associated with an increased prevalence of iSSNHL[31–34], while other authors found contradicting results[35]. In a recent meta-analysis, Simões et al. summarized that increased total cholesterol levels and hypertriglyceridemia are more frequently present in patients with iSSNHL compared to controls, while diabetes and hypertension are not[36]. There was, however, large heterogeneity between published studies resulting in a small number of studies used in the analysis[36]. We found higher prevalences of a medical history with myocardial infarction, anticoagulant use, smoking and hyperlipidaemia in the iSSNHL cohort than in the control cohort, but none of these differences was statistically significant.

Nevertheless, the hypothesis of vascular compromise in the onset of iSSNHL is biologically plausible. Sudden deafness resembles cardiovascular disease like myocardial infarction and stroke in acute and mostly unilateral presentation[1]. Also, the cochlea is supplied by a terminal artery without collateral circulation and would therefore be vulnerable to hypoxia[37].

It has been hypothesized that iSSNHL is either due to acute occlusion somewhere along the anterior inferior cerebellar artery and its peripheral branches or due to blood pressure dysregulation (BPD)[38].

Tange et al provided a theoretical diagram of the vestibulocochlear blood supply and proposed a classification of four types of vascular inner ear obstruction based upon the location of occlusion and its clinical presentation[37]. For example, the partition of the ramus cochlearis could lead to SSNHL in the frequencies 2000Hz and above without vertigo, since this artery is responsible for the supply of the lower part of the cochlea towards the basal turn[37]. Unfortunately, in clinical practice, this differentiation in presentation is difficult to establish.

The other hypothesis of vascular involvement in the onset of iSSNHL is BPD. BPD arises when, on the one hand, fibrous hyalinosis causes the tunica adventitia to thicken and lose fibromuscular cells resulting in a decreased adrenergic regulation, and on the other

hand the lumen of the vessel is decreased due to arteriosclerosis. BPD can thus cause permanent damage to nerve fibers[22].

When these hypotheses prove to be accurate, this could mean that patients with iSSNHL have a vascularly compromised brain. This might have serious consequences since CSVD is known to triple the risk of stroke[21,39]. Consequently, Lin et al were the first to report an increased risk of a cerebrovascular accident after experiencing iSSNHL[40]. Several other authors confirmed this increased risk, though all these studies were performed retrospectively[40–43]. Further prospective controlled analyses of cardiovascular risk factors, cerebrovascular damage and risk of stroke in patients with iSSNHL would be appropriate to assess whether our results are accurate and the possible association in elderly is negligible, or if there is indeed an association and elderly patients with iSSNHL should receive cardiovascular risk management including anticoagulants.

We have to address some limitations of this study. Most importantly, we did not perform a sample size calculation prior to this study. In the general population, Fazekas distributions are rarely described per age category. And if so, the difference in expected distribution for iSSNHL would remain completely arbitrary. Due to the ordinal character of the variable Fazekas score with 7 possible categories, slight changes in estimated Fazekas distribution could result in very large differences in sample size. Hence, we decided to evaluate the total number of patients we could retrieve from hospital records. A type II error is, therefore, a remote possibility. Consequently, the study is of an exploratory nature. A total population of 118 per study cohort is, however, in line with other similar studies.

Second, the MRI sequence that was used for assessment was non-uniform. Usually, an MRI cerebrum is performed in patients suspected of trigeminal neuralgia, while in the case of iSSNHL and vestibular paroxysmia an MRI of the cerebellopontine angle is performed with only a single sequence of the entire brain, either T2 or FLAIR. Also, per MRI protocol, the repetition time and echo time differs. In the regression analysis we demonstrated that the type of MRI sequence, the repetition time and echo time did not influence the assigned Fazekas score.

Finally, we did not include patients in whom hearing loss was accompanied by vertigo, since in our dizziness centre this combination of symptoms is diagnosed as labyrinthitis. In previous literature, patients experiencing combined hearing loss and vertigo have been included in the iSSNHL group. This is relevant, because combined hearing loss and vertigo has an increased risk of stroke compared to ISSNHL or vertigo alone[44].

In conclusion, we did not find an association between sudden sensorineural hearing loss and cerebral small vessel disease. We did find a higher prevalence of some cardiovascular risk factors in patients with iSSNHL compared to controls, though non-statistically significant. Further prospective controlled research with larger populations is needed to clarify the vascular involvement in the aetiology of iSSNHL.

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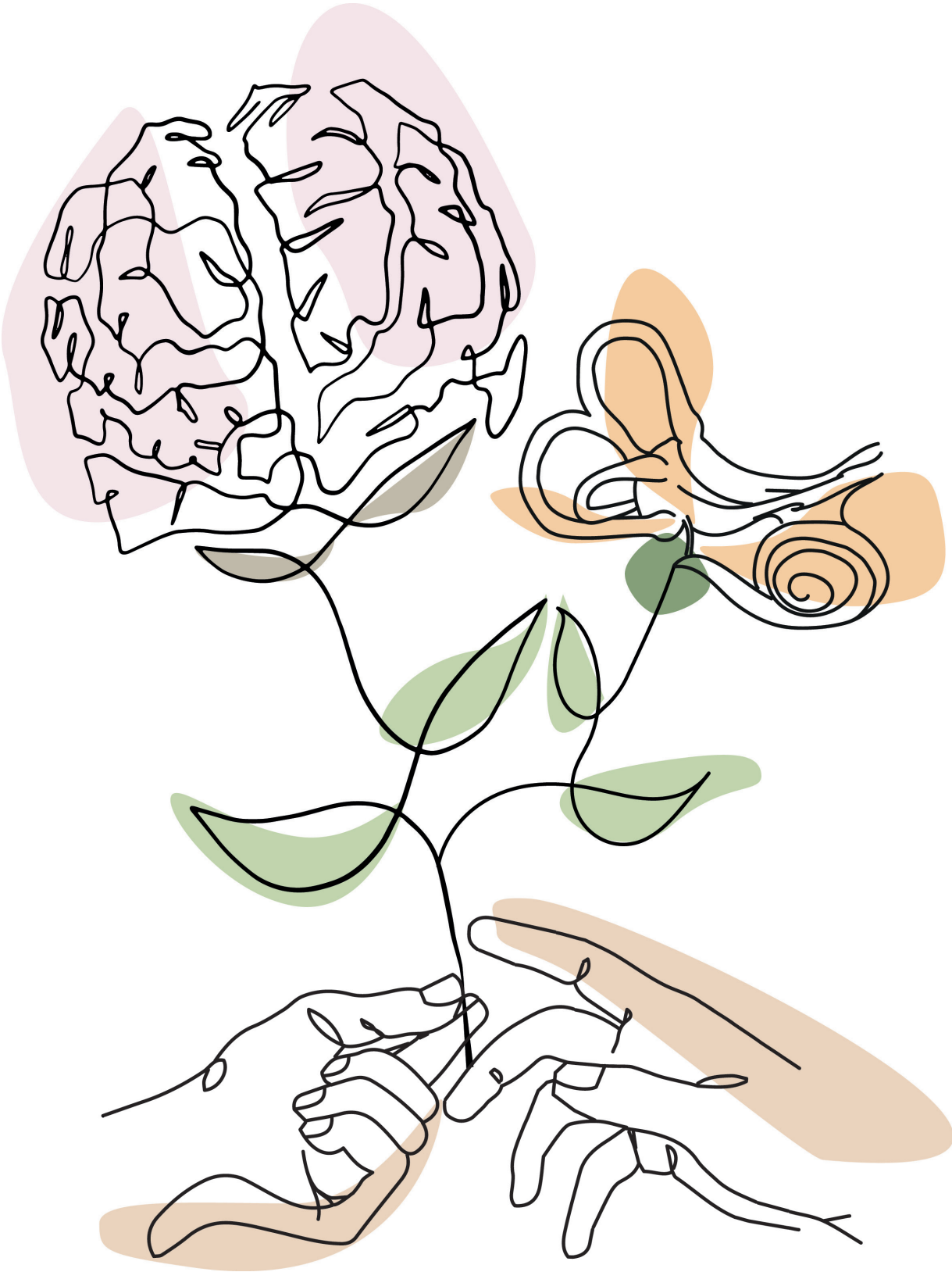

Chapter

5

Cerebral small vessel disease in elderly patients with Menière's disease

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Introduction

In 1861, the French physician Prosper Meniere first described the symptoms of a condition that would later be considered Menière's disease (MD)[1,2]. MD is a disease of the inner ear that causes sudden attacks of severe vertigo, progressive hearing loss, tinnitus, and the sensation of aural fullness[3]. At present, the pathophysiology of MD is still not unraveled. Endolymphatic hydrops (EH) is the histopathological hallmark of Menière's disease (MD), but the exact cause of this endolymphatic hydrops remains subject to debate.

Foster and Breeze launched the concept that MD results from a combination of hydrops with a variety of risk factors for cerebrovascular disease[4]. They hypothesized that 'endolymphatic hydrops acts as an intermittent Starling resistor to lower perfusion pressure in the inner ear, which is additive with other causes of lowered perfusion such as cerebrovascular disease'. This intermittent hypo- and hyper-perfusion of the brain would lead to transient ischemia and damage to nerve fibers[4].

The findings of Teggi et al. were in agreement with this hypothesis[5]. They studied the disease progression in a population of elderly MD patients and found that the frequency of vertigo episodes and Tumarkin attacks increases with age[5]. As age is the greatest contributor to cerebral small vessel disease, elderly patients would be especially prone to vascular involvement in the pathophysiology of MD[6].

If cardiovascular risk factors are more frequently present, it is reasonable to suspect that patients with MD exhibit more cerebral small vessel disease (CSVD) on magnetic resonance imaging (MRI) than the general population[7,8]. CSVD can be evaluated on MRI by white matter hyperintensities, brain infarctions, microbleeds, lacunes and dilated Virchow-Robin spaces[8-10].

In this study, we analyzed whether cerebral MRI imaging in elderly patients with MD exhibits more white matter hyperintensities and brain infarctions compared to a control cohort of patients suspected of trigeminal neuralgia or vestibular paroxysmia.

Materials and methods

This retrospective case-control study was performed with information extracted from hospital records of patients who visited the Apeldoorn Dizziness Centre (ADC) at Gelre Hospital in the city of Apeldoorn, The Netherlands. The ADC serves as a tertiary referral center that specializes in the diagnostic and therapeutic workup of dizziness. It is a multidisciplinary center involving the otorhinolaryngology, neurology, and clinical neurophysiology departments. This retrospective cohort study was approved by the institutional review board of Gelre Hospital.

Cohorts

The study cohort was formed with patients diagnosed with MD between January 2010 and March 2021 at the ADC, who received an MRI cerebrum to rule out the presence of an acoustic neuroma. According to the criteria developed by the Bárány Society and American Academy of Otolaryngology-Head and Neck Surgery (AAOHNS), patients were divided into a 'probable' and a 'definite' MD group[3]. In all patients with MD, the vestibular function was assessed by either a caloric test, a video head impulse test (video-HIT), or both.

The control cohort was compiled of patients who either visited the outpatient neurological department with facial pain, suspected of trigeminal neuralgia, or patients who visited the ADC with recurrent episodes of spontaneous vertigo lasting several seconds, suggestive of vestibular paroxysmia. These patients all received an MRI cerebrum to rule out the presence of an intracranial neoplasm and/or detect a neurovascular conflict. The control cohort was matched for gender and age with the MD cohort, with a maximum age difference between MD or control patients of 1 year.

Exclusion criteria were age 49 years or younger and a history of a cerebrovascular accident or transient ischemic attack. If during follow-up the type of dizziness changed and did not meet the aforementioned criteria of MD, these patients were excluded.

MRI protocol

An MRI was suitable for radiological assessment of white matter hyperintensities and brain infarctions if at least one sequence of the entire brain, either FLAIR or T2, was available. The cerebral sequence was depicted with a slice thickness of 5mm. The imaging was performed using a 1.5 Tesla MRI scanner. Thirty-five MRI scans were performed in local hospitals and details of the MRI scanners could therefore not be retrieved.

Outcomes

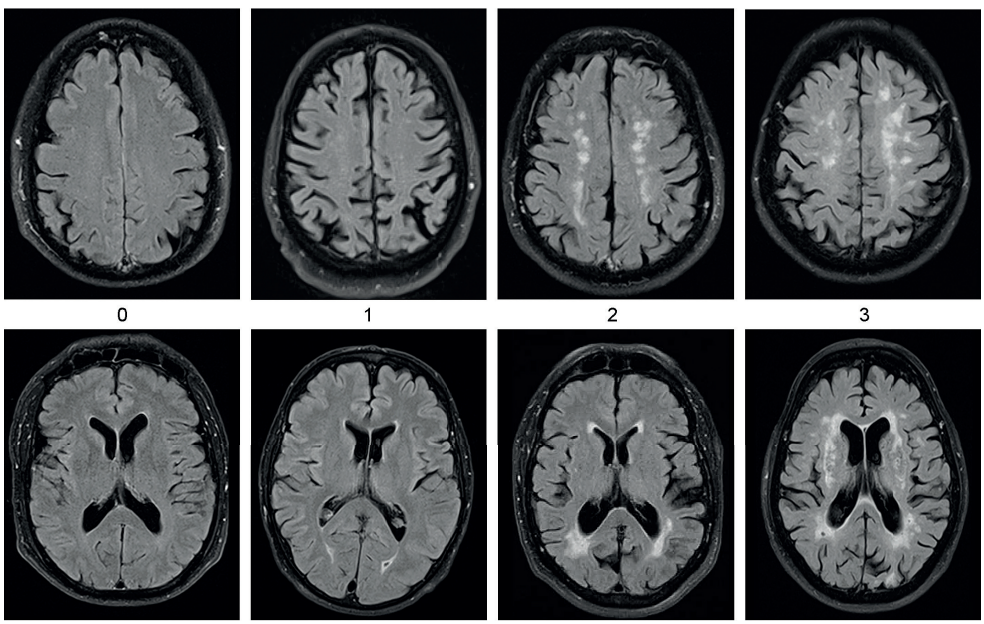
The presence of the following cardiovascular risk factors was identified from hospital records in all patients; smoking, hypertension, hyperlipidemia, diabetes, a history of myocardial infarction and atrial fibrillation. The criteria for hypertension were either having a medical history of physician-diagnosed hypertension or using antihypertensive drugs. The criteria for diabetes were having a medical history of physician diagnosed-diabetes or using antidiabetic drugs. In case no complete medical history could be obtained, the variable was defined as missing. Hyperlipidemia was defined as present when having a medical history of physician-diagnosed hyperlipidemia, when using statins, or having an elevated total cholesterol level of >4.9 mmol/L within a month before or after presentation at our dizziness centre.

The primary outcome was the degree of cerebral vascular damage assessed on MRI imaging by measuring the Fazekas score[9]. The Fazekas score is a validated diagnostic tool

for assessing the severity of white matter hyperintensities both periventricular and in the deep white matter. The total score is calculated by the sum of the degree of white matter hyperintensities in the periventricular white matter (PVWM) and the deep white matter (DWM). Total scores range form from 0 to 6, where 0 means no hyperintensities present, see figure 1.

The secondary outcome was the presence of brain infarctions on MRI imaging. Brain infarctions were defined by lesions of the brain of at least 3 mm with a cerebrospinal fluid appearance on T2 or FLAIR sequences and differentiable from leukoaraiosis and dilated Virchow-Robin spaces[11].

Figure 1.l. Fazekas scale for MRI imaging. The figure displays hyperintensities in the deep white matter (upper row) and periventricular (lower row)[30].



Deep white matter (DWM)	Periventricular white matter (PVWM)
0 = absent	0 = absent
1 = punctate foci	1 = “caps” or pencil-thin lining
2 = beginning confluence	2 = smooth “halo”
3 = large confluent areas	3 = irregular periventricular signal extending into the deep white matter

MRI assessment

MRI imaging was assessed by two radiologists separately, LP and JK. Both radiologists had multiple years of experience in examining MRI imaging of the head and neck. To limit observer bias, the radiologists were blinded to the patient’s study cohort and clinical characteristics. If there was a difference in Fazekas score between the two raters, the following rules were applied. If the inter-rater difference was 1 point, the highest score

was applied. If the difference was 2 points or more, the radiologists reviewed the case together until consensus was reached.

Baseline characteristics, data from diagnostic tests and MRI ratings were gathered, de-identified and entered into an electronic database (Castor EDC, Amsterdam, The Netherlands).

Rater reliability testing

Inter- and intra-rater reliability for the two radiologists was assessed for the Fazekas rating scale using 125 MRI imaging of patients who suffered from idiopathic sudden sensorineural hearing loss and 203 controls. All patients were rated by the same raters involved in the present study. Sample size calculation showed that thirty patients had to be rated twice by both raters to evaluate intra-rater reliability. A weighted Cohen's kappa coefficient was calculated using linear weighting, where the difference between low and high ratings is of equal importance.

Statistical analysis

Continuous variables were described using the following summary descriptive statistics: the number of non-missing values, mean and standard deviation in case of normally distributed data or median and interquartile range in case of non-normally distributed data. Categorical variables were described using frequencies and percentages.

Statistical testing was performed two-sided at a 0.05 significance level. Differences in the ordinal ranking of the Fazekas scale between the two cohorts were tested using the Mann-Whitney U test for ordinal non-paired data. The difference in the number of brain infarctions between the cohorts was compared using the Chi-square test.

An ordinal logistic regression analysis was performed to compare the primary outcome between both cohorts while adjusting for the potential confounders; gender, age and the MRI sequence used. To investigate variables within the MD cohort that might influence the Fazekas score, we performed an ordinal regression analysis where we entered age, either a definite or probable MD diagnosis according to the Bárány criteria, the degree of hearing loss upon diagnosis measured by the high Fletcher index, a vestibular canal paresis defined by an asymmetry in the vestibular function of >20 degrees measured by caloric testing or gain < 0.6 measured with video-HIT, and the duration of symptoms before presentation. Ordinal regression analysis was performed using SPSS version 25. The models used for multivariate analysis were based on forward elimination with a 0.05 significance level.

Results

Patient characteristics

A total of 111 patients with MD were included. The control cohort consisted of 74 patients suspected of trigeminal neuralgia and 37 suspected of vestibular paroxysmia. Patient characteristics are displayed in table 1. All patients included in the MD cohort had asymmetrical sensorineural hearing loss, but not all patients met the criteria for 'definite MD' and were therefore classified as having 'probable' MD. One patient had bilateral MD. In the MD cohort, the average duration of symptoms at the time of diagnostic imaging was 5 years (95%CI 3.4-6.7), with 78 patients having symptoms for over 1 year (70.3%). Sixty-two patients with MD had a caloric weakness. In only one patient with MD the video-HIT was also abnormal. Most patients with MD received a T2 scan of the cerebrum, only 26 out of 111 MRI's were assessed using a FLAIR sequence. In the control cohort 50 out of 111 MRI's were assessed using a FLAIR sequence.

