CHRONIC UNILATERAL VESTIBULAR HYPOFUNCTION:
From Symptoms to a Patient-Oriented Measure

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CHRONIC UNILATERAL VESTIBULAR HYPOFUNCTION:
From Symptoms to a Patient-Oriented Measure

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CHAPTER 1

General introduction and outline of this thesis

1 GENERAL INTRODUCTION

1.1 Anatomy and physiology of the vestibular system

The peripheral vestibular system is part of the inner ear, which is embedded in the petrous portion of the temporal bone. Together with the cochlea, it forms the labyrinth, which contains two parts: the bony labyrinth and the membranous labyrinth. The bony labyrinth surrounds and protects the membranous labyrinth, which is suspended in a fluid called perilymph. The labyrinth contains the semicircular canals and the otolith organs, filled with endolymph, which are responsible for detecting head movements (1, 2). Both inner ears contain three semicircular canals, (anterior/superior, horizontal/lateral, and posterior) that detect angular head movements, and two otolithic organs (utricle and saccule), that sense linear movements and head position relative to gravity (1, 2). These movements are registered through a change in deflection of hair cells within the semicircular canals and otolithic organs, which modulate the activity of afferent nerve fibers (3) (Figure 1).

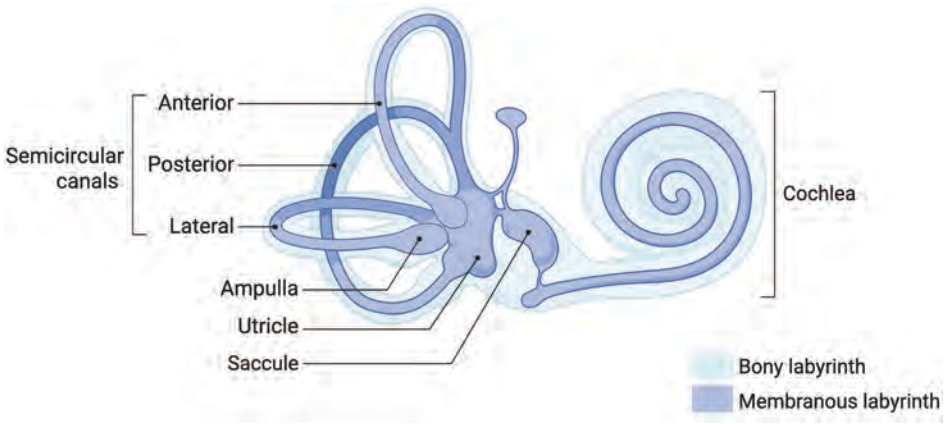


Figure 1. The vestibular labyrinth (adapted from BioRender)

In the semicircular canals, hair cells are located within a sensory area called crista ampullaris. These cells bear bundles of stereocilia on their apical surface, with the tallest one known as the kinocilium. These projections extend into a gelatinous structure called the cupula, which is surrounded by endolymph. When the head rotates, inertia causes the fluid to move relative to the canal, deflecting the cupula, which causes the hair cells to bend and send signals to the brain. Depending on the direction, the fluid moves toward or away from the ampulla, which influence whether the response is excitatory or inhibitory. All hair cells in each crista are aligned in the same direction, and are therefore most sensitive to movement in one specific direction depending on the canal's orientation. Since the cupula has the same density as the surrounding endolymph (close to unity), the semicircular canals do not respond to gravity (1-3) (Figure 2).

In the otolith organs, hair cells are located within a sensory area called macula, which is covered by tiny crystals called otoconia. The macula of the utricle detects movement in the horizontal plane (e.g., forward-backward or side-to-side), while the macula of the saccule detects movement in the vertical plane (e.g., up-down) and gravity (1-3). In the center of the macula, there is a curved region called the striola. The direction in which the hair cells are oriented changes around the striola predominantly pointing toward it in the utricle, and away from it in the saccule. The otoconia, which are located on top of the macula, are small crystals made of calcium carbonate. Since they are heavier than the surrounding endolymph (with a density ratio of about 2.7:1), movements of the head cause the otoconia to shift, which bends the hair cells underneath, and triggers a signal to the brain (1-3).

Hair cell activity is modulated depending on the direction of deflection. When the stereocilia bend toward the kinocilium, the hair cell becomes depolarized, increasing the firing rate of vestibular nerve fibers. In contrast, bending away from the kinocilium causes hyperpolarization, which decreases the firing rate. The orientation of the hair cells determines which type of head movement is detected (1, 2) (Figure 2).