Table 1.| Patient characteristics

	MD (n=111)	Control (n=111)	Missing	P-value
Bárány society criteria (%)				
Definite	84 (75.7)			
Probable	27 (24.3)			
Age (mean, (SD))	64 (9.4)	64 (9.5)	0	0.423
Gender (%)			0	1.000
Male	50 (45.0)	50 (45.0)		
Female	61 (55.0)	61 (55.0)		
Smoking (%)			27	0.027
Non	74 (77.9)	70 (70.0)		
Former	3 (3.2)	14 (14.0)		
Current	18 (18.9)	16 (16.0)		
History of MI (%)	8 (7.2)	5 (4.5)	0	0.569
Hypertension (%)	31 (29.0)	48 (43.6)	5	0.034
Hyperlipidemia (%)	22 (22.2)	30 (27.3)	13	0.427
Diabetes (%)	7 (6.4)	14 (12.6)	1	0.168
Atrial Fibrillation (%)	5 (4.5)	2 (1.8)	1	0.280
Anticoagulant use (%)	20 (18.0)	11 (9.9)	0	0.120

Patient characteristics of 111 patients diagnosed with MD and the control cohort of 111 patients, displayed in numbers and percentages. The missing cases are the total of missing cases in both cohorts combined. For age, the mean and standard deviation are displayed. n: number, SD: standard deviation, MD: Meniere's disease, MI: Myocardial infarction.

The prevalence of smoking was only slightly higher in patients with MD, whereas significantly more patients in the control cohort were former smokers (p=0.027). Hypertension was more frequently present in the control cohort.

Rater reliability testing (results based on a previously investigated cohort)

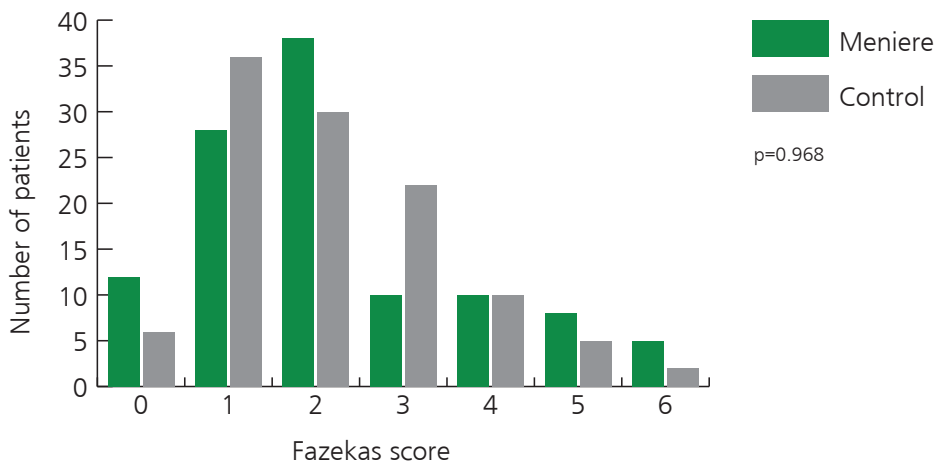
A total of 328 MRI scans were reviewed by both raters. In 201 cases both radiologists gave the same Fazekas score, the score differed by one point in 103 cases and by 2 or more points in 24 cases. This resulted in a kappa-coefficient of 0.74, suggesting a substantial inter-rater reliability.

Thirty subjects were rated twice by each rater, which resulted in a weighted kappa-coefficient of 0.80 and 0.82 for rater 1 and 2 respectively, suggesting an excellent intra-rater agreement for both raters.

Fazekas score

Most patients with MD received a Fazekas score of 2 (34.2%), while Fazekas 1 was most frequently present in the control cohort (32.4%). The differences in the distribution of the Fazekas scores in the two cohorts, taking an ordinal ranking into account, were not statistically different (p=0.968), see figure 2. When we analyzed the Fazekas scores for PWM and DWM separately, the distribution between both cohorts was not statistically different either, p=0.972 and p=0.958 for PWM and DWM respectively.

Figure 2.| Distribution of Fazekas scores.



The distribution of Fazekas score among patients with MD and controls. A Mann-Whitney U test was performed to compare the differences in the ordinal variable Fazekas score between both cohorts which demonstrated a nonsignificant result (P = 0.968).

The univariate ordinal logistic regression model demonstrates that MD did not influence the Fazekas score (i.e., odds ratio (OR) = 0.967 (95%CI 0.605-1.546) for MD patients relative to control patients). In the multivariate analysis, both age and the MRI sequence used for assessment were associated with the Fazekas score, but the MD was not. Within the cohort of MD patients, age and a disease duration of over 1 year at the time of imaging were associated with a higher Fazekas score in the multivariate analysis, see table 2.

Table 2.|. Results of ordinal logistic regression analysis

Variables	Univariate			Multivariate		
	Odds ratio	**p-value**	**95% CI**	**Odds ratio**	**p-value**	**95% CI**
a Meniere cohort	0.967	0.889	0.605-1.546	1.137	0.607	0.697-1.853
Age	1.109	<0.001	1.078-1.140	1.108	<0.001	1.077-1.140
Gender (female)	1.376	0.196	0.851-2.195			
FLAIR sequence	2.128	0.003	1.288-3.518	2.163	0.004	1.285-3.641
b Age	1.058	<0.001	1.044-1.127	1.092	<0.001	1.050-1.136
Definite MD	1.355	0.443	0.624-2.941			
Abnormal caloric testing	0.696	0.166	0.417-1.162			
Fletcher index	1.013	0.099	0.998-1.028			
Duration of symptoms[#]	2.384	0.023	1.130-5.029	2.879	0.006	1.345-6.162

CI: Confidence Interval, FLAIR: Fluid-attenuated inversion recovery, Sig: significance, MD: Meniere's disease.

a. Outcomes of the univariate (left) and multivariate (right) ordinal regression analysis including all 222 patients. Estimated odds ratio, its significance and 95%CI, of receiving a higher Fazekas score when having female gender, MRI sequence used and the study arm. The reference of interpretation of the odds for the Meniere cohort was the control cohort.
b. Outcomes of a second univariate ordinal regression analysis including only MD patients to evaluate the influence of abnormal caloric testing, the Fletcher index, probable vs definite MD disease and the duration of symptoms on the Fazekas score within MD patients. The reference for interpretation of the odds for the Fletcher index is a 1-point higher Fletcher index. [#]Duration of symptoms is a binary variable with symptoms existing either shorter or longer than one year, the reference in the regression analysis is symptoms shorter than one year.

Brain infarctions

Brain infarctions were present in 8 patients (7.2%) in the MD cohort and 14 (12.6%) in the control cohort. This difference was not statistically significant (p=0.261).

Discussion

To date, the exact pathophysiology of MD is not clarified. As a consequence, treatment options are limited and often non-superior to the natural disease progression[4,12]. Although a vascular cause has been suspected in certain cases of MD, neither the degree of white matter hyperintensities nor the presence of brain infarctions differed between elderly patients with MD and controls in this study.

In 2013, Foster and Breeze presented a hypothesis of hypoperfusion induced ischemia as the pathophysiological mechanism of MD. They proposed that a Meniere's attack is caused by three interacting factors. First, pre-existing hydrops is necessary, but not sufficient by itself, to cause an attack[4]. This is emphasized by the fact that endolymphatic hydrops is present in all patients with MD, but can also be radiologically diagnosed in up to 31% of the healthy population[13].

Second, inner ear pressure fluctuates heavier in patients with MD than in the healthy population in response to changes in atmospheric pressure, head position etcetera. Since cerebral perfusion pressure is determined by arterial pressure, intracerebral fluid pressure and venous outflow resistance, disturbances in one of these factors can cause hydrops. This hydrops in turn causes intermittent hypo- and hyperperfusion of the vasculature of the ear when the volume capacity is exceeded[4].

Third, the arterial blood supply to the labyrinth is provided by the arteria labyrinthi, while the endolymphatic sac is believed to be supplied by a branch of the external carotid artery[14]. There is little collateral circulation, hence the cochlea and vestibule are vulnerable to ischemia by hypoperfusion.

Foster further hypothesizes that "in young individuals, with normal vasculature and normal oxygen levels, the highest pressure reached in the hydropic ear does not exceed the critical perfusion pressure for the tissues and is therefore not sufficient to cause ischaemia"[4]. The cardiovascular comorbidity in elderly makes them more prone to hypoperfusion-induced ischemia in comparison with young individuals, due to their reduced arterial pressure[4]. Foster advocated screening all patients with MD for cardiovascular risk factors and modifying their treatments accordingly[15]. So far, the hypothesis proposed by Foster and Breeze is not supported by clinical research.

In recent years, hypoperfusion and ischaemia has also been suspected to cause sudden deafness. A recent meta-analysis demonstrated a higher risk of stroke in patients who had experienced sudden deafness compared to healthy controls[16]. Also, cardiovascular risk factors were more common in patients with sudden deafness than in the general population[17,18]. The recurring nature of the vertigo spells in MD differs from the hearing loss in sudden deafness, which has a very low recurrence rate[19]. One would expect that, if ischemia in excitatory fibers within the labyrinth causes endolymphatic hydrops, this would be irreversible and result in persistent vestibular loss of function. Persistent

vestibular loss, however, does not occur in all patients and the course of the vestibular function does not correlate with the subjective severity of vertigo attacks[20].

To investigate the plausibility of ischemia in the pathophysiology of MD, one can analyze the correlation between cardiovascular disease and MD. Fazekas et al. and Wardlaw et al. have demonstrated that the cardiovascular risk factors hypertension, hyperlipidemia, age and cardiovascular comorbidity like myocardial infarction, raise the risk of developing stroke[8-10,21,22.] These cardiovascular risk factors are responsible for cerebral small vessel disease, visible on MRI as white matter hyperintensities, microbleeds, silent brain infarctions, and lacunes[22]. Our study is the first to evaluate the presence of white matter hyperintensities in an MD population. We did not find a difference in the degree of CSVD between patients with MD and controls. Therefore, our results do not support the hypothesis of Foster and Breeze[4]. According to this hypothesis, one would suspect that Meniere attacks to be caused by hypoperfusion-induced ischemia in elderly patients with cardiovascular comorbidity. It is likely that this ischemia would not be limited to the vestibule and cochlea, but would also affect other vulnerable areas of the brain with little collateral vascular supply, which should be visible on MRI by the previously mentioned characteristics.

In the present study, none of the cardiovascular risk factors were more frequently present in the MD cohort. However, due to the retrospective design of this study, the prevalence rates of the cardiovascular risk factors are not entirely reliable. So far, Rego et al. were the only ones investigating cardiovascular comorbidity in patients with MD and its association with the course of the disease[23]. They found a statistically significant association between the occurrence of Meniere's disease attacks and cardiovascular risk factors, with 74% of the population having at least one risk factor. This result, however, was based upon a small study population consisting of only 31 patients, without comparison with a control cohort[23].

In agreement with existing literature, Kim et al. recently demonstrated an increased risk of migraine in patients with MD and vice versa[24]. Kim et al. also reviewed the incidence of several cardiovascular risk factors in patients with MD, migraine and controls. Overall, controls had a higher systolic and diastolic blood pressure, higher blood glucose levels and were more frequently smokers than patients with MD or migraine[24]. This non-elevated cardiovascular risk does not correspond with the theory suggested by Foster and Breeze.

Nonetheless, our results do not rule out the possibility of vascular involvement in the pathophysiology of MD through another mechanism. Sarna et al suggested that, in addition to their shared epidemiological association[25], migraine and MD may have a similar pathophysiological mechanism. Spreading cortical depression is believed to result in a release of vasoactive neurotransmitters like calcitonin gene related peptide and substance P from the trigeminal nerve ganglion, causing vasodilatation, increased vascular permeability and extravasation of plasma[25]. This process is believed to be responsible for migraine headaches. Likewise, innervation of the cochlear vasculature by the trigeminal

nerve stimulation has been described to cause extravasation of fluid in the cochlea[26]. This mechanism could theoretically cause endolymphatic hydrops. The effect of agents blocking the receptors of these vasoactive neurotransmitters and their effect on migraine headaches and generalized cardiovascular disease is currently being investigated[27].

Our study has several limitations due to its retrospective design. First and most importantly, the control cohort was compiled of patients who had an indication for an MRI of the brain, which was to detect a neurovascular conflict of the fifth or eighth cranial nerve. These patients, therefore, cannot entirely be considered healthy controls and might have more cardiovascular comorbidity than healthy subjects. It is unlikely, however, that healthy subjects would have a lower Fazekas score than our control cohort, since a mean Fazekas score of 1 has been previously documented in healthy elderly in a similar age category[28,29].

Second, several assumptions were made in the recording of cardiovascular risk factors as described in the methods section and the actual presence of these risk factors in the MD patients and controls is, therefore, not entirely reliable. Also, the duration of disease in patients with MD had a significant range. However, we did not find a correlation between the duration of disease and Fazekas score.

Third, the MRI sequence that was used for assessment was non-uniform. Usually, an MRI cerebrum is performed in patients suspected of trigeminal neuralgia, while in the case of MD an MRI of the cerebellopontine angle is performed with only a single sequence of the entire brain, either T2 or FLAIR. In the regression analysis, we did see that the FLAIR sequence correlated significantly to a higher Fazekas score. This might have biased our results, since the MRI scans of patients with MD were less frequently assessed using a FLAIR sequence compared to controls. Nevertheless, when we entered the sequence in the multivariate analysis the odds did not change.

In conclusion, cerebral small vessel disease and cardiovascular risk factors were not observed more frequently in patients with MD than in matched controls. This result does not support the hypothesis of hypoperfusion induced ischemia in the pathophysiology of MD in elderly patients.

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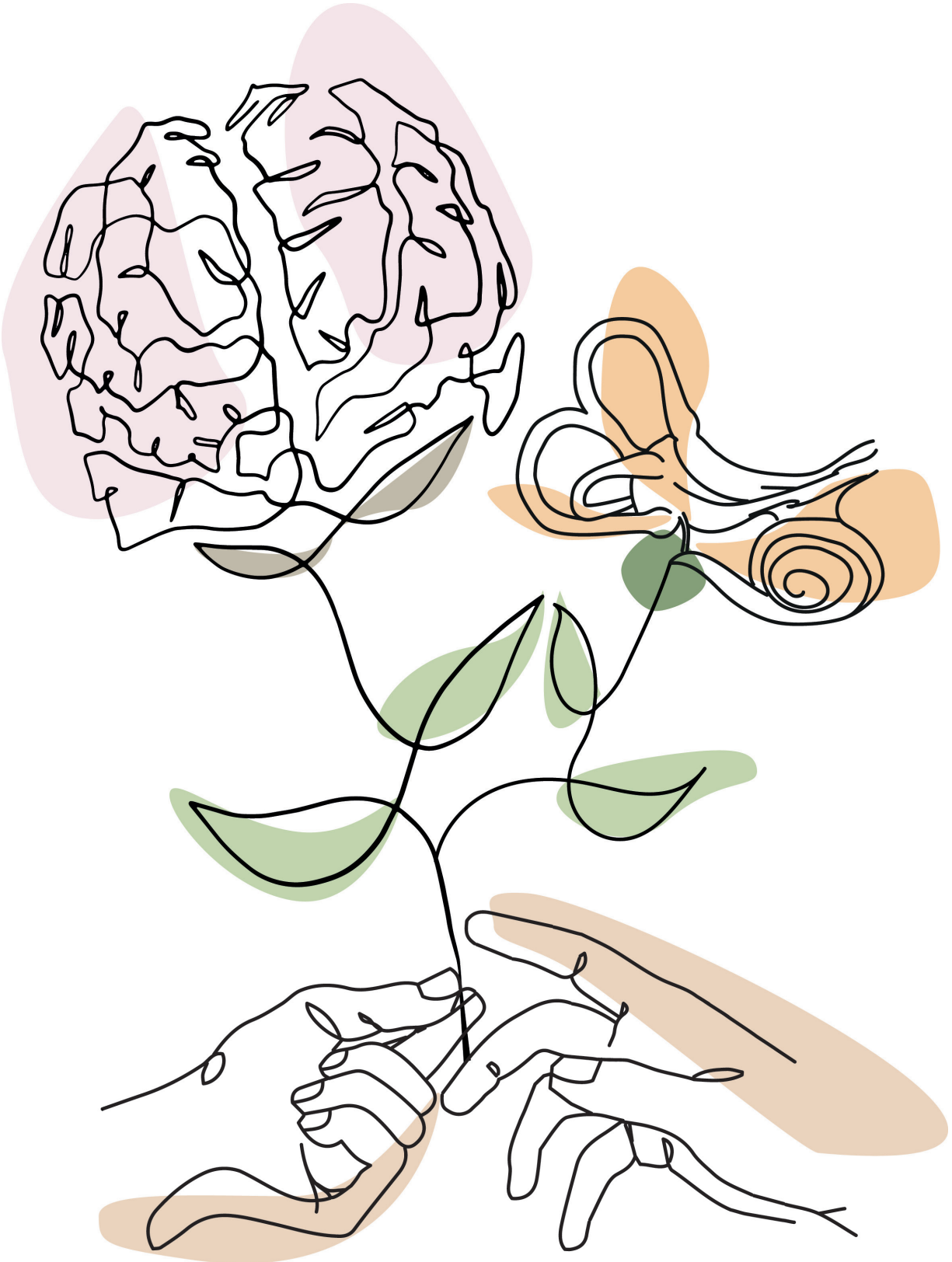

Chapter

6

Assessing risk of stroke after idiopathic sudden sensorineural hearing loss using data from general practice

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Introduction

The exact cause of sudden sensorineural hearing loss (SSNHL) remains unknown in a significant number of cases. Suspected causes for SSNHL include infectious diseases, particularly of viral origin, auto-immune disease, vascular insufficiency, or neoplasms. The current therapy with high dose corticosteroids is based on the assumption that sudden deafness is caused by inflammation secondary to viral infection. However, the clinical benefit of this therapy remains questionable, with hearing recovery reported in only 30-50% of cases[1].

In 2008, Lin et al. proposed vascular involvement in the pathophysiology of acute hearing loss[2]. They observed a higher risk of stroke following sudden sensorineural hearing loss compared to a control group. Various other researchers have reported higher incidence rates of a cerebrovascular accident (CVA) in patients who experienced SSNHL compared to the general population[3–7]. These authors hypothesized that acute hearing loss may serve as a prodrome to a CVA, potentially warranting targeted therapy with anticoagulants[3–7].

One of the primary concerns with this hypothesis is that available literature relies on data sources from non-medical organizations, such as health insurance databases[6,8]. This may introduce inclusion bias, wherein patients with sensorineural hearing loss who did not meet the global criteria could still be assigned the administrative billing code for SSNHL because it appeared to be the most appropriate choice. Also, when utilizing these databases, the available information regarding cardiovascular comorbidity and risk factors, its treatments, and their duration is limited. Consequently, establishing associations between cardiovascular involvement in SSNHL and the preventive impact of appropriate therapy is challenging.

The objectives of this retrospective study were to analyze cardiovascular comorbidity and cardiovascular risk factors at the time of an idiopathic SSNHL event, and to assess the subsequent risk of a CVA in these patients. We accomplished this using data extracted from electronic health records from general practices in the Netherlands.

Methods

Study population

This is a retrospective matched case-control study based on de-identified electronic health records from the Radboud University Medical Center primary care database, which contains data from 84 general practices in the Netherlands. Health records spanning from January 1st 2011 until December 31st 2021 were analyzed. Cases included individuals of 18 years or older who experienced an episode of idiopathic SSNHL (iSSNHL) within this study period. Cases were compared to a control cohort without iSSNHL. Subjects with a documented medical history of SSNHL before the start of the study date were excluded.

The diagnosis of iSSNHL was established by using ICD-10 codes (International Classification of Diseases) as well as ICPC-1 codes (International Classification of Primary Care). In the ICD-10 system, sudden hearing loss is defined by the code H91.2. As the ICPC coding system lacks a specific code for sudden hearing loss, cases were identified using their episode title, the presence of an ear related issue marked with "H", and through manual searching free text fields. The latter could include descriptions entered by the GPs such as "sudden hearing loss", "sudden deafness", or equivalent synonyms.

Controls were randomly selected from the same primary care database and were matched to cases based on age, sex, general practice, and a similar registration year at the GP practice, with a matching ratio of 1 iSSNHL case to 4 controls.

Outcomes

The primary outcome was the difference in incidence of a CVA or a transient ischemic attack (TIA) within a 5-year follow-up period between the patients with iSSNHL and the controls. A secondary outcome was the prevalence of cardiovascular comorbidity between patients with iSSNHL and controls. Information on the following cardiovascular comorbidities and their corresponding ICPC codes was gathered from the general practice health records: arterial aneurysm (K99.01), atrial fibrillation (K78), CVA (K90), congestive heart failure (K77), hypertension (K74-K87), ischemic heart disease (K74-K76), lipid spectrum disorders (T93), peripheral occlusive arterial disease (PAOD) (K91, K92), thrombosis (K93, K94.01) and TIA (K89).

Other secondary outcomes were differences between iSSNHL cases and controls in terms of cardiovascular risk factors: smoking (P17), diabetes mellitus (T90), Body Mass Index (BMI), systolic and diastolic blood pressure, and laboratory results for fasting glucose, glycated hemoglobin (HbA1c), low-density lipoprotein (LDL) cholesterol, non-high-density lipoprotein (HDL) cholesterol and triglycerides. These data were extracted from the nearest available visit or measurements within a specified time interval before or after the iSSNHL episode data or (for the matched controls) the selected control date. The maximum interval between disease onset and the measurement or lab results we allowed was defined in accordance with the Dutch guideline for cardiovascular risk management[9]. Final secondary outcomes were differences in therapy administered for the treatment of cardiovascular comorbidity and cardiovascular risk factors. These were investigated using ATC codes (Anatomical Therapeutic Chemical Classification System) for various drug therapies: antidiabetics (A10), antihypertensives (C02), diuretics (C03), beta0blocking agents (C07), calcium channel blockers (C08), agents acting on the renin-angiotensin system (C09), lipid modifying agents (C10), and organic nitrates (C01DA).

Statistical analysis

Categorical variables are displayed as numbers and percentages, while continuous variables are reported as means and standard deviations (SD) for normally distributed data

or as median and interquartile ranges (IQR) for skewed data. Population characteristics and the presence of cardiovascular comorbidity and risk factors and their therapies were compared between cases and controls using Chi-squared tests for categorical variables and independent sample t-tests for continuous variables.

The incidence of CVA events alone and of CVA or TIA events combined was analyzed using Cox proportional hazard regression analysis. Initially a univariable Cox model was used with a 5-year follow-up period. If patients did not complete the full five-year follow-up, they were censored on the time of death or departure from the general practice. A multivariable Cox model was subsequently used to analyze the difference between both groups while accounting for potential confounding variables (i.e., cardiovascular comorbidity and cardiovascular risk factors). Finally, to specifically address the effect of age, the study population was divided into two subgroups: subjects aged 60 years and older and subjects younger than 60, respectively. The cut-off value for older age was set on 60 years as this was the median age in the entire cohort. In a separate Cox model an interaction term (age subgroup * iSSNHL) was entered to assess potential effect modification of the risk of CVA or TIA due to iSSNHL by (older) age. Results of all Cox models are presented as hazard ratios (HR) with 95% confidence intervals (CI).

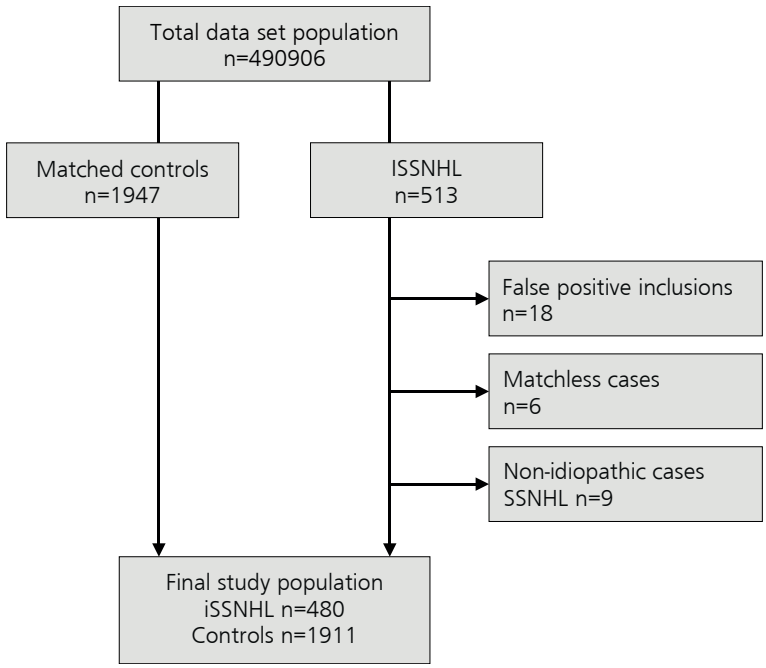
The data were analyzed using SPSS (IBM Corp. Released 2019. IBM SPSS Statistics for Windows, Version 27.0. Armonk, NY: IBM CorpS). A significance level of two-tailed P values <0.05 was used to define statistical significance.

Results

Selection of iSSNHL cases and controls

A total of 513 sudden deafness cases were identified. Among these, 18 cases had received an unjust positive diagnosis of SSNHL, as became clear from the free text fields. Additionally, nine cases were excluded as they were non-idiopathic cases of SSNHL. This resulted in 480 iSSNHL cases that could be matched to controls. For 9 of these iSSNHL cases only three (instead of the intended four) suitable controls could be identified, while all other cases were matched with 4 controls each. This resulted in a total of 1,911 controls. Figure 1 illustrates the selection process.

Figure 1.| Selection of cases and matched controls.



The figure illustrates the inclusion process of 480 eligible cases with idiopathic sudden sensorineural hearing loss and 1,911 matched controls from a total of 490,906 subjects in the primary care database containing coded health record data from 84 general practices in the Nijmegen region, the Netherlands.

iSSNHL=idiopathic sudden sensorineural hearing loss

Baseline characteristics

Table 1 provides an overview of the patient characteristics, cardiovascular comorbidity and cardiovascular risk factors for the iSSNHL cases and controls. Atrial fibrillation was the only cardiovascular comorbidity that appeared significantly more prevalent in the iSSNHL cohort than in the control cohort (P=0.037). Angina pectoris, congestive heart failure, diabetes, hypertension, obesity, PAOD, thrombosis and history of a CVA were more frequently seen in patients experiencing iSSNHL, but these apparent differences in prevalence did not reach statistical significance. Importantly, table 1 also shows the substantial amount of missing data for the cardiovascular risk factors in both cohorts.

Table 1 | Patient characteristics, cardiovascular comorbidity and cardiovascular risk factors of patients with idiopathic sudden sensorineural hearing loss and matched controls. Figures are n (%) unless stated otherwise.

	iSSNHL (n=480)	Controls (n=1,911)	P-value
Demographic characteristics			
Age (SD)	59.1 (14.3)	59.0 (14.2)	0.846
Sex, n (%) males	268 (55.8)	(55.6)	0.959
Cardiovascular comorbidity			
Aneurysm [a]	4 (0.8)	19 (1.0)	1.00
Angina pectoris	24 (5)	82 (4.3)	0.535
Atrial fibrillation	28 (5.8)	69 (3.6)	0.037
Congestive heart failure	11 (2.3)	28 (1.5)	0.225
schemic heart disease [j]	29 (6.0)	130 (6.8)	0.609
PAOD [b k]	33 (6.9)	109 (5.7)	0.332
Thrombosis [m]	10 (2.0)	29 (1.9)	0.312
TIAn [o]	11 (2.3)	62 (3.2)	0.372
CVAn [o]	18 (3.8)	56 (2.9)	0.376
Cardiovascular risk factors			
BMI [i] (kg/m^2)			0.752
< 24.9	72 (45.0)	265 (45.3)	
25 – 29.9	43 (26.8)	162 (27.6)	
30 – 39.9	42 (26.2)	155 (26.5)	
> 39.9	3 (1.9)	9 (1.5)	
Number of missings	320	326	
Smoking [b l]	36 (7.5)	162 (8.5)	0.518
Number of missings	444	1,749	
Diabetes Mellitus [b c]	46 (9.6)	168 (8.8)	0.592
Mean venous glucose [d] (mean (SD) mmol/l)	6.0 (1.4)	6.1 (1.5)	0.522
Number of missings	356 (74.2)	1483 (77.6)	
Mean HbA1c [e] (mean (SD) mmol/mol)	50.1 (12.1)	50.0 (13.2)	0.959
Number of missings	440 (90.7)	1732 (90.6)	
Dyslipidemia [b f]	59 (12.3)	239 (12.5)	0.939
LDL cholesterol [g] (mean (SD) mmol/l)	3.24 (1.0)	3.13 (1.0)	0.116
Number of missings	156 (32.5)	687 (35.9)	
Non-HDL cholesterol [g] (mean (SD) mmol/l)	3.7 (1.1)	3.8 (1.1)	0.343
Number of missings	438 (91.3)	1732 (90.6)	
Triglycerides [g] (mean (SD) mmol/l)	1.4 (0.8)	1.6 (0.9)	0.051
Number of missings	223 (46.5)	939 (49.1)	
Hypertension [b h]	148 (30.8)	531 (27.8)	0.193
Mean systolic blood pressure [i] (mean (SD) mmHg)	139 (18.1)	137 (18.8)	0.138
Mean diastolic blood pressure [i] (mean (SD) mmHg)	80 (10.1)	79 (10.7)	0.239
Number of missings	276 (57.5)	1214 (63.5)	

BMI=body mass index, CVA=cerebrovascular accident, HbA1c= hemoglobin A1c, HDL=high-density lipoprotein, iSSNHL=idiopathic sudden sensorineural hearing loss, LDL=low-density lipoprotein, PAOD=peripheral arterial occlusive disease, SD=standard deviation, TIA=transient ischemic attack

a = Fisher exact test for difference in aneurysm prevalence
b = Based on notifications in patients' health records
c = Diabetes mellitus type 1 and type 2
d = Measured within half a year interval (180 days) before or after episode of ISSNHL or control date
e = Measured within two-thirds years interval (210 days) before or after episode of ISSNHL or control date
f = Dyslipidaemia includes fat metabolism disorder(s), hypercholesterolemia, hypertriglyceridemia, mixed hyperlipidaemia, and familial hypercholesterolemia
g = Measured within one-and-a-half-years interval (731 days) before or after episode of ISSNHL or control date
h = Hypertension includes increased blood pressure, essential hypertension without organ damage, and hypertension with organ damage/secondary hypertension
i = Measured within one year interval (365 days) before or after episode of ISSNHL or control date
j = Ischemic heart disease includes acute myocardial infarction, other/chronic ischemic heart disease, coronary artery sclerosis, previous myocardial infarction (> 4 weeks ago)
k = Peripheral Arterial Occlusive Disease includes atherosclerosis, intermittent claudication, Raynaud's syndrome, Buerger's disease, and other disease(s) peripheral arteries
l = Former and current smokers
m = Thrombosis includes deep vein thrombosis and lung embolism
n = TIAs and CVAs up to the ISSNHL or control date
o = CVA includes subarachnoid haemorrhage, intracerebral haemorrhage, and cerebral infarction

Table 2 | Treatment of cardiovascular comorbidity and cardiovascular risk factors

	iSSNHL (n=480)	Controls (n=1,911)	P-value
No medication use, n (%)	217 (45.2)	984 (51.5)	0.016
Medication use, n (%)	263 (44.8)	927 (48.5)	
Antidiabetics	40 (8.33)	160 (8.4)	1.000
Antihypertensives	**15 (3.1)**	**23 (1.2)**	**0.006**
Diuretics	113(23.5)	419 (21.9)	0.425
Beta-blocking agents	**153 (31.9)**	**508 (26.6)**	**0.022**
Calcium channel blockers	91 (19.0)	326 (17.1)	0.313
Agents acting on renin angiotensin system	137 (28.5)	565 (29.6)	0.695
Lipid modifying agents	164 (34.2)	600 (31.4)	0.250
Organic nitrates	44 (9.2)	174 (9.1)	0.929

Medication use to treat cardiovascular risk factors. Statistically significant associations are marked bold. n=number.

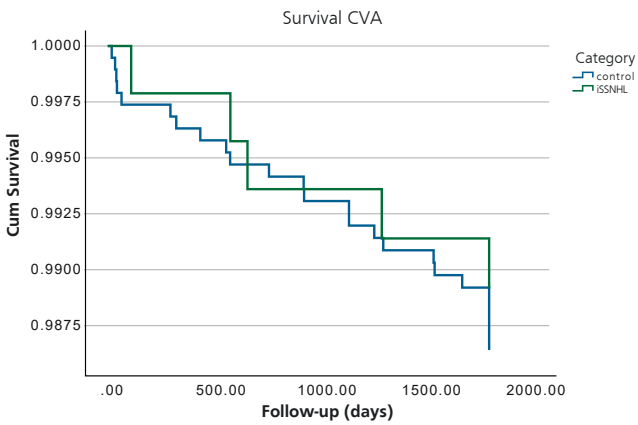
Table 2 presents an overview of the pharmacotherapy for cardiovascular comorbidity and risk factors. A significantly higher proportion of patients with iSSNHL used medication for cardiovascular comorbidities. A statistically significant higher proportion of iSSNHL used antihypertensive drugs and beta-blocking agents. The percentage of patients using other therapeutic agents was comparable between both cohorts.

Risk of CVA and TIA

During the 5-year follow-up, a total of 30 CVAs and 31 TIAs were recorded within the entire study population. Five cases of a CVA (1.0%) and 8 cases of transient ischemia (1.7%) occurred in the iSSNHL cohort, compared to 25 cases of CVA (1.3%) and 23 cases of transient ischemia (1.2%) in the control cohort.

Figure 2.| Selection of cases and matched controls. The figure illustrates the inclusion process of 480 eligible cases with idiopathic sudden sensorineural hearing loss and 1,911 matched controls from a total of 490,906 subjects in the primary care database containing coded health record data from 84 general practices in the Nijmegen region, the Netherlands. Cox regression survival curves for CVA alone (panel a), and CVA and TIA combined (panel b) in the two cohorts during the 5-year follow-up period.

a.



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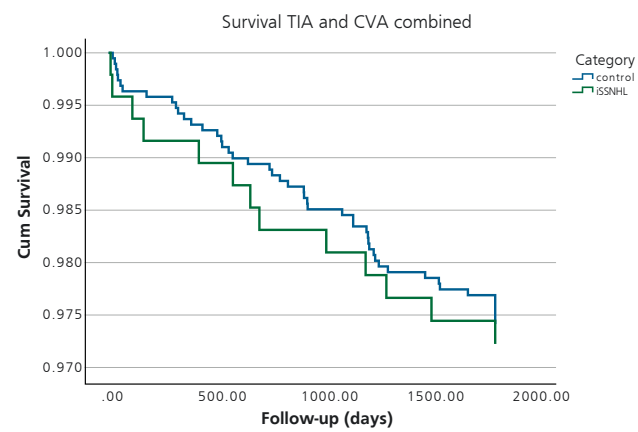

Table 3 | Hazard ratios from univariable and multivariable Cox regression analyses for occurrence of CVA and CVA or TIA combined within 5 years follow up

	Univariable analysis		Multivariable analysis	
Characteristic	*Hazard ratio (95%CI)*	*P-value*	*Hazard ratio (95%CI)*	*P-value*
Outcome: CVA				
iSSNHL	1.25 (0.50, 3.27)	0.646		
Age	**1.10 (1.07, 1.14)**	**<0.01**	**1.06 (1.04, 1.09)**	**<0.001**
Angina Pectoris	0.29 (0.10, 0.82)	0.020		
Aneurysm	0.26 (0.04, 1.92)	0.188		
Atrial fibrillation	0.56 (0.13, 2.33)	0.422		
Cardiac disease	**0.27 (0.11, 0.67)**	**0.004**	0.67 (0.33, 1.35)	0.258
Congestive heart failure	0.40 (0.06, 2.95)	0.370		
CVA [a]	0.88 (0.12, 6.43)	0.896		
Diabetes mellitus	0.48 (0.18, 1.25)	0.130		
Dyslipidaemia	0.93 (0.32, 2.65)	0.882		
Hypertension	**0.34 (0.17, 0.70)**	**0.003**	0.68 (0.41, 1.15)	0.151
Obesity	1.07 (0.15, 7.83)	0.949		
PAOD	0.38 (0.13, 1.10)	0.074		
Smoking	2.61 (0.35, 19.1)	0.346		
Thrombosis	**0.22 (0.05, 0.92)**	**0.038**	0.80 (0.19, 3.34)	0.760
Outcome: CVA or TIA				
iSSNHL	0.92 (0.50, 1.71)	0.804		
Age	**1.07 (1.05, 1.10)**	**<0.01**	**1.06 (1.04, 1.10)**	**<0.001**
Angina Pectoris	0.50 (0.20, 1.24	0.136		
Aneurysm	0.55 (0.08, 3.95)	0.550		
Atrial fibrillation	0.45 (0.18, 1.12)	0.084		
Cardiac disease	**0.35 (0.18, 0.69)**	**0.002**	0.68 (0.34, 1.37)	0.282
Congestive heart failure	0.84 (0.12, 6.10)	0.865		
CVA [a]	1.81 (0.25, 13.1)	0.555		
Diabetes mellitus	**0.43 (0.23, 0.84)**	**0.013**	0.77 (0.39, 1.50)	0.437
Dyslipidaemia	1.30 (0.56, 3.02)	0.540		
Hypertension	**0.40 (0.24, 0.67)**	**<0.001**	0.70 (0.41, 1.18)	0.180
Obesity	2.21 (0.31, 15.96)	0.431		
PAOD	0.54 (0.23, 1.26)	0.156		
Smoking	1.28 (0.47, 3.53)	0.633		
Thrombosis	0.46 (0.11, 1.89)	0.281		

CVA=cerebrovascular accident, iSSNHL=idiopathic Sudden Sensorineural Hearing Loss, PAOD=Peripheral Aortic Occlusive Disease, TIA=transient ischemic attack. Statistically significant associations are marked bold. [a] before the iSSNHL episode or selected starting date for the 5-year follow-up in the controls (i.e., history of CVA)

In the univariable Cox regression models, iSSNHL alone did not show a statistically significant hazard ratio for CVA or for CVA and TIA combined (see figure 2 and table 3); the hazard ratio for iSSNHL compared with controls was 1.25 (95%CI 0.50 to 3.27; P=0.646) for CVA alone and 0.92 (95%CI 0.50 to 1.71; P=0.804) for CVA and TIA combined. Only age, cardiac disease, hypertension and diabetes univariately showed significant associations with the hazard of CVA.

In the multivariable Cox regression models, increased age (defined as one year older) showed a slightly increased hazard for an ischemic cerebral event, with hazard ratios of 1.06 (95%CI 1.04 to 1.09; P<0.001) and 1.06 (95%CI 1.04 to 1.10; P<0.001) for CVA alone and CVA and TIA combined, respectively (Table 3). iSSNHL nor any of the cardiovascular comorbidities or cardiovascular risk factors showed statistically significant hazard ratios in the two multivariate Cox models.

Table 4 | Hazard ratios from the Cox regression model for occurrence of a CVA or TIA with iSSNHL, age category (i.e. <60 or ≥60 years), and the interaction term of these two variables.