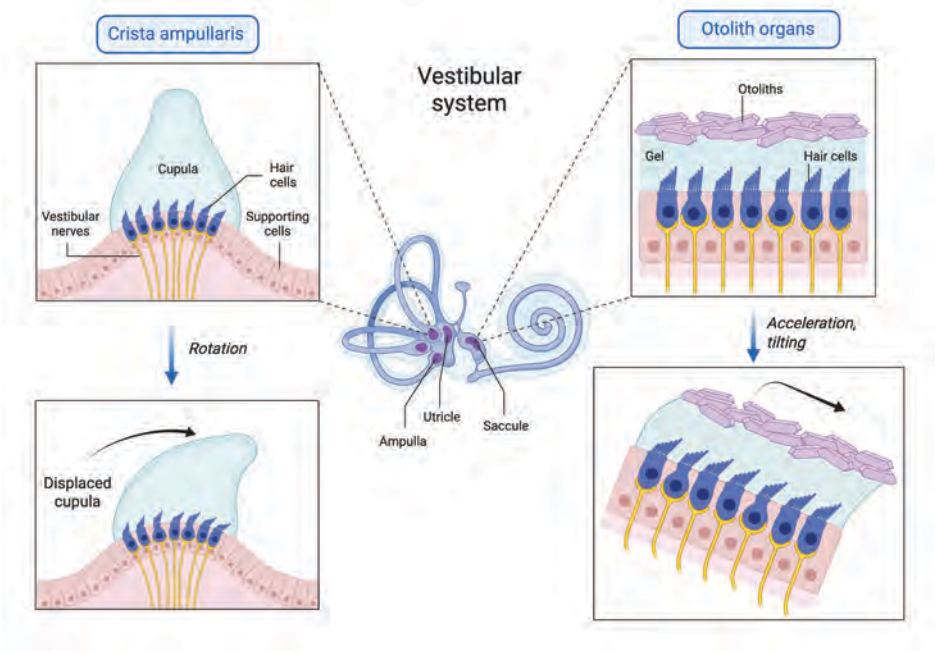


Figure 2. The vestibular labyrinth with the crista ampullaris and otolith organs in detail (adapted from BioRender)

The labyrinth is innervated by the eighth cranial nerve, called the vestibulocochlear nerve. It consists of two main branches: the cochlear nerve, which carries auditory information,

and the vestibular nerve, which transmits balance-related signals. The vestibular nerve is further divided into a superior and inferior branch. The superior branch receives input from the anterior and lateral (horizontal) semicircular canals and the utricle, while the inferior branch carries signals from the posterior semicircular canal and the saccule. These sensory signals converge in the vestibular (Scarpa's) ganglion and then travel through the pontomedullary junction to reach the vestibular nuclei in the brainstem (1, 2) (Figure 3).