	Hazard ratio	*95%CI*		*P-value*
		Lower	*Upper*	
iSSNHL	0.25	0.06	1.01	0.051
Age ≥60	2.11	0.65	6.86	0.214
Age ≥60 * iSSNHL	**4.84**	**1.02**	**23.05**	**0.048**

CI = Confidence interval, iSSNHL= idiopathic sudden sensorineural hearing loss Statistically significant associations are marked **bold**.

In an additional Cox model we further explored the role of older age (i.e., above 60 years) as an effect modifier when considering iSSNHL as a potential risk factor for CVA or TIA. This model showed that the hazard ratio for the interaction term between iSSNHL and age category was statistically significant at 4.84 (95%CI 1.02 to 23.05; P=0.048) (Table 4). This indicates that in the subgroup aged ≥60 iSSNHL increased the risk of CVA or TIA while this was not the case in the subgroup aged <60.

Discussion

In this retrospective matched case-control study using data from general practices we observed no overall increased hazard rate for CVA or TIA in the five years after an episode of iSSNHL when compared to controls. The only cardiovascular risk factor that was significantly more prevalent in the iSSNHL cohort was atrial fibrillation. Patients with iSSNHL seemed to use more medication to treat cardiovascular comorbidity. Beta-blocking agents and antihypertensives, not belonging to the group of diuretics, calcium channel blockers or agents acting on renin angiotensin system, were significantly more used by patients with iSSNHL than by controls. Age was related to increased risk of CVA

or TIA, and in subjects aged 60 years and older iSSNHL appeared to increase the risk of CVA or TIA compared to younger subjects.

Since 2008, seven papers have investigated the risk of CVA following sudden sensorineural hearing loss, as several authors previously proposed being vascular compromised as a contributing factor in the pathophysiology of iSSNHL[2–4,6,7,10]. The potential vascular involvement in the pathophysiology of SSNHL could have a significant impact on the treatment approach of iSSNHL. Currently, acute hearing loss is primarily treated with corticosteroids, based on the assumption of inflammation secondary to viral infection as the underlying mechanism (or auto-immune). To the best of our knowledge, the consideration of cardiovascular risk management, including anticoagulant therapy, as a therapeutic approach of acute hearing loss is only practiced in Germany[11].

In 2020, Lammers et al. conducted a meta-analysis comparing the results of studies investigating the risk of a CVA after SSNHL[12]. Due to significant heterogeneity in results they could only include 3 articles in the meta-analysis. This resulted in a hazard ratio of 1.42 (95%CI 1.15 to 1.75) for CVA compared with controls without sudden hearing loss. In contrast, our study did not find an overall increased risk of CVA following iSSNHL. The main issue with the outcome of the included studies in the meta-analysis is their study design. Most articles relied on non-medical data from national health insurance databases, where all patients with the same billing code were assumed to have had sudden sensorineural hearing loss. However, the degree of the hearing loss could not be retrieved and patients who may not have met the criteria for iSSNHL, may nonetheless have received a billing code for iSSNHL for administrative reasons. In addition, assessing cardiovascular comorbidity, cardiovascular risk factors and related treatment is challenging in such a database.

Similar to our findings, Ciorba et al, the only European study investigating the incidence of CVA in an iSSNHL cohort, did not report an association between iSSHNL and CVA. However, the study design of this study also had some limitations. The authors compared the incidence of CVA in patients with iSSNHL to the expected incidence of CVA based on population estimates. Also, the cohorts were not matched for age or other potential confounders.

Our study's primary strength lies in the use of data derived from general practices. In the Netherlands, it is common for patients with iSSNHL to see their GP before receiving an emergency referral to an ENT outpatient clinic if there is suspicion of sudden deafness. Consequently, our cohort offers an estimation of the incidence of iSSNHL in the entire population. In the Dutch health system, GPs are responsible for cardiovascular risk management. Thus, we could compare cardiovascular risk factors in subjects with SSNHL to the matched controls. Cardiovascular risk factors nor cardiovascular comorbidity were more prevalent in the iSSNHL cohort than in the control cohort. Objective measurements of glucose, blood pressure and lipid levels also did not significantly differ between both cohorts. It is noteworthy that for most of the cardiovascular risk factors their presence

appeared to reduce the hazard rates of a CVA or TIA, which may seem unusual given the hypothesis of vascular involvement in iSSNHL. However, factors such as older age, obesity, and smoking , which cannot (easily) be altered by medical treatment, showed an increased risk of CVA or TIA, although not all were statistically significant. This suggests that cardiovascular risk management of modifiable cardiovascular risk factors effectively reduces the incidence of a CVA or TIA, which aligns with the desired effect of these therapies. Our finding that more patients with iSSNHL used medication to treat cardiovascular risk factors aligns with this suggestion.

In this cohort, age was the sole risk factor that significantly increased the risk of a CVA or TIA. While increasing age did not appear to affect the overall risk of these events differently in subjects with and without iSSNHL, subjects with iSSNHL aged 60 or older did have a significantly higher hazard ratio for a CVA or TIA than controls of a similar age. This suggests that older individuals with iSSNHL may have a greater CVA risk compared to both younger individuals with iSSNHL and older individuals without iSSNHL.

The main limitation of this study is that we could not access audiometry results. Consequently, we relied on the GPs' ability to diagnose SSNHL accurately. Fortunately, GPs in the Netherlands probably adhere to the Dutch medical guidelines for acute hearing loss, which is based on worldwide accepted criteria for SSNHL. Despite the extensive dataset comprising almost half a million of individuals, the overall incidence of CVAs and TIAs in the entire cohort was rather low. Therefore, conclusions drawn from our analyses should be interpreted with caution.

In conclusion, our study did not find an overall significant difference in the risk of a CVA or CVA and TIA combined between subjects with iSSNHL and matched controls. However, the hazard ratio for a CVA or TIA was increased in subjects with iSSNHL aged 60 and older compared to younger subjects with iSSNHL and to older subjects without iSSNHL. This suggests that iSSNHL could have vascular involvement in older subjects, but further research is needed to confirm this observation.

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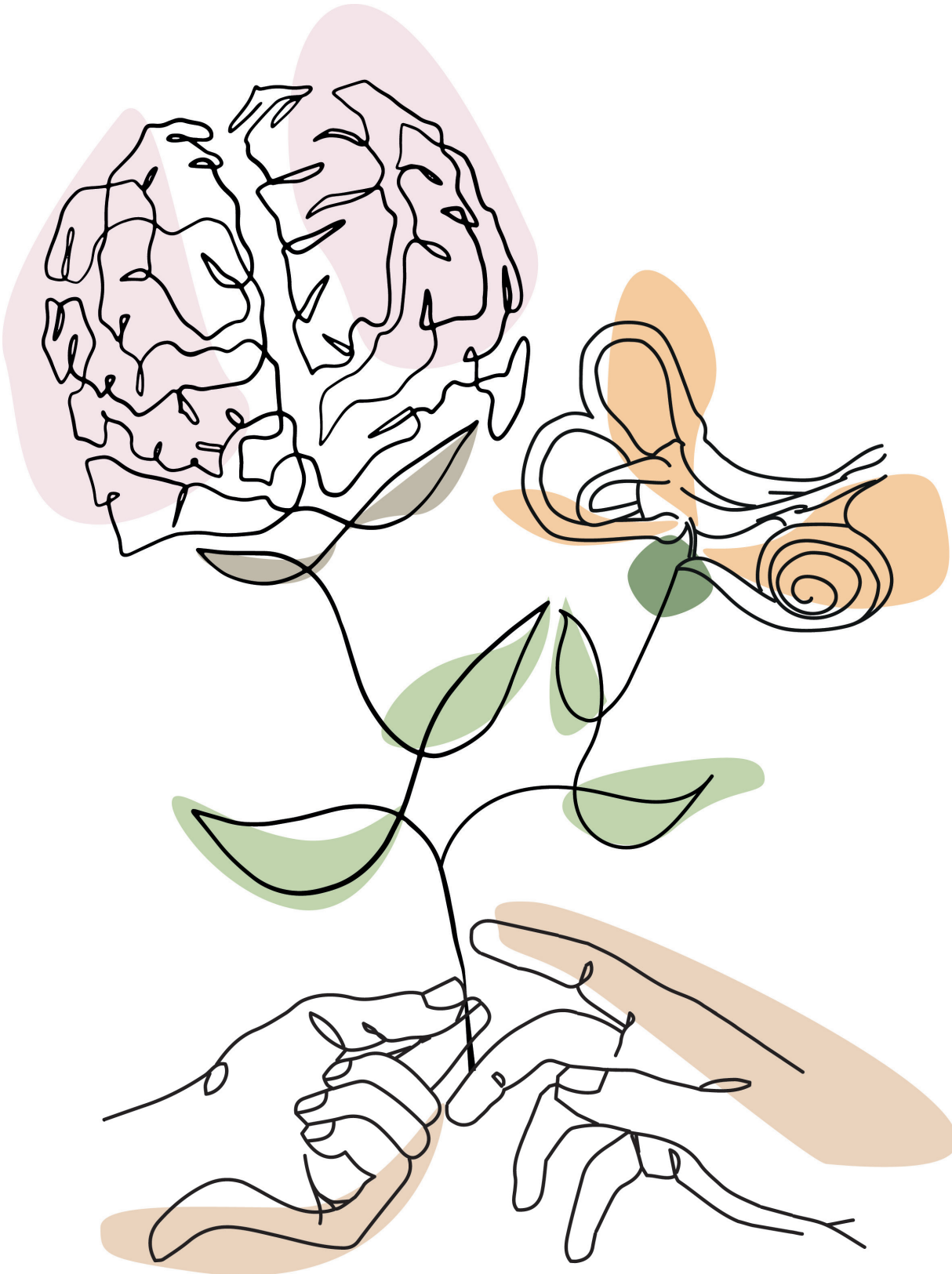

Chapter

7

Idiopathic labyrinthitis: symptoms, clinical characteristics and prognosis

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Introduction

Labyrinthitis is an inner ear disorder that manifests itself with acute hearing loss and vertigo. The population incidence of labyrinthitis is unknown[1,2]. In the past, suppurative labyrinthitis was a well-known complication of bacterial meningitis and otitis media, but since the global use of antibiotics, these have become rare entities[3–5]. Nowadays, in the absence of signs of meningitis or otitis, it is assumed that the most common cause of labyrinthitis is a viral infection, although the viral agent usually cannot be identified. In some, especially elderly patients, labyrinthitis might be caused by vascular disease, just like in certain cases of sudden deafness and vestibular neuritis[6–8]. Since a clear cause cannot be identified in the majority of patients, the term idiopathic labyrinthitis may be more suitable than viral labyrinthitis. Although the term acute idiopathic unilateral vestibulopathy in combination with sudden sensorineural hearing loss (SSNHL) may be more appropriate, in this paper we will continue the use of 'idiopathic labyrinthitis' until the pathophysiology of acute vestibulopathy and sudden sensorineural hearing loss are clarified. Several empirical biomedical studies concerning labyrinthitis have been published[3,4,9], but cohort studies are nonexistent. This retrospective study was conducted to describe the demographic and clinical characteristics, comorbidity and prognosis in terms of balance difficulty and activity avoidance of patients diagnosed with idiopathic labyrinthitis.

Materials and Methods

The study design is a retrospective cohort study that consisted of two components, i.e. retrospectively gathered data regarding medical history, diagnostic tests and treatment from electronic patient files, and follow-up interviews to assess balance difficulty and activity avoidance by telephone. The study gained ethics approval from the institutional review board of the hospital (LTC number 2021_36).

The cohort consisted of all patients diagnosed with idiopathic labyrinthitis between January 2006 and May 2022 at the outpatient tertiary dizziness clinic and the department of otorhinolaryngology.

Worldwide accepted diagnostic criteria for labyrinthitis do not exist. Therefore, we adapted the preliminary criteria for unilateral vestibulopathy/vestibular neuritis of the Bárány society[10], see Table 1. We included patients with either definitive acute idiopathic labyrinthitis or a history of acute idiopathic labyrinthitis. Definite acute labyrinthitis is characterized by acute onset vertigo, sudden sensorineural hearing loss and the presence of either a spontaneous horizontal torsional nystagmus or objectified vestibular loss of function in the (sub)acute phase. A history of acute labyrinthitis is characterized by a past episode of acute onset vertigo, sensorineural hearing loss and currently objectifiable vestibular loss of function. Patients with labyrinthitis secondary to a herpes zoster ear infection, meningitis, syphilis, HIV, or an auto-immune disorder were excluded. Patients

who developed a different form of dizziness or recurrent episodes of dizziness, resulting in a change of diagnosis, were reported and excluded from the analysis.

Table 1. | Diagnostic criteria for idiopathic labyrinthitis.

Definite acute idiopathic labyrinthitis	History of acute idiopathic labyrinthitis
A. Acute or subacute onset of sustained spinning or non-spinning vertigo (i.e., an acute vestibular syndrome) lasting for at least 24 hours. B. Spontaneous peripheral vestibular nystagmus i.e., generally horizontal-torsional, direction-fixed, and enhanced by removal of visual fixation. C. Unambiguous evidence of reduced VOR function on the side opposite the direction of the fast phase of the spontaneous nystagmus, measured by video-HIT or caloric testing. D. Unilateral sensorineural hearing loss of at least 30 dB over 3 consecutive frequencies occurring in a 72-hour window. E. Not better characterized by another disorder, such as physical exam evidence of acute otitis media or cholesteatoma, or imaging evidence of retrocochlear cause for acute hearing loss and vertigo such as vestibular schwannoma	A. History of acute or subacute onset of sustained spinning or non-spinning vertigo lasting at least 24 hours (i.e., an acute vestibular syndrome) and slowly decreasing in intensity over days. B. Evidence of unilaterally reduced VOR function, measured with video-HIT or caloric testing. C. Evidence of unilateral sensorineural hearing loss of at least 30 dB over 3 consecutive frequencies occurring in a 72-hour window. D. Not better characterized by another disorder, such as physical exam evidence of acute otitis media or cholesteatoma, or imaging evidence of retrocochlear cause for acute hearing loss and vertigo such as vestibular schwannoma

The definition is divided in a definite idiopathic labyrinthitis and history of idiopathic labyrinthitis. This definition is derived from the Bárány society criteria for unilateral vestibulopathy/vestibular neuritis [10].

The vestibulo-ocular reflex (VOR) function was measured using a commercially available mono-ocular video oculography system (ICS Impulse System, version 1.20 up to version 4.00, OTOsuite Vestibular software; Otometrics, Taastrup, Denmark). VOR gain was defined as the ratio of the eye movement velocity to the head movement velocity. The video head impulse test (v-HIT) was considered abnormal if the VOR gain was below 0.6, preferably confirmed by the presence of corrective saccades.

Caloric testing was performed using a bithermal open-loop water irrigation system. Each ear was irrigated with a constant flow alternating between hot and cold water. The maximum slow peak velocity of nystagmus was evaluated after irrigation. We used Jongkees' equation to calculate canal paresis. Details of the technique used have been described in detail elsewhere[11]. The threshold for canal paresis was set at ≥ 22%.

Hearing thresholds were evaluated on 0.5, 1, 2, 4 and 8kHz using standardized methods for pure tone threshold audiometry[12]. Following the AAO-HNS guideline, sudden sensorineural hearing loss was defined as > 30dB hearing loss on 3 consecutive

frequencies occurring within a 72-hour window[13]. In case no audiometry was available from before the onset of symptoms, the uninvolved ear was considered normal.

The primary study outcome was the number of patients with ongoing self-reported balance problems at follow-up. Ongoing balance problems and their associated fear-avoidance behavioral responses, the co-primary outcome, were assessed using the Dutch translation of the 9-items Vestibular Activity Avoidance Inventory (VAAI-9)[14], see Table 2. This instrument evaluates limitations of dizziness in job responsibilities, household chores, social events, physical activity, and exercise, and fears about making dizziness worse, engaging in exercise, and going outside the home[15]. These items are rated on a 7-point scale; strongly disagree, disagree, somewhat disagree, neutral, somewhat agree, agree and completely agree, where 7 indicates completely agree[16]. The total score ranges from 0 to 63. The VAAI-9 strongly correlates with activity limitations and participation restrictions and has shown moderate associations with anxiety and depression symptoms and quality of life among persons with vestibular disorders[15]. The VAAI-9 was administered during a follow-up interview by telephone in early 2022 in all patients. The questionnaire was administered and the balance problems the patients experienced were identified by two researchers, FO and CC, for logistical reasons. Prior to the interview, patients were asked for verbal informed consent of participation in the study.

Table 2.| Vestibular Activities Avoidance Instrument – 9 Items. The right column displays the questionnaire each item is derived from.

Item	Text	Adapted from[1]
1	It is difficult for me to do strenuous homework or yard work because of my dizziness.	DHI
2	My participation in social activities, such as going out to dinner, going to the movies, dancing, or going to parties is significantly restricted because of my dizziness.	DHI
3	My dizziness interferes with my job or household responsibilities.	DHI
4	I cannot do physical activities, which might make my dizziness worse.	FABQ
5	I can't do all the things normal people do because of my dizziness.	TSK
6	I am afraid that I might make myself dizzy or unsteady if I exercise.	TSK
7	I am afraid to leave my home without having someone go with me because of my dizziness.	DHI
8	I should not do my regular work with my present dizziness.	FABQ
9	My work makes my dizziness worse.	FABQ

1 DHI=Dizziness Handicap Inventory, FABQ=Fear Avoidance Beliefs Questionnaire, TSK= Tampa Scale of Kinesiophobia. Table derived from PhD thesis of P. Dunlap.

The secondary study outcome was an overview of demographic and clinical characteristics, the results of the diagnostic workup including v-HIT and caloric testing, and the therapy given to patients presenting with idiopathic labyrinthitis. This information was gathered retrospectively from electronic patient files.

Statistical analysis was performed using SPSS version 25. Frequencies and percentages were calculated for sex, type of idiopathic labyrinthitis, type of diagnostic test performed, and results of the VAAI-9 instrument. In addition, means and standard deviations, or median and IQR in case of non-normally distributed data, were calculated for age, time span to presentation, the v-HIT gain, the vestibular asymmetry with caloric testing and the mean VAAI-score based on non-missing data. For analyzing the percentages of patients either with or without complaints, we reduced the seven-point VAAI-9 scale to a three-point scale, where somewhat agree, agree and strongly agree are merged into the category agree, and somewhat disagree, disagree and strongly disagree are merged into the category disagree.

Results

Study population

Ninety-six patients presented with simultaneous acute hearing loss and vertigo in the ~16-yr study period, representing 0.39% of the entire population referred to our center. Thirty-five patients were excluded. Eleven of these patients had clinical signs of middle ear infection with otoscopic examination. In two cases a varicella-zoster infection was suspected because of ipsilateral vesicular eruption. One patient had developed labyrinthitis secondary to meningitis. Two patients were excluded since they developed Menière's disease over time. The remaining 21 excluded patients did not meet the diagnostic criteria for idiopathic labyrinthitis. Eight of these patients were suspected of labyrinthitis but did not have objectified vestibular weakness. Table 3 shows the characteristics of the 61 patients who met the inclusion criteria.

Table 3.1 Demographic and clinical characteristics of 61 patients diagnosed with idiopathic labyrinthitis.

	Percentage (%)
Age (mean, (SD))	58 (12)
Sex	
Male	44.3
Female	55.7
Time span to presentation (months) (median, (IQR)) 8 (12)	
Labyrinthitis criteria	
Definite acute labyrinthitis	4.9
History of acute labyrinthitis	95.1

N=number of non-missing cases, IQR= interquartile range, SD=standard deviation.

All patients underwent pure tone audiometry at presentation in the outpatient setting. The average sensorineural hearing loss in the affected ear was 58.1 dB (high Fletcher index, SD 25.1). Figure 1 displays the average hearing threshold in the affected versus the non-affected ear.

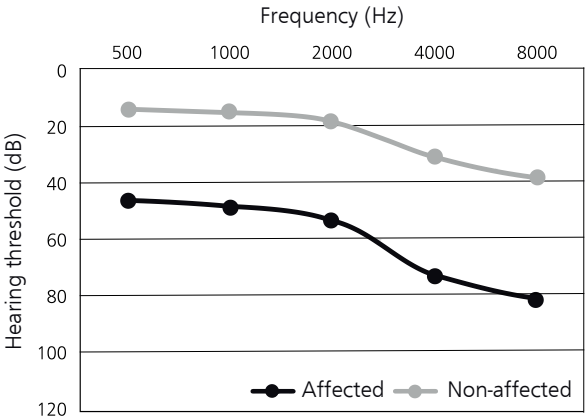

Figure 1.| Average PTA results of the affected and non-affected ear in 61 patients with idiopathic labyrinthitis. dB=decibel. PTA=pure tone audiometry

In 36 patients (59.0%) a v-HIT was done, in 54 patients (88.5%) caloric testing was performed and 29 patients (47.5%) received both diagnostic tests. All patients showed loss of vestibular function; twelve patients (19.6%) had a VOR-gain below 0.6 with either covert, overt or both types of saccades and 53 patients (86.9%) had a unilateral weakness with caloric testing. The average unilateral vestibular weakness measured by caloric testing was 54.0% (SD 20) and the average VOR-gain using v-HIT was 0.465 (SD 0.08). One patient had bilateral vestibulopathy, measured with caloric testing. In one patient, the v-HIT demonstrated no abnormal gain, but overt saccades were seen on both sides.

Forty-one patients (67.2%) received a referral for vestibular rehabilitation after presentation at the dizziness clinic or had previously undergone vestibular rehab in primary care clinics. Details of the exact vestibular rehab protocol patients received could not be retrieved.

3.1. Follow-up

Follow-up information was obtained from 40 patients (65.6%) after a median duration of 61 months (IQR 32-113). Three patients had died, in nine patients the contact information was not up to date, three patients did not give informed consent and the remainder could not be reached despite multiple attempts. Seven patients (17.5%) experienced some or complete hearing recovery, while 32 patients (80%) noticed no hearing improvement. Twenty-nine patients (72.5%) still experienced balance problems.

Figure 2 shows the results for the different questions from the VAAI-9. The mean VAAI score was 20.4 (SD 12.9). Forty-two and a half percent of the follow-up patients had trouble performing heavy tasks in and around the house, 45% experienced difficulty in social activities due to balance problems or vertigo, and 40% experienced difficulty in work or household. Fifty-seven and a half percent of patients could not perform activities they knew would provoke their dizziness and 62.5% could not perform all daily tasks they did before experiencing labyrinthitis; this percentage increased to 77% when the patients who did not report any complaints of dizziness at follow-up (n=11) were removed from the calculation.

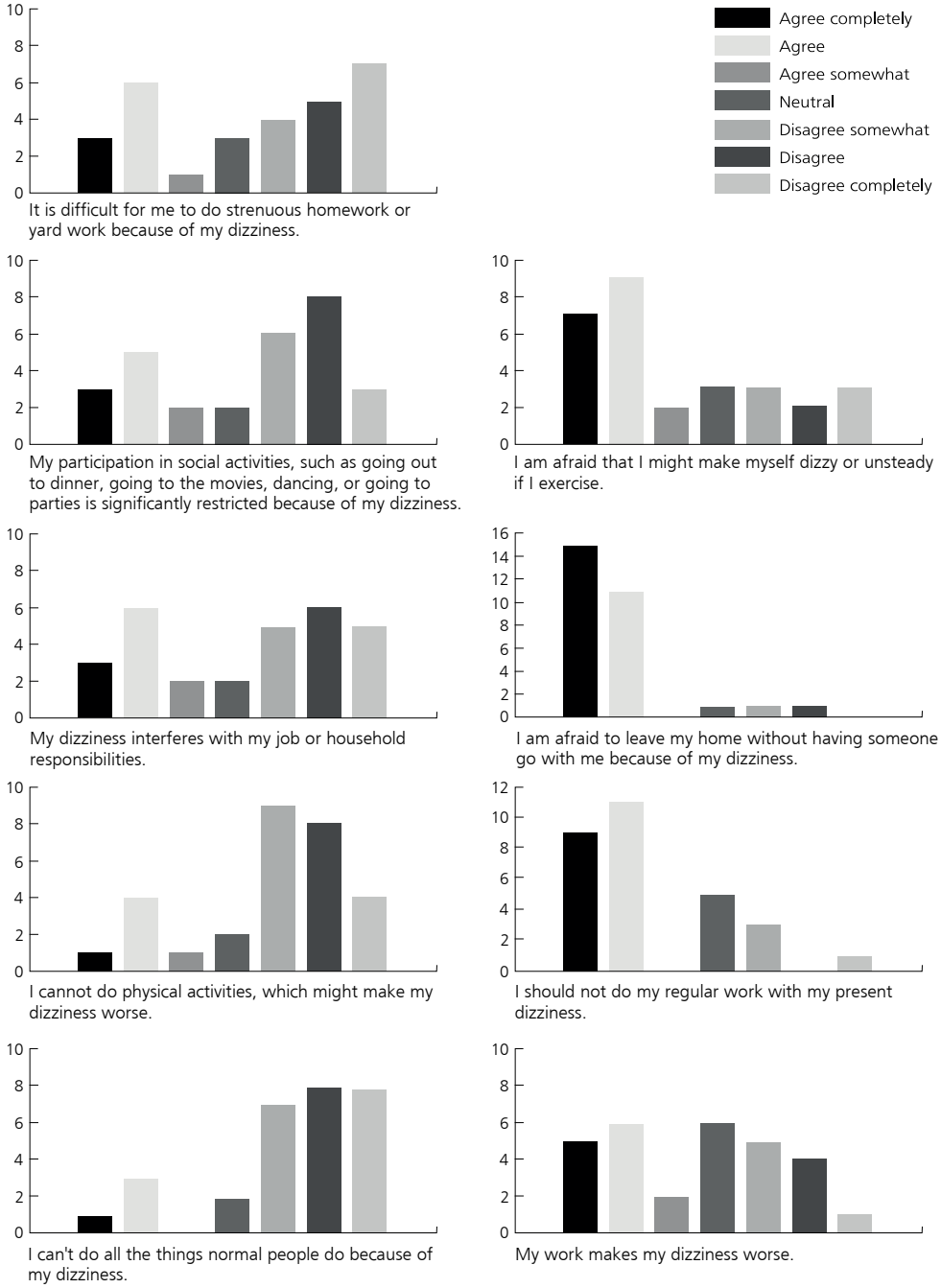

Figure 2.| Results of the VAAI-9 instrument in 40 patients after a median of 61 months of disease. For each item on the x-axis the number of patients in each category is displayed on the y-axis. The seven-point VAAI-9 scale is reduced to a three-point scale, where somewhat agree, agree and strongly agree are merged into the category agree and somewhat disagree, disagree and strongly disagree are merged into the category disagree. VAAI-9 = 9-item Vestibular Activities Avoidance Instrument.

Almost all patients reported having adjusted to their symptoms. At follow-up, 5% of patients were afraid to some degree of leaving the house unaccompanied and 20% of patients were afraid of performing specific movements that might provoke dizziness. Finally, five out of 34 patients (17.4%) of working age were not allowed to perform their current job due to their vertigo complaints and in 32.5% of working patients, their work aggravated their dizziness complaints. Nine patients had to change jobs or reduce their workload as a consequence of their dizziness complaints.

Discussion

This study aimed to describe the clinical and demographic characteristics, comorbidity and prognosis in terms of balance difficulty and associated fear-avoidance behavioral responses in patients diagnosed with idiopathic labyrinthitis. To date, little is known about the characteristics and clinical course of this disorder since cohort studies are nonexistent.

We retrospectively evaluated 61 patients diagnosed with idiopathic labyrinthitis in our tertiary dizziness clinic in the last 16 years. This comprised only a small proportion of the entire population presenting at our clinic during this period. All patients included in the cohort had vestibular function loss at initial presentation. They presented at our dizziness clinic a median 8 months after disease onset (IQR 12 months). After a median follow-up of 61 months (i.e., ~5 years), 72.5% of patients still experienced balance problems. Of these patients, 77% had not returned to their daily life activities due to these problems.

After experiencing acute vestibular loss of function, vertigo generally lasts only a few hours up to days, while balance difficulty and oscillopsia may persist for a much longer period of time[17]. This persisting imbalance is thought to slowly disappear after several weeks due to central compensation with restoration of spontaneous activity in the affected vestibular nucleus, explaining the good prognosis that has been ascribed to labyrinthitis by other authors[1,2,17,18]. However, the findings in our study contradict this statement. After a median of 61 months after disease onset, 72.5% of patients still experienced balance problems. The mean score on the VAAI questionnaire at follow-up was 20.4 (SD 12.9), which is lower than the mean score of 28 (SD 12) Vereeck et al. found in a subset of 43 patients with dizziness of variable origin and considerably higher than the average 2.4 (SD 5.9) point score in healthy volunteers[14]. It is important to note that Vereeck also included patients with recurrent vertigo, central vestibular disorders and functional disorders[14]. Especially patients with functional disorders and central vestibular disorders had high VAAI values, which might be explained by the association of functional disorders with anxiety and the chronic nature of central vestibular disorders[19]. The relatively high VAAI scores in our cohort indicate a poor improvement in balance and consequent limitations in terms of associated fear-avoidance behavioral responses for patients with labyrinthitis in the course of time.

In case of unilateral vestibulopathy due to vestibular neuritis, complete caloric recovery after 12 months has been reported in 44.4 up to 70.2% of cases, regardless of corticosteroid use[20]. In our study, only 8 out of all 96 screened patients were primarily excluded because they did not have objectified vestibulopathy, but otherwise matched the criteria for labyrinthitis. This resulted in 61 out of 69 (89%) patients suspected of idiopathic labyrinthitis with objectified vestibulopathy after a median of 8 months after the onset of vertigo. Vestibular neuritis might therefore have a better vestibular recovery than labyrinthitis. This statement should be considered with care. Up to now, there is insufficient knowledge of the ratio of concurrent sudden deafness and vestibulopathy in primary care compared to the hospital and specialized centers.

Subjective hearing recovery was found in only 20% of follow-up patients, with complete recovery in only 3 out of 40 patients. Yu et al. performed a meta-analysis on the prognosis of hearing loss in patients experiencing SSNHL with and without vertigo[21]. Vertigo was a prognostic factor for worse hearing recovery, implying a possible different pathophysiology in patients experiencing combined sudden deafness and vertigo versus sudden deafness alone[22,23]. However, patients with concurrent vertigo who received intratympanic corticosteroids did not demonstrate a poorer hearing recovery.

Since labyrinthitis appears to have a smaller chance of hearing recovery than sudden deafness and a smaller chance of vestibular recovery than vestibular neuritis, we recommend using criteria to distinguish these three entities clearly. In this study, we used a set of criteria, for which we adapted the proposed criteria for unilateral vestibulopathy/vestibular neuritis from the Bárány Society and combined these with the guideline for sudden sensorineural hearing loss[10,13]. We believe this can be used as a framework for creating universally accepted diagnostic criteria for labyrinthitis.

Why in some patients the symptoms due to vestibular loss recover completely, while others keep experiencing problems is not entirely understood. Antiemetics or benzodiazepine use could influence the vertigo symptoms since there is some evidence suggesting that VOR function decreases upon intake of sedatives[24–26]. Unfortunately, in our cohort, the use of antiemetics and sedatives was not explicitly mentioned in patient files and could therefore not be analyzed.

Dysfunctional vestibular perception, fear of falling or becoming dizzy when resuming daily tasks and consequent activity avoidance might be another factor that contributes to disability following vestibulopathy caused by labyrinthitis or otherwise[16,27]. Dunlap et al. have investigated this fear-avoidance behavioral response in patients with vestibular disorders since there is a well-studied association between psychiatric symptoms and vestibular disorders, indicating shared neural networks that link anxiety, fear, and dizziness[28]. They objectified that stronger fear-avoidance responses at presentation were associated with more reported disability after three months follow-up[28]. After a long follow-up with a median of 61 months, 5% of patients in the present cohort were afraid of leaving the house unaccompanied, and 20% of patients were afraid to

perform specific movements as they believed this would provoke their vertigo. These relatively low percentages are likely caused by the follow-up of almost 5 years. After several years, people stated they had altered their lifestyle to match their complaints, and most importantly, patients were not afraid anymore that another episode of vertigo might occur. In contrast, Dunlap et al. only followed patients for up to 3 months [16], so this acceptation and adaptation had not yet occurred presumably.

Most patients in our cohort had received vestibular rehabilitation, which may have improved their functional outcomes. In the literature, there is moderate to strong evidence to support the use of vestibular rehabilitation in patients with unilateral and bilateral vestibulopathy to reduce symptoms and improve vestibular recovery [29,30]. Unfortunately, there is no standardized protocol for vestibular rehabilitation in case of unilateral or bilateral vestibulopathy [29], which complicates comparing different rehab protocols and evaluating their influence on vestibular recovery and activity avoidance.

Several limitations of the current study should be pointed out. First and most importantly, patients that are referred to a tertiary center are likely to have more severe symptoms, a longer duration of disease or a worse recovery than the average patient experiencing labyrinthitis who does not require a hospital visit. Also, patients referred to our tertiary dizziness clinic are not seen in an acute setting. In these cases, the diagnosis is based upon a persistent objectified loss of vestibular function. This may have resulted in selection bias because patients in whom the vestibular function has been sufficiently restored before their visit to our center are not included. Second, in the absence of baseline outcome measurements, we could not compare the limitations in activity and fear-avoidance behavioral response between disease onset and follow-up. Finally, we did not perform PTA or vestibular testing at follow-up and could thus not assess the differences in hearing thresholds at presentation and follow-up, nor could we relate this to the participants' self-reported subjective hearing recovery.

Regardless of the limitations of this study, we found that a significant number of patients with idiopathic labyrinthitis have a poor prognosis for both hearing and balance function. When comparing our observations to the literature their prognosis appears to be worse than in sudden deafness or vestibulopathy alone.

Conclusions

Patients presenting with idiopathic labyrinthitis in a specialized dizziness clinic, have a poor prognosis, with a subjective hearing recovery in only 20% of cases and persistent balance difficulty. After a median follow-up of five years, 72.5% of patients diagnosed with idiopathic labyrinthitis still complained of balance problems or instability. Of these patients, 77% could not resume their normal daily activities. Prospective cohort studies are necessary to objectify persistent balance difficulty and relate this to the vestibular function.

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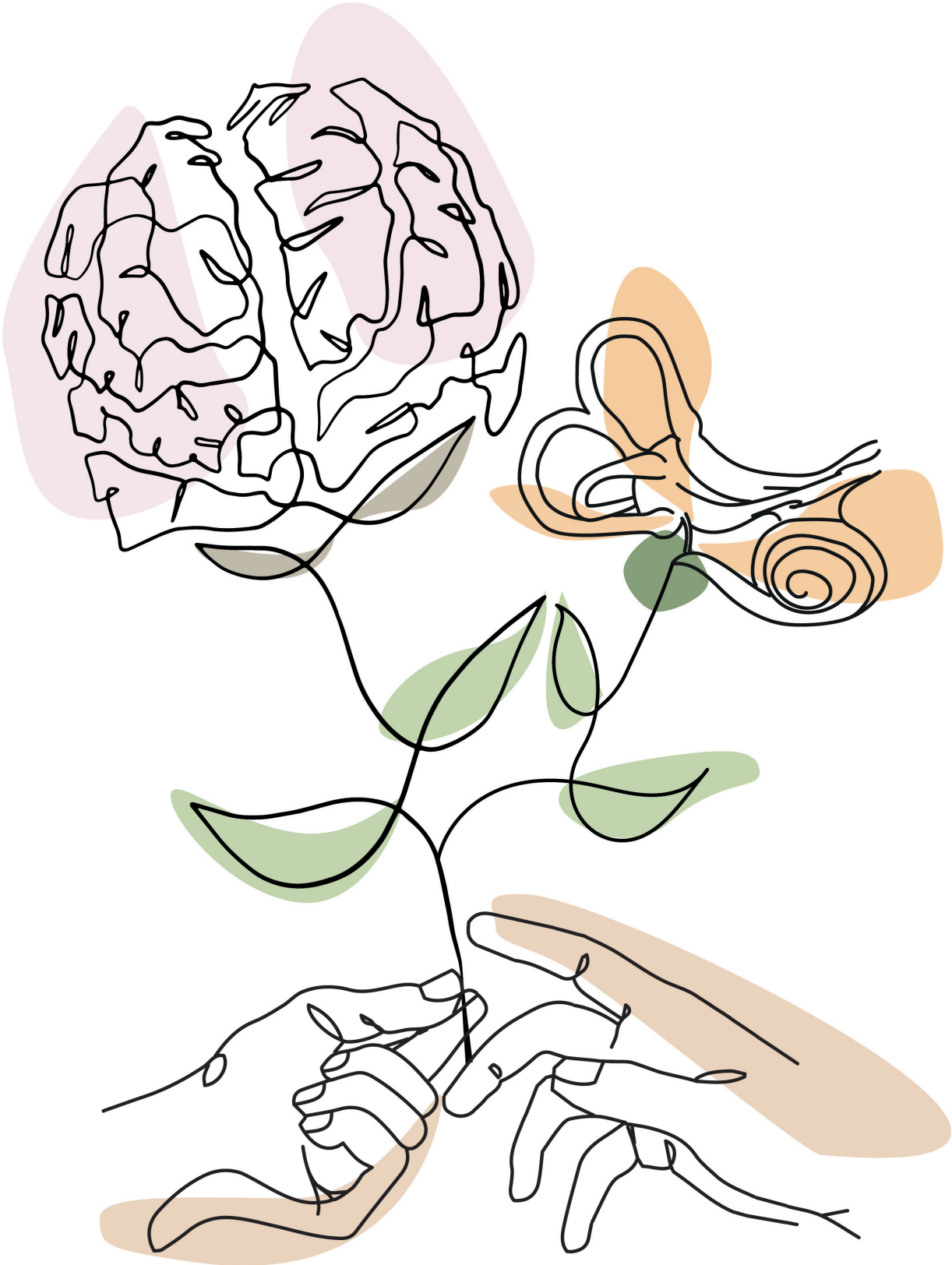

Chapter

8

Risk factors and Occurrence of Small vessel disease in Acute sensorineural hearing Loss In the Elderly: protocol for a multicenter cross-sectional study

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Introduction

Sudden sensorineural hearing loss (SSNHL) is an otologic emergency, commonly defined as the abrupt onset of sensorineural hearing loss exceeding 30dB in at least 3 contiguous audiometric frequencies, manifesting within a span of 72 hours[1–3].

The annual incidence of SSNHL is approximately 5-20 cases per 100.000 individuals. In 32-72% of the cases the hearing loss recovers spontaneously[4,5]. Unfortunately, in 30-50% percent of cases, hearing loss does not improve after treatment with high-dose corticosteroids, which is the generally accepted treatment modality in the Netherlands, based on the suspicion of an infectious etiology[6].