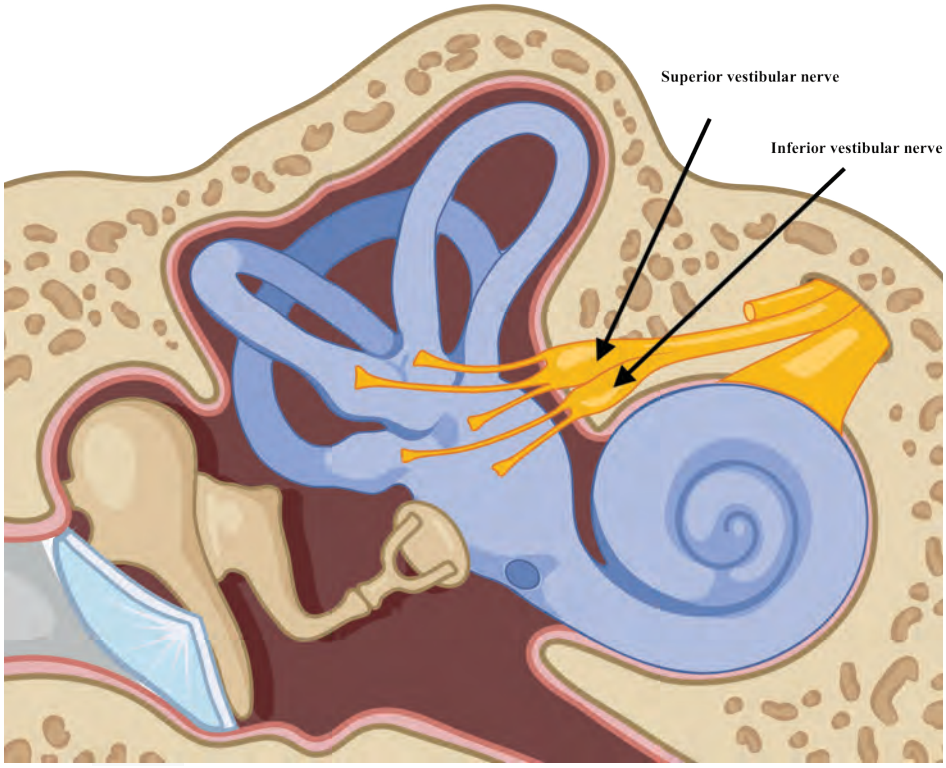


Figure 3. The innervation of the vestibular system

The afferent vestibular nerves of the semicircular canals have a resting firing rate of about 70-100 spikes per second (4, 5). This firing rate increases with stimulation (movement towards the canal) and decreases with inhibition (movement away from the canal). The firing rate ranges between 0 and 400 spikes per second (6). Since the excitatory range exceeds the inhibitory range, there is a bidirectional sensitivity with an excitation–inhibition asymmetry (7). As a result, canals that are aligned in the same plane work as functional pairs; with every movement, one canal will be excited while the contralateral canal is inhibited. For example, rotating the head to the left excites the left lateral semicircular canal and inhibits the right lateral semicircular canal. These push-pull

interactions also occur between the left anterior and right posterior canals (LARP plane), and between the right anterior and left posterior canals (RALP plane). Together, these three canal pairs allow the vestibular system to detect both the direction and amplitude of any head rotation (8).

The vestibular nuclei, located within the medulla and pons, contains neurons that play a key role in regulating several reflex pathways, such as the vestibulo-ocular reflex (VOR), vestibulospinal reflex, and vestibulo-collic reflex. The VOR generates rapid, compensatory eye movements in response to head motion, which maintains stable vision during activities such as walking or running (9). Here, the eyes move in the opposite direction of the head, stabilizing the visual field and preventing blurred vision (9, 10). Besides the VOR, the vestibular nuclei also mediate other reflexes, including the vestibulospinal reflex, which supports postural stability, and the vestibulo-collic reflex, which helps stabilize the head (2, 9, 11). For example, when a person starts falling to one side, the vestibular organs detect the motion and sends signals to spinal motorneurons, which trigger activation of antigravity muscles to restore balance.

In addition to gaze stabilization and postural control, vestibular information integrates with higher brain levels to support spatial orientation, body representation, and navigation (12, 13). Beyond these sensorimotor functions, it is also closely linked to brain regions involved in emotional, cognitive, and autonomic regulation (14, 15). It is demonstrated that the vestibular system connects to areas such as the limbic system, insula, cingulate gyrus, hippocampus, parabrachial nucleus, and dorsal raphe, which form what is now known as the vestibulo-limbic network (16). Autonomic symptoms like nausea and sweating during vestibular disturbances are thought to arise from vestibular connections with the dorsal raphe and neurons in the pontine reticular formation, indicative of a vestibulo-autonomic network (17). Together, these networks help explain the psychological and autonomic symptoms frequently observed in patients with vestibular disorders.

Overall, while the peripheral vestibular system detects and transmits head motion signals, the central vestibular system interprets this input to guide reflexes and higher-order functions. Sensory signals from the peripheral vestibular organs are initially processed by the vestibular nuclei in the brainstem. These nuclei activate reflexes such as the VOR, VSR, and VCR to stabilize gaze, posture, and head position. They also transmit information to higher brain regions involved in motion perception, spatial orientation, and self-location. Additionally, connections to limbic and autonomic centers may explain the emotional and physiological symptoms reported by patients with vestibular hypofunction. Building on this background, this thesis focuses on unilateral vestibular hypofunction, which aims to demonstrate the complaints, clinical characteristics, and impact on quality of life.

1.2 Unilateral vestibular hypofunction (UVH)

Unilateral vestibular hypofunction (UVH) refers to a partial or complete loss of function in one vestibular organ. Patients with UVH experience symptoms in both static and dynamic conditions (2) (18). Static conditions refer to situations without head movement while dynamic conditions refer to situations with head movements. Static symptoms include oculomotor disturbances (e.g., spontaneous nystagmus, skew deviation, and ocular cyclotorsion), postural deficits (e.g., leaning toward the lesion side), and perceptual impairments (e.g., vertigo and increased deviation in the subjective visual vertical test) (19). Dynamic symptoms involve decreased VOR gain, VOR phase shift, reduced VOR time constant, loss of head stabilization, and spatial disorientation (20). In case UVH symptoms occur, a neurological process called vestibular compensation initiates, to decrease these symptoms. While static symptoms typically resolve completely over time, dynamic compensation is often inadequate, takes longer, and may remain incomplete (20-22). In most cases, VOR recovery remains insufficient at low frequencies, whereas high-frequency VOR function can be improved through vestibular rehabilitation exercises (20). Vestibular compensation and vestibular rehabilitation facilitate new head-eye coordination strategies and promote the use of alternative sensory inputs to support balance and gaze stability (20, 23). However, despite these adaptive processes, a subset of patients with UVH continues to experience persistent symptoms, with UVH transitioning from an acute to a chronic condition.