While the etiologic factor in most cases cannot be identified, one hypothesis under examination implicates vascular involvement in the pathophysiology of SSNHL. Given that the internal auditory artery (IAA) is an end artery with little collateral blood supply, the cochlea is particularly susceptible to ischemia[7,8]. Research has focused on the potential link between idiopathic SSNHL (iSSNHL) and systemic cardiovascular disease, aiming to investigate the plausibility of vascular involvement in the pathophysiology of SSNHL. Multiple studies have reported higher prevalence's of cardiovascular risk factors, such as smoking, alcohol abuse and hypercholesterolemia, in patients with SSNHL compared to controls.

Additionally, several cohort studies in Taiwan and Korea have reported increased incidence of stroke following iSSNHL[9–12,13]. In a meta-analysis, Lammers et al. calculated the hazard risk of developing stroke after experiencing SSNHL to be 1.42[14]. Kim et al. reported that in 8-31% of patients experiencing posterior circulation cerebrovascular accidents (CVA) exhibited preceding hearing or vestibular loss within a month[15]. Sudden hearing loss might therefore be an indicator of stroke and warrant interventions to prevent cardiovascular events, known for their significant morbidity and mortality.

While the exact pathophysiology of cerebral small vessel disease (CSVD) is not clarified, it is widely believed to result from systemic cardiovascular disease, particularly hypertension[16]. The presence of CSVD elevates the risk of stroke and other vascular neurodegenerative conditions, including vascular dementia[17–19]. We hypothesize that patients with iSSNHL will exhibit a higher prevalence of cerebral small vessel disease than healthy individuals, due to their increased cardiovascular comorbidity. CSVD can be visualized on MRI by the presence of white matter hyperintensities (WMH), cerebral microbleeds, lacunes and silent brain infarctions[18].

To investigate this hypothesis, we will conduct a multicenter cross-sectional analysis based on hospital derived data. Our study aims to investigate the presence of WMH and brain infarctions on MRI in elderly patients with iSSNHL, comparing these findings with a carefully matched control cohort. Additionally, we will compare the prevalence of cardiovascular risk factors and comorbidity between both cohorts.

Method and analysis

Design

Patients will be included within a two-year period at participating hospitals in both the Netherlands and Belgium. The participating centres are Gelre Hospital Apeldoorn and Zutphen, Leiden University Medical Centre, Groene Hart hospital Gouda, Rijnstate hospital Arnhem, Treant Emmen, Saint Franciscus Gasthuis Rotterdam, Medisch spectrum Twente, Isala Zwolle, Rivierenland Tiel and the University Hospital of Antwerp. A total of 410 patients will be included, 205 patients with idiopathic SSNHL and 205 subjects without iSSNHL in the control cohort. Patients will be recruited in the participating centres, but all data collection and subsequent analysis will be centralized and conducted at the Apeldoorn Dizziness Centre (ADC).

The ADC, located within the Gelre Hospital location Apeldoorn, serves as a multi-disciplinary tertiary referral centre involving the Neurology, Otorhinolaryngology and Clinical Neurophysiology departments. The ADC specialises in the diagnostic and therapeutic workup of Dizziness.

Inclusion

The study cohort will comprise patients diagnosed with iSSNHL and reside within the service areas of participating hospitals. A detailed description of the inclusion and exclusion criteria can be found in table 1.

Inclusion criteria sudden deafness cohort	**Inclusion criteria control cohort**
• Sudden deafness defined by acute onset sensorineural hearing loss of at least 30dB on 3 consecutive frequencies occurring withing 72 hours or less. • An MRI of the cerebellopontine angle or MRI cerebrum with at least one T2 or FLAIR sequence of the entire brain. • Age ≥ 50 years	• Patients diagnosed with trigeminal neuralgia, hemifacial spasm, vestibular paroxysmia or a cerebellopontine neoplasm. • Absence of sudden sensorineural hearing loss • An MRI of the cerebellopontine angle or MRI cerebrum with at least one T2 or FLAIR sequence of the entire brain. • Age ≥ 50 years
Exclusion criteria	
• Diagnosis of sudden deafness prior to the study period.	
• Significant cerebral damage due to a pre-existing medical condition that will impede an adequate assessment of the degree of cerebral small vessel disease. For instance, a medical history of multiple sclerosis.	
• Presence of an enlarged vestibular aqueduct on MRI that could be responsible for SSNHL	
• An identifiable cause of iSSNHL such as a Borrelia Burgdorferi infection.	

Table 1. Inclusion and exclusion criteria for participation in the ROSALIE study. FLAIR=fluid attenuated inversion recovery, iSSNHL=idiopathic sudden sensorineural hearing loss.

The control cohort will consist of patients presenting at the ADC or Gelre hospital with suspected diagnoses of trigeminal neuralgia, hemifacial spasm or vestibular paroxysmia, as well as patients with cerebellopontine neoplasms who have been referred to and are treated at the Leiden University Medical Centre or University Hospital of Antwerp.

Sample size calculation

A sample size calculation was conducted using nQuery software (Statsols, San Diego, CA, USA). Since the main outcome variable, the Fazekas score, is an ordinal variable, the sample size was calculated using a Mann-Whitney U rank-sum test with a two-sided significance level of 0.05. To perform this calculation, we used the proportions of patients falling into each Fazekas score category, as was previously observed in our retrospective case-control study comparing cerebral small vessel disease in patients with vestibular neuritis (VN) and a control cohort[20]. The control population in this previous study aligns with literature, where a Fazekas score of 2 is expected in individuals aged 60-70 years[21]. Given our hypothesis of greater cardiovascular comorbidity in patients with SSNHL compared to the general population, we expect the median Fazekas score in the SSNHL patients to be 3.

Figure 1 displays the output of the sample size calculation, demonstrating that the inclusion of 205 patients in each of the two groups (i.e., SSNHL and controls) yields 80.72% power to reject the null hypothesis. This null hypothesis posits that the distribution of patients across the 7 Fazekas categories in the SSNHL cohort and the control cohort is equal (i.e. the latter is derived from our previous study[20] and shown in the bottom part of Figure 1).

Study outcomes

The primary objective of this study is to assess the difference in prevalence of cerebral small vessel disease on MRI between patients diagnosed with iSSNHL and controls. This evaluation is based on two parameters, the extent of white matter hyperintensities, quantified using the Fazekas score and the presence of brain infarctions. The Fazekas score is the most frequently used diagnostic tool to assess the severity of white matter hyper-intensities in both periventricular and deep white matter regions[19, 22]. It is an ordinal scale ranging from 0 to 6, see figure 2. Brain infarctions are defined as lesions of the brain with a minimal diameter of 3mm, displaying cerebrospinal fluid like intensity on FLAIR or or T2 MRI sequences and clearly differentiable from leukoaraiosis and dilated Virchow-Robin spaces[23]

The secondary outcome is the prevalence of the cardiovascular risk factors age, gender, hypertension, hypercholesterolemia, smoking status, Body Mass Index (BMI) and cardiovascular comorbidities; diabetes, stroke and myocardial infarction. Hypertension is defined by meeting either of the following criteria: a. having a medical history of physician diagnosed hypertension and/or b. taking antihypertensive drugs. Hypercholesterolemia is defined by meeting either of these criteria: a. having a medical history of physician diagnosed hypercholesterolemia and/or b. the use of lipid-lowering medication. BMI is

calculated by dividing the patients' weight in kilogram by the square of their height in meters at the time of iSSNHL diagnosis. Smoking status is recorded as either former, current or non-smoker. Diabetes is defined by either having a medical history of physician diagnosed diabetes mellitus and/or the use of oral hypoglycemic drugs or insulin.

Aditionally, to account for potential confounding factors, binary and multinomial logistic regression analyses will be performed to compare the primary and secondary outcomes between both cohorts.

MTT2-1 / Wilcoxon (Mann-Whitney) Rank-Sum Test for Ordered Categories

	1
Test Significance Level, a	0.050
1 or 2 Sided Test?	2
Number of Categories, k	7
Side Table Name	MTT2S-1
p1 P(X<Y) Power (%)	 80.72
Sample Size per Group, n	205

MTT2S-1

Σ Compute ⇕Transfer X Clear

Category	Proportion in Controls (X)	Proportion in SSNHL (Y)
1	0.079	0.070
2	0.296	0.191
3	0.300	0.264
4	0.192	0.307
5	0.079	0.103
6	0.039	0.041
7	0.015	0.024
$\Sigma\pi\imath$	1.000	1.000
p1 = P(X<Y)	0.578	

Figure 1.| The nQuery (Statsols, San Diego, CA, USA) sample size output shows that 205 patients in each group to yields a power of at least 80%. The lower part of the figure displays the expected proportions of the 7 ordinal categories (i.e., Fazekas scores 0 up to 6) for the SSNHL cohort and the control cohort that were used for the sample size calculation. p1 is the probability that an observation in controls(X) will be in a lower Fazekas score category than an observation in the SSNHL group (Y) when the alternative hypothesis is true. The null hypothesis being tested is that p1 = ½.

Treatment modalities

Corticosteroid therapy

The standard treatment for patients with iSSNHL is an oral corticosteroid regimen, consisting of 1mg/kg/day of prednisolone with a maximum of 60mg, administered for a period of 7 up to 14 days, Subsequently, the dosage is gradually reduced to zero over the same timeframe[24]. In case of a contraindication for oral corticosteroid use, intratympanic corticosteroid therapy is recommended. A 0.4ml to 0.8ml injection of either dexamethasone (10mg/ml) or methylprednisolone (30 to 40mg/ml) is injected into the middle ear every 3 to 7 days, for a maximum of 4 sessions. If no significant improvement in hearing is observed following oral corticosteroid therapy, intratympanic corticosteroid injection can be considered for salvage therapy.

Hyperbaric oxygen therapy

In Belgium, hyperbaric oxygen therapy (HBOT) is commonly used as treatment option for sudden sensorineural hearing loss. Hyperbaric oxygen therapy can either be combined with oral corticosteroids or used as a salvage therapy when corticosteroid therapy fails to result in hearing recovery. The procedure involves administering hyperbaric oxygen via a facemask in a pressurized chamber at around 2.5 atmospheres, with each session lasting 90 up to 120 minutes. This session will be repeated 10 times[25,26].

It is important to note that In the Netherlands HBOT is not part of the regular therapeutic workup due to the limited supporting evidence and high costs[27].

Study procedures

Subject identification and inclusion

Patients eligible for the study cohort will be recruited by their respective Ear, Nose and Throat (ENT) surgeons at participating centres in both The Netherlands and Belgium. Patients eligible for the control cohort will be recruited by neurologists or ENT-surgeons at Gelre Hospital and ENT-surgeons in Leiden University Medical Center and University Hospital Antwerp.

Data collection

Informed consent will be obtained during a telephone interview conducted several days after the patient receives the written patient information about the study. During this telephone interview, the patient will sign the informed consent form and return it to the research team at Gelre Hospitals, through postal mail. The interview will also include the identification of the patient's symptoms at the onset of iSSNHL, verification of their medical history and medication use.

Once the signed informed consent form is received by the coordinating investigator, relevant data from the participating hospitals will be sought. This data includes the

patient's age, weight, height, medical history, current medication uses and their most recent MRI scan. MRI scans from University Hospital Antwerp will not be shared due to international data transfer restrictions. For the SSNHL cohort, results from pure tone audiometric tests conducted before and after corticosteroid therapy, as well as results from video-head impulse testing and/or calorimetric tests, if performed, will be gathered. Additionally, details regarding the received treatment strategy will be collected.

MRI assessment

MRI scans will be included in the study if they were performed within six months prior to the onset of sudden deafness or within 3 months afterwards. In order to be adequately analysed, the MRI requires either a T2 or FLAIR sequence of the entire brain. While an MRI of the cerebellopontine angle or entire brain is part of regular diagnostic work-up, the scanning protocol might vary somewhat between participating centres.

Figure 2.| MRI assessment sheet.

1. Fazekas score

A. periventricular white matter (PVWM)	
	0 = absent
	1 = "caps" or pencil-thin lining
	2 = smooth "halo"
	3 = irregular periventricular signal extending into the deep white matter
B. deep white matter (DWM)	
	0 = absent
	1 = punctate foei
	2 = beginning confluence
	3 = large confluent areas
	Total: 0 up to 6.

2. Brain infarctions*

	Yes= 1 / No= 0	Remarks
Presence		
Size (in mm)		

*Bi's need to meet the following criteria:
1. Minimal size of 3mm
2. Cerebrospinal fluid (CSF) appearance in all MRI sequences.
3. Can be differentiated from dilated Virchow-Robin spaces (dVRS)

The Fazekas score is used to evaluate the severity of white matter hyperintensities in both the periventricular and deep white matter. Brain infarctions will be scored in presence and size.

The MRI scans retrieved in the Netherlands will be assessed by 2 neuroradiologist separately, each with multiple years of experience in MRI assessment of head and neck pathology. The MRI scans of patients included in Antwerp will be assessed by a neuroradiologist of the University Hospital Antwerp. Figure 2 shows the scoring sheet used for MRI assessment. In case the degree of white matter hyperintensities differs 2 or more points on the Fazekas scale, the radiologist will review the MRI together until consensus is reached. Previous MRI assessments performed by both radiologists involved in this study demonstrated substantial interrater agreement in white matter hyperintensity assessment using the Fazekas score, with a kappa value of 0.74[20].

Ethics and dissemination

Informed consent

Prior to seeking consent to enter the study, participants will receive an explanation of the study along with an information leaflet, followed by a minimum of 5 days for consideration. Participants have the right to decline participation without the need to provide a specific reason. If patients do not give consent in participating in the study, their contact information will thereafter be deleted from our records.

Data handling

Personal data, including medical history and diagnostic test results, will be sent to the investigating site via digitally protected email, after informed consent has been obtained.

Upon arrival at Gelre Hospital, the relevant information will be extracted from the received files. Subsequently, this data will be pseudonymized and stored in a research database, using Castor EDC (Castor EDC, Amsterdam, The Netherlands). The original files will be stored on a protected data drive at the ADC.

MRI scans obtained from hospitals in the Netherlands will be shared electronically via the national Twiin platform for data exchange, developed by Vereniging van Zorgaanbieders voor Zorgcommunicatie (VZVZ), Den Haag, The Netherlands. The MRI scans will be pseudonymised and uploaded to a secured Picture Archiving and Communication System (PACS) worklist at the radiology department of Gelre Hospital Apeldoorn. Following assessment of the pseudonymised MRI-scans, this PACS worklist will be deleted, while the MRI scans themselves have been stored on a protected data drive of the ADC.

MRI scans from Antwerp will be assessed by their respective neuroradiologists due to international data transfer restrictions.

The assembled document files, digital files and MRI-scans will be saved for a period of 15 years on a protected data drive at the ADC. When this period has passed, all data will be deleted and all files will be destroyed.

Risks and benefits

Participants in this study will not be subjected to any additional study-related interventions beyond standard medical practices, such as MRI scans and audiometric testing, which are typically performed when SSNHL is suspected. No blood investigations or procedures beyond the established iSSNHL treatment guidelines in the Netherlands and Belgium will be included in this study.

Implications for future research

The identification of vascular involvement in the onset of sudden deafness could have serious implications for the current treatment guideline of sudden hearing loss. Specifically, for a subset of patients that appears to have increased cardiovascular comorbidity, consideration of cardiovascular risk management, including anticoagulant administration, could be warranted. If the results of the cross-sectional study, as described in this paper, provide evidence for vascular involvement in the pathophysiology of sudden sensorineural hearing loss, follow-up investigation of the included study population could be beneficial. This follow-up could imply a retrospective investigation of the incidence of stroke in the five years after inclusion in this study.

Data deposition

Upon reasonable request, the dataset and statistical code may be shared. The dataset will not be publicly accessible. To stimulate transparency and improve future research, this protocol will be published open access.

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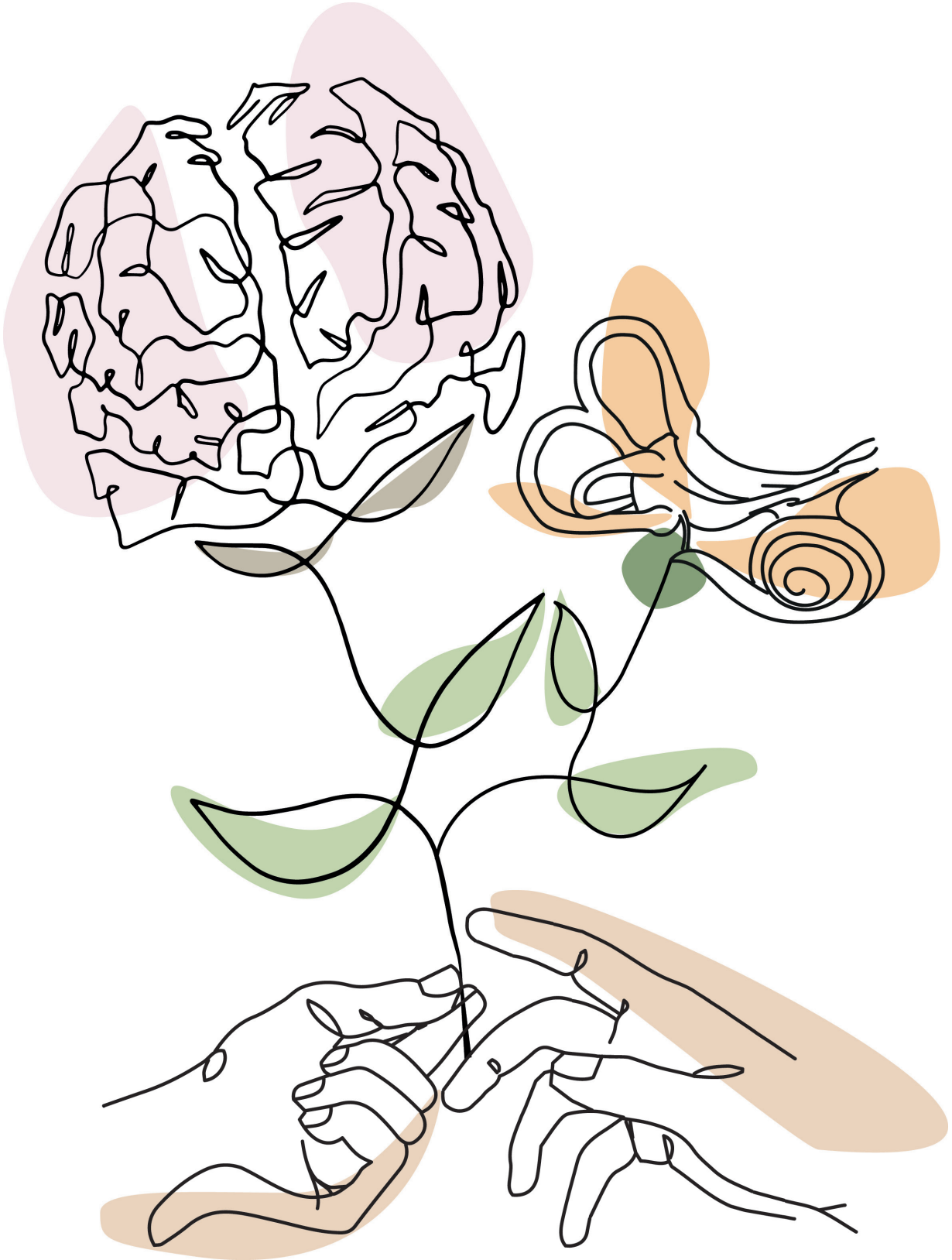

Chapter

9

Summary and general discussion

Sudden sensorineural hearing loss (SSNHL), vestibular neuritis (VN) and labyrinthitis are conditions that affect the cochlea, vestibule, semicircular canals and vestibulocochlear nerve, or a combination of these structures. Possible causes of these conditions include infections, autoimmune disorders, neoplasms, ototoxic drugs and trauma, but in over 90% of cases the precise underlying mechanism remains unclear[1,2].

Most cases of acute vertigo or hearing loss without an apparent cause are attributed to inflammation secondary to viral infection. While recent upper respiratory tract infections have been associated with several cases of acute hearing loss or acute vestibulopathy, not all patients experience flu-like symptoms before the onset of disease[3]. Furthermore, treatments with antiviral medication or corticosteroids have not been proven to result in more hearing recovery, balance restoration or shortened illness duration, when compared to a placebo[4–7].

First documentation of vascular involvement in sudden deafness can be traced back to the seventies, originating from case reports of temporal bone studies[8,9]. In recent years, several cohort studies were published describing the prevalence of generalized cardiovascular disease in patients presenting with acute hearing or vestibular loss[10–16]. The hypothesis of vascular involvement in acute hearing or vestibular loss is based on the limited collateral blood supply to the inner ear, rendering this an end organ with great susceptibility to ischemia. Additionally, the abrupt onset of symptoms bears a resemblance to cardiovascular events such as amaurosis fugax or myocardial infarction. If cardiovascular involvement exists in certain cases, adequate cardiovascular risk management and anticoagulant therapy should be considered. In this thesis we will investigate associations between cardiovascular risk factors, generalized cardiovascular disease and sudden sensorineural hearing loss, vestibular neuritis and labyrinthitis.

Chapter 2

Chapter 2 provides a comprehensive overview of the body of literature investigating the prevalence of cardiovascular comorbidity, the degree of cerebral small vessel disease, and the consequent risk of stroke in patients with acute hearing loss diagnosed as iSSNHL.

The first meta-analysis in this chapter investigates the cardiovascular risk factors and comorbidity in patients with SSNHL. Overall, patients with SSNHL exhibited, on average, a higher BMI, elevated total and low-density-lipoprotein (LDL) cholesterol, as well as increased odds of having diabetes, hypertension and a medical history of myocardial infarction when compared to healthy controls. HDL-cholesterol levels were significantly lower in SSNHL cases than in controls. While there was a trend towards higher smoking rates among SSNHL patients, this difference did not reach statistical significance. The increased prevalence of cardiovascular risk factors among SSNHL patients suggests a vascular involvement in the pathophysiology of SSNHL. It is worth noting that our analysis included mean values for continuous variables such as total cholesterol levels. Previously,

Simoes et al compared studies that exclusively considered abnormal cholesterol values, above the hyperlipidemia threshold[17]. In their meta-analysis, they found no significant difference in abnormal cholesterol values between patients with SSNHL and controls. After our primary analysis, we electively excluded articles that included patients with cholesterol values below the hyperlipidemia threshold to compare our results with that of Simoes et al using similar inclusion criteria. The statistically significant difference in total cholesterol levels remained. This could be attributed to the higher number of included articles in our analysis, executed later in time.

In the second meta-analysis we summarize the existing literature that investigated the degree of cerebral small vessel disease in patients with SSNHL. Our analysis did not demonstrate an elevated likelihood of SSNHL patients having a pathologically increased Fazekas score – an ordinal scale to measure the degree of white matter hyperintensities. Yet, the outcomes reported in the articles included in the review showed substantial heterogeneity. The final outcome was primarily based on our own findings, outlined in chapter 4 of this thesis. Other authors have reported evidence of higher Fazekas scores in patients aged 48-60 years old and patients with more profound hearing loss[18–20]it could be considered as an early sign of a vascular disease and not only a specific local condition. Chronic hypoperfusion in the brain districts leads to a chronic ischemic damage, called cerebral small vessel disease (CSVD). Interpreting these results proves challenging, as establishing causation within correlations involves multiple interacting variables, such as age. Adequate matching and/or correction for confounding factors is necessary, but is often lacking or insufficient.

In the third section of this chapter, we conducted a systematic analysis of all research on the occurrence of stroke following sudden deafness. In total we included 7 articles, of which 5 articles described a higher risk of stroke in patients diagnosed with iSSNHL than in controls.

Chapter 3

Chapter 3 focuses on the presence of white matter hyperintensities - a type of small vessel lesion detectible on MRI - in patients with acute vestibulopathy diagnosed as vestibular neuritis (VN). We observed an increased degree of white matter hyperintensities in elderly patients diagnosed with vestibular neuritis (VN) compared to the control cohort, consisting of patients with trigeminal neuralgia or vestibular paroxysmia. After correction for potential confounding factors, patients with VN demonstrated an estimated odds ratio of 1.6 for having a higher Fazekas score than controls. While this is a statistically significant increase in risk, the effect size remains relatively modest. Other authors reported higher prevalences of cardiovascular risk factors in patients with VN[21], which could support vascular involvement in some cases of VN. It is essential to acknowledge that both our study and prior investigations are characterized by small sample sizes and retrospective

study designs. Consequently, conclusions should be drawn with caution. There is the possibility that certain cases diagnosed with VN could have been misdiagnosed and could, in fact, be associated with brain infarctions, mimicking symptoms of peripheral dizziness. Still, it would be of considerable interest to prospectively explore whether patients diagnosed with VN are at higher risk of vascular complications such as ischemic stroke or vascular dementia.

Chapter 4

In chapter 4 we analyze the degree of white matter hyperintensities in a cohort of patients who experienced sudden sensorineural hearing loss and compared this to a control cohort. We found no difference in the degree of white matter hyperintensities among elderly patients with SSNHL, when compared with controls diagnosed with trigeminal neuralgia or vestibular paroxysmia. These findings do not entirely align with previous literature that described higher incidences of white matter hyperintensities in patients with iSSNHL[19], especially those aged 45-60 compared to controls[18]. The differences in the results found may be due to the small sample sizes of previous cohorts, the difference in inclusion criteria or the lack of power analyses. Also, there could be several interacting factors, genetic, acquired as well as environmental, that could influence cerebral small vessel disease in people in a way that we simply do not (yet) understand.

Chapter 5

In chapter 5 we investigate the degree of white matter hyperintensities in a cohort of patients diagnosed with Meniere's disease. While this study population does not exactly meet the primary focus of this thesis, the analysis was inspired by a hypothesis put forward by Foster and Breeze[22] This hypothesis proposes a vascular component in the pathophysiology of MD, suggesting that (transient) ischemia could occur in patients with MD due to the combination of endolymphatic hydrops, an increased sensitivity to oxygen deficiency in labyrinthine tissue, and reduced cerebral blood flow due to cardiovascular comorbidity[22].

Our results do not align with this hypothesis. We did not observe an increase in WMH in patients with MD, which would have been expected if patients develop MD due to the combination of endolymphatic hydrops 'and cardiovascular disease. In fact, also clinical observations do not provide an indication of hypoperfusion-induced ischemia. The recurring nature of MD does not resemble the course of disease in cardiovascular diseases such as myocardial infarction and stroke. Furthermore, if ischemia is indeed responsible for hearing loss or vestibular loss in MD patients, this would likely be irreversible and persistent. However, persistent vestibular loss is not a universal feature among MD patients.

Chapter 6

In chapter 6 we describe the results of a retrospective cohort study investigating the risk of stroke after SSNHL. Many articles included in our systemic review on the risk of stroke following SSNHL (see chapter 1) had limitations, including the possibility of selection bias because of the study design. Due to the relatively low incidence of stroke, investigating an association between iSSNHL and stroke requires a very large dataset. In several articles, data was derived from national health insurance databases, lacking audiometry results or diagnosis confirmation from medical records. Furthermore, information on confounding factors such as cardiovascular comorbidity was limited. This prompted us to perform a retrospective cohort study using primary health care data, derived from a database comprising 84 general practices. The study did not reveal a higher overall incidence of stroke following sudden deafness compared to a control cohort matched for age and gender. However, iSSNHL patients aged 60 or higher did demonstrate a higher risk of stroke than controls of a similar age, regardless of their comorbidity. Important limitations of this study included the absence of audiometry results and hospital data, thereby relying solely on the adequacy of diagnoses from general practitioners. The overall incidence of stroke in the study cohorts was low.

Chapter 7

In chapter 7 we report the results of a retrospective cohort study assessing the limitations encountered by patients who experienced acute hearing and vestibular loss (usually referred to as viral labyrinthitis). After a median follow-up of 61 months, the mean VAAI (vestibular activity avoidance instrument) score was 20.4 (SD 12.9). Fifty-seven and a half percent of patients refrained from activities that triggered dizziness and 62.5% could not perform daily tasks as before the onset of complaints. Due to the retrospective design of the study, we were unable to retrieve the cardiovascular comorbidity in these patients. With no information about cardiovascular comorbidity we were unable to report on the likelihood of vascular involvement in the pathophysiology of labyrinthitis.

Since there is no conclusive evidence of viral involvement in the pathophysiology of labyrinthitis, we decided to use the term idiopathic labyrinthitis instead of viral labyrinthitis for patients with concurrent hearing loss and vestibulopathy. Yu et al. described vestibular organ involvement in iSSNHL even in the absence of vertigo, while concurrent vertigo is a marker for worse prognostic hearing outcomes in patients with iSSNHL[23,24]. To date, however, a significant number of patients with iSSNHL do not undergo vestibular testing, even in the presence of vertigo. Adequate diagnosis of concurrent vestibulopathy and SSNHL is essential to start targeted therapy and manage patients' expectations. In this chapter we propose a set of criteria to diagnose idiopathic labyrinthitis, thus improving differentiation between iSSNHL and concurrent vestibulopathy or vestibular neuritis and possibly facilitating research into these entities.

Chapter 8

Chapter 8 encompasses the protocol for a prospective cross-sectional multicenter study investigating the presence of cerebral small vessel disease in elderly patients with iSSNHL. As described in chapter 4, we encountered limitations in accurately linking white matter hyperintensities observed on MRI with cardiovascular comorbidities. To address this limitation, we decided to design a prospective study including 205 patients with SSNHL and 205 controls who undergo MR imaging for a non-vascular indication. Patients will be included from 10 centers in the Netherlands and one center in Belgium. Currently the study is up and running in all centers, we hope to finalize inclusion by July 2025. Because of limited funding, we are unable to perform laboratory tests to quantify the severity of cardiovascular risk factors. Also, patients who have complete hearing recovery after corticosteroid therapy will generally not undergo MR imaging which may result in selection bias. These are two potential limitations of this study.

Future perspectives

The outcomes reported in this thesis emphasize the complex nature of acute sudden sensorineural hearing loss, acute vestibulopathy or a combination of both. The pathophysiology is complex and probably multifactorial. In a specific subset of patients, cardiovascular involvement seems probable, warranting thorough monitoring of cardiovascular risk factors and comorbidities. The current evidence does not support the justification of anticoagulant therapy for all patients suffering from sudden sensorineural hearing loss. Maybe the use of larger databases incorporating data from both general practices and hospitals could allow the drawing of more robust conclusions. Still, finding a causal relationship between cardiovascular disease and acute hearing loss or vestibulopathy using similar study designs is hampered by numerous potentially interacting factors.

It would be ideal to visualize the pathological mechanism of inner ear disease itself. Current imaging techniques face limitations in depicting all anatomical structures involved in hearing and maintaining equilibrium. Higher resolution imaging, like the 7 Tesla (T) MR scan could offer more insight into the inner ears' complex vasculature, eventually contributing to a clearer understanding of the pathogenesis of inner ear diseases. 7T MRI's has several advantages over 1.5 and 3T MR scans as 7T MR provides an enhanced sensitivity to detect blood brain barrier dysfunction and has the ability to visualize perforating arteries and microinfarctions of these vessels[25]. Additionally, the ongoing DYNAMIC project in the Netherlands, a consortium of seven partners led by the prof. dr. Norris from the Radboud University, aims to construct a 14 Tesla dedicated to improving MR research. While the technology behind high-resolution MR appears promising, implementation of these scanners in everyday healthcare poses considerable financial and technical challenges.

Another way to research the pathological mechanism in acute hearing or vestibular loss is by studying a representative model. While animal experiments may offer some insight, the labyrinth of animals differs from that of humans. Promising developments, such as "organs on a chip" show potential for understanding inner ear physiology[26,27]. Using human derived pluripotent stem cells, a model that includes all relevant cell types of the inner ear can be cultivated. Hypothetically, this model can then be exposed to suspected circumstances leading to inner ear disease, such as hypoxia or inflammation. This approach would enable investigation of the pathological response to hypoxia or inflammation on a cellular level, providing insights into the damage believed to result in conditions like sudden sensorineural hearing loss, vestibular neuritis or labyrinthitis.

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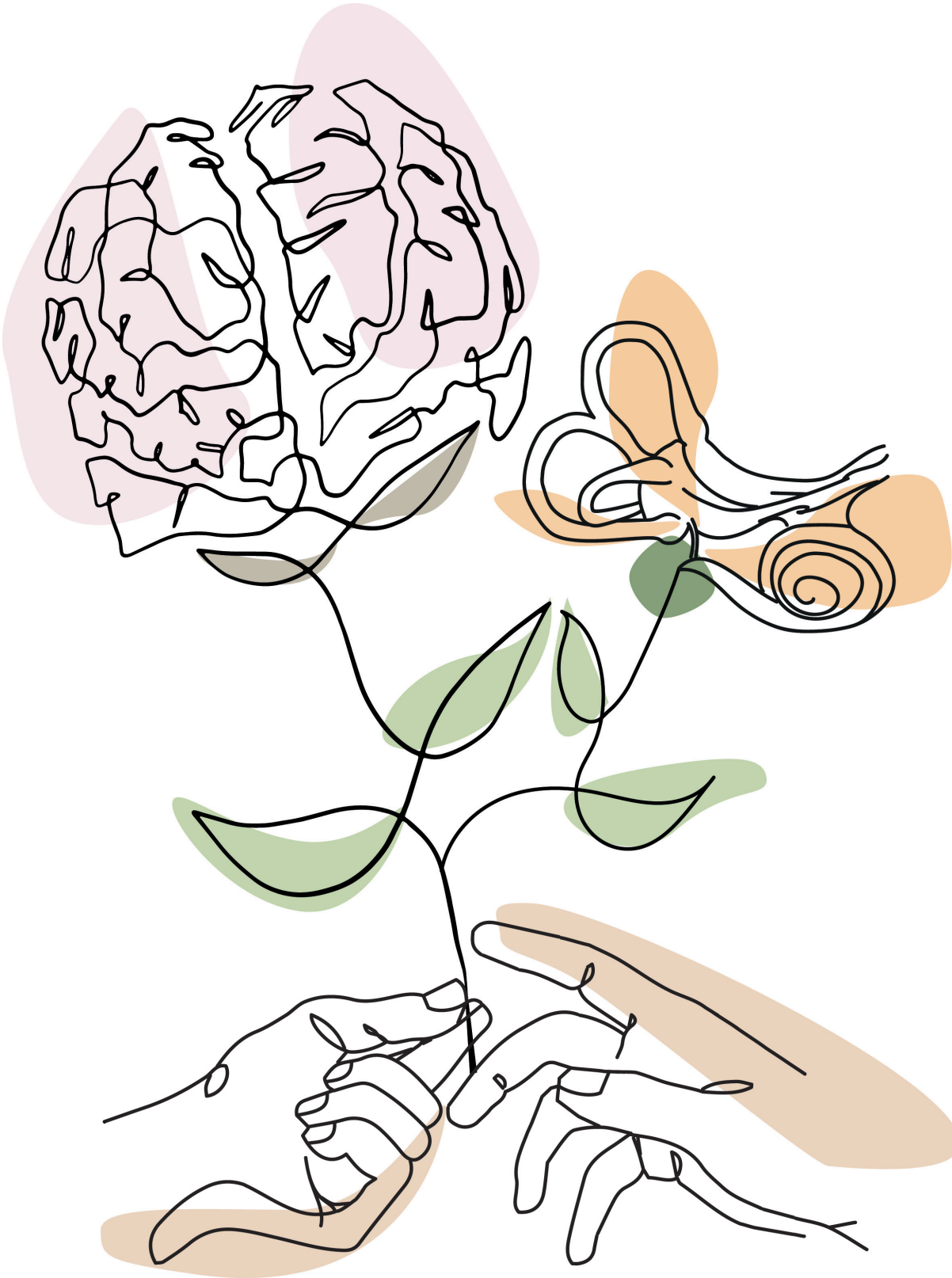

Appendices

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Nederlandse Samenvatting

Plotsdoofheid (sudden deafness) neuritis vestibularis (vestibular neuritis, VN) labyrinthitis zijn aandoeningen waarbij een of meer structuren van het binnenoor zijn aangedaan, waaronder het slakkenhuis (de cochlea), het vestibulum, de semicirkelvormige kanalen of een combinatie van deze structuren. Dit resulteert in acuut gehoorverlies, acute draaiduizeligheid of beide, en brengt een aanzienlijke morbiditeit met zich mee. Mogelijke oorzaken van deze aandoeningen zijn infecties, auto-immuunziekten, tumoren, ototoxische medicijnen en traumata. In veel gevallen blijft de exacte oorzaak voor het ontstaan van de klachten echter onduidelijk.

Meestal wordt acute duizeligheid of gehoorverlies toegeschreven aan een ontsteking van het binnenoor door een virale infectie. Hoewel een recent doorgemaakte bovenste luchtweginfectie in verband is gebracht met enkele gevallen van plotsdoofheid of acute vestibulaire uitval, ervaren niet alle patiënten griepachtige symptomen voor het begin van de ziekte. Daarnaast bestaat er geen bewijs dat behandeling met antivirale medicijnen of corticosteroïden leiden tot gehoorherstel, herstel in evenwichtsfunctie, reductie van balansklachten of verkorte ziekteduur in vergelijking met behandeling met een placebo. Dit roept de vraag op of een virale origine van plotsdoofheid, neuritis vestibularis of labyrinthitis wel terecht is en of er een andere behandeling moet worden overwogen.

De eerste hypothesen van vasculaire betrokkenheid bij het ontstaan van plotsdoofheid dateren uit de jaren zeventig van de vorige eeuw, waarbij ischemie in enkele pathologierapporten van onderzoek aan het binnenoor werd beschreven. Recente case-control studies in cohorten met neuritis vestibularis en plotsdoofheid beschrijven een hogere prevalentie van cardiovasculaire risicofactoren en cardiovasculaire comorbiditeit in vergelijking met de algemene populatie. De beperkte bloedtoevoer naar het binnenoor maakt het orgaan zeer gevoelig voor de gevolgen van ischemie. Daarnaast lijkt het acute ontstaan van symptomen op cardiovasculaire gebeurtenissen zoals amaurosis fugax of een hartinfarct. Als er daadwerkelijk cardiovasculaire betrokkenheid bestaat, zou adequaat cardiovasculair risicomanagement en antistollingstherapie moeten worden overwogen.

Onderzoek en Bevindingen

Hoofdstuk 2

Dit hoofdstuk biedt een uitgebreid overzicht van de literatuur over de correlaties tussen cardiovasculaire ziekte en plotsdoofheid, te weten de prevalentie van cardiovasculaire risicofactoren en cardiovasculaire comorbiditeiten, de mate van schade aan de kleine hersenvaten en het risico op een beroerte. De eerste meta-analyse toont aan dat patiënten die plotsdoofheid doormaken in vergelijking met gezonde controles gemiddeld een hogere BMI en verhoogde totaal cholesterol- en LDL-cholesterolniveaus hebben, alsmede een verhoogde kans op diabetes, hypertensie en een voorgeschiedenis met hartinfarct.

Hoewel er een trend zichtbaar is van een hoger percentage rokers onder patiënten met plotsdoofheid, was het verschil met gezonde controles niet statistisch significant.

De tweede meta-analyse toonde bij patiënten met plotsdoofheid geen verhoogde kans op pathologisch verhoogde Fazekas-scores (een maat voor de aanwezigheid van cerebrale witte stofafwijkingen). Het aantal studies hierover was echter beperkt.

De derde analyse laat een overzicht zien van artikelen die het risico op een beroerte na plotsdoofheid beschrijven. Daarin werd in vijf van de zeven artikelen een verhoogd risico op een beroerte gezien bij patiënten met plotsdoofheid in de 5 jaar daarop volgend.

Hoofdstuk 3

Dit hoofdstuk richt zich op de aanwezigheid van wittestofafwijkingen op MRI-beelden bij patiënten met neuritis vestibularis. We constateerden vaker een Fazekas score van 5 of 6 bij patiënten met neuritis in vergelijking met een controlegroep, wat suggereert dat vasculaire factoren een rol kunnen spelen bij sommige gevallen van neuritis. Na correctie voor mogelijke interacterende factoren hadden patiënten met neuritis vestibularis een odds ratio van 1,6 voor een hogere Fazekas-score dan controles van dezelfde leeftijd en hetzelfde geslacht.

Hoofdstuk 4

Dit hoofdstuk beschrijft de analyse van de mate van wittestofafwijkingen bij een cohort van patiënten met plotsdoofheid vergeleken met een controlegroep. Er werd geen statistisch significant verschil gevonden in de verdeling van de Fazekas-scores tussen patiënten met of zonder plotsdoofheid. De gemiddelde Fazekas-score was 2 in de groep met plotsdoofheid en 1 in de groep met controles, bij een gemiddelde leeftijd van 65 jaar. Op basis van de beschikbare literatuur was dit niet de uitkomst die werd verwacht. Mogelijke oorzaken voor deze verschillende uitkomsten zijn de kleine studiepopulatie, de ontbrekende power-analyse en de beperkte beschikbaarheid van data over cardiovasculaire comorbiditeit en daardoor mogelijke onderschatting van interacterende factoren.

Hoofdstuk 5

Dit hoofdstuk analyseert de mate van cerebrale wittestofafwijkingen op MRI in een groep patiënten met de ziekte van Menière. Deze groep is meegenomen in dit proefschrift omdat tijdens achtergrondonderzoek ten behoeve van dit proefschrift er aanwijzingen waren over een mogelijk vasculaire oorzaak bij het ontstaan van Menière. Onze case-control studie met 111 patiënten met Ménière die vergeleken weren met controles toonde geen verhoogde aanwezigheid van wittestofafwijkingen bij deze patiënten, wat de hypothese van een vasculaire component in de pathofysiologie van Menière tegenspreekt.

Hoofdstuk 6

In dit hoofdstuk beschrijven we de resultaten van een retrospectieve cohortstudie naar het risico op een beroerte na plotsdoofheid met gebruik van huisartsendata. Vierhonderdtachtig patiënten uit huisartspraktijken in en rondom Nijmegen, gediagnostiseerd met plotsdoofheid, werden vergeleken met 1911 controles. In de gehele groep met plotsdoofheid werd geen verhoogd risico op een beroerte gevonden. Echter, wanneer specifiek werd gekeken naar patiënten van 60 jaar en ouder werd er een 4,6 keer hoger risico op het ontwikkelen van een beroerte in de vijf jaar volgend op de plotsdoofheid gezien in vergelijking met controles van dezelfde leeftijd, ongeacht de aanwezigheid van cardiovasculaire risicofactoren. Deze bevinding ondersteunt een relatie tussen cardiovasculaire ziekte en plotsdoofheid bij oudere patiënten.

Hoofdstuk 7

Dit hoofdstuk rapporteert de resultaten van een retrospectieve cohortstudie naar de symptomen, mate van gehoorverlies en vestibulaire functie bij patiënten met acuut gehoorverlies en vestibulaire uitval, geduid als labyrinthitis. Het cross-sectionele deel van deze studie beschrijft de beperkingen waarmee patiënten na het doormaken van een labyrinthitis worden geconfronteerd. Na een mediane follow-up van 61 maanden bleek dat 57,5% van de patiënten met labyrinthitis (nog altijd) activiteiten vermeden die duizeligheid veroorzaakten en 62,5% niet meer in staat was dagelijkse taken uit te voeren zoals voorafgaande aan de ziekte. Het retrospectieve design van deze studie beperkte onze mogelijkheid om ook cardiovasculaire comorbiditeit te rapporteren.

Hoofdstuk 8

Eerder onderzoek, beschreven in hoofdstuk 4, kampte met beperkingen in het studiedesign, waaronder een kleine studiegroep, het ontbreken van een sample size berekening en beperkt inzicht in cardiovasculaire comorbiditeit. Om de kwaliteit van onderzoek naar cardiovasculaire betrokkenheid bij het ontstaan van plotsdoofheid te verbeteren, werd een protocol geschreven voor een prospectief opgezette cross-sectionele multicenter studie naar de aanwezigheid van cerebrale vaatziekte (waaronder wittestofafwijkingen) bij oudere patiënten met plotsdoofheid. We streven ernaar 205 patiënten met plotsdoofheid en 205 controles te includeren binnen de 12 deelnemende centra. Zowel de patiënten met plotsdoofheid als de controles ondergaan een MRI scan van het brein. Daarnaast kijken we naar de cardiovasculaire comorbiditeit en mate van gehoorverlies bij presentatie.

Door beperkte financiering zijn we helaas niet in staat laboratoriumtests uit te voeren om de ernst van cardiovasculaire risicofactoren te kwantificeren, wat op voorhand een potentiële beperking van de studie vormt.

Conclusie en toekomstperspectieven

De resultaten van dit proefschrift benadrukken de complexe en vaak multifactoriële aard van plotsdoofheid en acute vestibulaire uitval. Bij een specifieke subgroep van patiënten lijkt cardiovasculaire betrokkenheid waarschijnlijk, wat bij hen een gedegen cardiovasculair risicomanagement rechtvaardigt. Op basis van de huidige wetenschappelijke bewijslast kan het starten van antistolling bij patiënten met plotsdoofheid of neuritis vestibularis niet worden aanbevolen.

Bij onderzoek naar correlaties bestaat het probleem dat tal van variabelen kunnen interacteren met de uitkomstmaat, waardoor een causaal verband niet kan worden aangetoond. Een prospectief cohortonderzoek met aanzienlijke studiepopulatie, waarbij gecorrigeerd kan worden voor potentieel interacterende factoren, wordt aanbevolen om een causaal verband waarschijnlijker te maken.

Het aantonen van cardiovasculaire ziekte in het binnenoor wordt bemoeilijkt door de locatie, waarbij het geheel is omgeven door bot, evenals het microscopisch formaat.

Idealiter kan de fysiologie van het binnenoor op microscopisch niveau in kaart worden gebracht. Hiervoor zijn ontwikkelingen binnen beeldvormingstechnieken van belang. Zo zou de nieuwe generatie 7 Tesla MRI scan wellicht meer inzicht kunnen bieden in de complexe vascularisatie van het binnenoor.

Een andere methode van verder onderzoek kan zijn een representatief studiemodel te vervaardigen en daar vervolgens de hypothetische pathofysiologie in simuleren. ‘organ on a chip’ technologie, waarbij menselijke pluripotente stamcellen worden verwerkt naar specifieke celtypen van het binnenoor, kan wellicht worden gebruik om pathofysiologische reacties op hypoxie of ontsteking op celniveau te onderzoeken en het effect van gerichte behandeling hiertegen te bestuderen.

Afkortingen

AAOHNS	American Academy of Otolaryngology-Head and Neck Surgery
ADC	Apeldoorn Dizziness Centre
AICA	Anterior inferior cerebellar artery
ATC	Anatomical Therapeutic Chemicals
BPD	Blood pressure dysregulation
BMI	Body Mass Index
CI	Confidence interval
CSVD	Cerebral small vessel disease
CVA	Cerebrovascular Accident
CVRFs	Cardiovascular risk factors
dB	Decibel
DM	Diabetes Mellitus
DWM	Deep white matter
EH	Endolymphatic hydrops
ENT	Ear, Nose an Throat
FABQ	Fear Avoidance Beliefs Questionnaire
FLAIR	Fluid-Attenuated Inversion Recovery
GP	General practitioner
HBOT	Hyperbaric Oxygen Therapy
HDL-C	High-Density Lipoprotein Cholesterol
HIT	Head impulse Test
HINTS	Head Impulse, Nystagmus, Test of Skew
HTN	Hypertension
Hz	Herz
IAA	Internal Auditory Artery
ICD	International Classification of Diseases
ICPC	International Classification of Primary Care
iSSNHL	Idiopathic Sudden Sensorineural Hearing Loss
IQR	Interquartile range
LDL-C	Low-Density Lipoprotein Cholesterol
MD	Meniere's Disease
MRI	Magnetic Resonance Imaging

PACS	Picture Archiving and Communication System
PBMCs	Peripheral blood mononuclear cells
PRISMA	Preferred Reporting Item for Systematic Reviews and Meta-analyses
PTA	Pure-tone audiometry
PVWM	Periventricular white matter
SD	Standard Deviation
SSNHL	Sudden Sensorineural Hearing Loss
TC	Total cholesterol
TIA	Transient Ischemic Attack
TSK	Tampa Scale of Kinesiophobia
VAAI	Vestibular Activity Avoidance Instrument
VOR	Vestibulo-ocular reflex
VN	Vestibular Neuritis
VZVZ	Vereniging van Zorgaanbieders voor Zorgcommunicatie
WMH	White Matter Hyperintensity

Nawoord

Dit proefschrift is het resultaat van vele jaren van onderzoek en samenwerking met verschillende disciplines en instellingen. Zonder de hulp, begeleiding en inspiratie van deze mensen zou dit werk niet mogelijk zijn geweest. Ik wil graag van deze gelegenheid gebruik maken om iedereen te bedanken die op welke manier dan ook heeft bijgedragen aan de totstandkoming van dit proefschrift.

Allereerst wil ik mijn promotor, Prof. dr. Tjasse Bruintjes bedanken voor de kans die hij mij heeft gegeven om dit onderzoektraject aan te gaan en vorm te geven. Zijn kritische blik, motiverende woorden, maar ook zeker de laagdrempelige samenwerking en snelle feedback, op ieder willekeurig moment van de dag, wordt enorm gewaardeerd. Wat mooi om onze fijne samenwerking na Apeldoorn voort te kunnen zetten in Leiden.

Daarnaast wil ik mijn copromotor Dr. Roeland van Leeuwen bedanken. Zijn expertise binnen neurologie en toewijding aan het onderzoek van het Apeldoorns Duizeligheidscentrum hebben een onschatbare bijdrage geleverd aan de grondlegging en uitvoering van dit onderzoekstraject. Daarnaast heb ik kennis op kunnen doen over vestibulologie en gesprekstechnieken tijdens de multidisciplinaire duizeligheidspoli op de dinsdagmiddag, wat goed van pas komt tijdens mijn huidige opleiding tot KNO-arts.

Dr. Tjard Schermer, copromotor en epidemioloog, hartelijk dank voor de onmisbare ondersteuning rondom medisch-etische toetsing en statistiek, je was meermaals mijn leidraad om de crypten van SPSS doorgronden. Bedankt voor de kritische noot bij het schrijfproces en de “out of the box” initiatieven om deze thesis te maken tot wat het is geworden.

Het starten met dit onderzoek temidden van de COVID-pandemie was niet gemakkelijk. Tijdens de start van het onderzoek werkte ik noodgedwongen gedeeltelijk vanuit huis, wat de samenwerking en communicatie soms uitdagend maakte. Daarom wil ik mijn oprechte dankbaarheid uiten aan de medewerkers van de afdeling Biometrie en de afdelingen Keel-, Neus- en Oorheelkunde (KNO) en Neurologie in Apeldoorn voor hun ondersteuning en samenwerking gedurende mijn onderzoek. Carla Colijn, bedankt voor alle hulp met de Castor databases, de eindeloze administratie en het voortzetten van de Rosalie studie. Hanna, mede PhD student bij het ADC, bedankt voor de fijne samenwerking en gezelligheid tijdens de congressen.

Ook mijn vrienden, Anouk, Camille, Diede, Joost, Jill, Karlijn, Larissa, Maartje, Marieke, Marjolein, Moniek, Pauline, Robert, Tia en Lucas, bedankt voor jullie lieve woorden, “slechte” grappen en aanmoediging gedurende mijn promotietraject en de vele sollicitaties die tot mijn huidige carrière hebben geleid.

Collegaatjes van de KNO in LUMC, jullie zijn toppers. Bedankt voor zo’n warm welkom aan de andere kant van het land en de goede sfeer in de assistentenkamer tijdens een druk eerste jaar van de opleiding en de laatste loodjes van mijn PhD.

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Chris, dank voor al je inzet om mijn proefschrift zo mooi weer te geven.

Mijn diepste dank gaat uit naar mijn ouders, Jaco en Gerda, zonder jullie onvoorwaardelijke steun en liefde was ik hier niet gekomen. Ik kon altijd op jullie rekenen. Bedankt voor de vele uren langs de lijn van het voetbalveld, het verslepen van de meubels bij alle verhuizingen tijdens en na mijn studie en het doorlezen van mijn verslagen gedurende mijn gehele academische carrière. Broertjes, dank voor de jaren van vriendschappelijke competitie die mij de nodige "drive" heeft gebracht om dit avontuur te volbrengen.

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A

Biografie

Fieke Oussoren werd geboren op 2 oktober 1994 in het UMC Utrecht. Ze groeide op in Amerongen met haar ouders Gerda en Jaco Oussoren en haar 2 broers, Olaf en Lasse. In 2012 studeerde ze af aan het Revius Lyceum in Doorn. Hierna is ze Geneeskunde gaan studeren aan de Radboud Universiteit Nijmegen. Het laatste jaar van haar opleiding heeft ze coschappen gelopen bij de afdeling Keel-neus en oorheelkunde van het Radboudumc, een tropencoschap in Biharamulo Tanzania gedaan, gevolgd door een wetenschappelijke stage naar de effecten van Laxvox spraaktherapie bij hypernasaliteit ten gevolge van schisis bij kinderen.

Na haar afstuderen heeft ze een jaar gewerkt als artsassistent chirurgie in het Rijnstate ziekenhuis te Arnhem, gevolgd door een half jaar op de spoedeisende hulp in het Viecuri in Venlo. In december 2020 begon ze aan haar promotietraject in het Apeldoorns Duizeligheidscentrum in Apeldoorn onder de begeleiding van prof. Tjasse Bruintjes en dr. Roeland van Leeuwen naar de vasculaire betrokkenheid bij het ontstaan van plotsdoofheid en/of evenwichtsuitval.

Momenteel werkt in het Leids Universitair Medisch Centrum, waar ze in oktober 2022 begonnen is aan de opleiding Keel-Neus en Oorheelkunde.

Curriculum Vitae

Fieke Oussoren

Opleiding en cursussen

Periode	Opleiding/Cursus
MEI 2024	Refresher course Regulations and Organization of Clinical Trials (BROK)
MRT 2021	Basic Course on Regulations and Organization of Clinical Trials (BROK)
JULI 2019	Advanced Trauma Life Support
MEI 2019	Master Geneeskunde
AUG 2015	Bachelor Geneeskunde
JUN 2013	Instructeur vaardigheden acute geneeskunde
JUN 2012	VWO Atheneum NG&NT (8.1 gem)

Werkervaring

Periode	Functie	Organisatie
OKT 2023 – HEDEN	KNO arts in opleiding	Leids Universitair Medisch Centrum
NOV 2020 – HEDEN	PhD student KNO	Apeldoorns Duizeligheidscentrum, LUMC
MAA 2023 – JUL 2023	Vaccinatiearts	Premeo Thuisvaccinatie.nl
JUL 2020 – NOV 2020	ANIOS Spoed Eisende Hulp	Viecuri Venlo
JUL 2019 – JUN 2020	ANIOS Chirurgie	Rijnstate Arnhem
NOV 2017 – OKT 2021	Onderzoeker	Rijnstate Arnhem
NOV 2013 – DEC 2018	EHBO instructeur	Radboud UMC Nijmegen

A

Wetenschappelijke Publicaties

Datum	Publicatie
Mei 2024	Oussoren FK, Schermer TR, Horn LR, van Leeuwen RB, Bruintjes TD. Assessing risk of stroke after idiopathic sudden sensorineural hearing loss using data from general practice. Sci Rep. 2024 May 1;14(1):10026.
Nov 2023	Oussoren FK, Schermer TR, Bruintjes TD, Leeuwen RBV. Idiopathic Labyrinthitis: Symptoms, Clinical Characteristics, and Prognosis. J Int Adv Otol. 2023 Nov;19(6):478-484.
Aug 2023	Oussoren FK, Schermer TR, van Leeuwen RB, Bruintjes TD. Cardiovascular Risk Factors, Cerebral Small Vessel Disease, and Subsequent Risk of Stroke in Patients with Idiopathic Sudden Sensorineural Hearing Loss: Systematic Review and Meta-Analyses of the Current Literature. Audiol Neurootol.
Jun 2023	Oussoren FK, van Leeuwen RB, Schermer TR, Poulsen LNF, Kardux JJ, Bruintjes TD. Cerebral Small Vessel Disease in Elderly Patients With Menière's Disease. Otol Neurotol Open.
Mrt 2023	Oussoren FK, van Leeuwen RB, Schermer TR, Poulsen LNF, Kardux JJ, Bruintjes TD. Cerebral Small Vessel Disease in Elderly Patients with Sudden Sensorineural Hearing Loss. Otol Neurotol. 2023 Mar 1;44(3):e171-e177.
Mrt 2022	Oussoren FK, Poulsen LNF, Kardux JJ, Schermer TR, Bruintjes TD, van Leeuwen RB. Cerebral Small Vessel Disease in Elderly Patients With Vestibular Neuritis. Front Neurol. 2022 Mar 31;13:818533.
Okt 2021	Oussoren FK, Maldonado TS, Reijnen MMPJ, Heyligers JMM; SIBES Study Group; Akkersdijk G, Attisani L, Bellosta R, Heyligers JMM, Hoencamp R, Garrard L, Maldonado T, Naslund TC, Nolthenius RT, Oderich GS, Ponfoort ED, Reijnen MMPJ, Schouten O, Sybrandi JEM, Tenorio ER, Trimarchi S, Verhagen HJM, Veroux P, Wever J, Wiersema A, Wikkeling ORM. Solitary iliac branch endoprosthesis placement for iliac artery aneurysms. J Vasc Surg. 2022 Apr;75(4):1268-1275.e1.
Jan 2020	Oussoren FK, Holewijn S, Claessens N, van der Veen D, Reijnen MM. Pulmonary complications and survival after elective infrarenal endovascular abdominal aneurysm repair in patients with documented chronic obstructive pulmonary disease. Vascular. 2020 Oct;28(5):557-567.
Apr 2019	Katundu DR, Shija PS, Nyombi B, Semvua H, Oussoren FK, van Heerbeek N. The effect of antibiotics on post-adenotonsillectomy morbidity in Tanzanian children: study protocol for a randomized, double-blind, placebo-controlled trial. Trials. 2019 Dec 9;20(1):683.