1.3 From acute to chronic: The ongoing burden of unilateral vestibular hypofunction

Despite the expectation that vestibular compensation mitigates symptoms in the acute stage of UVH, research shows that 29–66% of affected patients develop chronic symptoms, which persists for more than three months after the onset (24-29). These chronic symptoms can significantly interfere with daily activities and social interactions (30). The transition from the acute to the chronic UVH is not solely determined by the extent of peripheral recovery but also depends on vestibular compensation, behavioral responses, and psychological adaptation (31). Evidence suggests that maladaptive compensation strategies, such as reduced physical activity or heightened visual dependence, may contribute to symptom persistence (32, 33). It is suggested that early identification of psychological factors, including fear-avoidance beliefs and anxiety, along with careful assessment of static balance and activity levels, may help prevent the progression to chronic dizziness (34). However, as many patients do not fully recover after the acute phase and progress to a chronic phase, it is essential to gain a deeper understanding of patients with chronic UVH. This thesis specifically examines the following key aspects of chronic UVH:

- The spectrum of chronic symptoms

- Etiologies, clinical subtypes, and diagnostics
- Quality of life
- Vestibular implants as potential future management

1.4 Chronic symptoms in patients with chronic UVH

A lack of compensation may contribute to the development of chronic UVH, which leads to a broad range of persistent symptoms (35-38). Despite the growing number of studies describing these symptoms, a structured overview of chronic UVH-related symptoms remains lacking. Furthermore, given the diversity of symptoms in chronic UVH, various intervention strategies such as vestibular rehabilitation therapy (39), medical management (40), surgery (41), and psychotherapy (42) are used to manage chronic UVH symptoms. However, the overall effectiveness of these interventions across the broad symptom spectrum remains unclear. **Therefore, the aim of chapter two was to systematically review the full spectrum of chronic symptoms associated with UVH and to examine the effectiveness of these interventions in alleviating these symptoms.**

In clinical and research settings, chronic UVH is assessed using history taking (43), patient-reported outcome measures (PROMs) (44), and interviews (45). While PROMs are useful to quantify symptoms, they may overlook less common complaints, limiting their ability to capture the full symptom spectrum (46). Thus, there is a need to better capture the full range of symptoms experienced by patients with chronic UVH, as well as their effect on daily life. Furthermore, clear and standardized symptom definitions are essential to avoid misdiagnosis and improve patient care (47). Objective classification systems can help in standardizing symptom assessment. One such framework is the International Classification of Functioning, Disability, and Health (ICF), which offers a structured approach to describe health conditions, functional limitations, and their impact on daily life (48)**. Therefore, the aim of chapter three was to identify the full spectrum of symptoms and their impact on patients with chronic UVH, and to evaluate whether these symptoms and impacts are adequately represented by existing PROMs when interpreted through the ICF framework.**

1.5 Etiologies, clinical subtypes and diagnostics in patients with chronic UVH

Chronic UVH can arise from diverse etiologies, such as Menière's disease, infection/inflammation, vascular events, iatrogenic factors, and others (49). However, identifying the exact etiology is often difficult due to the heterogeneous nature of chronic UVH and significant symptom overlap with other vestibular disorders. In addition, chronic UVH can also present with different clinical subtypes, such as recurrent vertigo-associated UVH or rapidly progressive types (50). These variations in presentation further complicate the diagnostic process and may contribute to under- or misdiagnosis (51). Additionally, no

standardized diagnostic criteria exist for chronic UVH. Ancillary tests are often used to aid diagnosis and detect possible etiologies (52). Given the diversity of etiologies, clinical subtypes, and limitations in current diagnostic approaches, a more detailed investigation is needed to better understand and define these aspects of chronic UVH. **Therefore, the aim of chapter four was to investigate the etiologies, clinical subtypes, and diagnostics in patients with chronic UVH.**

1.6 Quality of life (QoL) in patients with chronic UVH

Considering the challenges described above, assessing QoL is essential to better understand the impact of chronic UVH. A detailed QoL assessment should take into account various factors, including symptom severity, duration, etiology, co-morbid conditions, psychological status, physical activity levels, demographic characteristics, functional limitations, and the level of vestibular compensation (53-56). This thesis addresses these factors through various methodological approaches across different chapters. In addition to chronic UVH, a bilateral vestibular loss of function (bilateral vestibulopathy, or BVP) also presents with significant challenges (57). These two conditions share common symptoms such as unsteadiness, chronic dizziness, and oscillopsia, and are both linked to reduced QoL and substantial socioeconomic impact (58, 59). However, the severity and overall impact may differ. Previous studies examined each condition separately, which leaves a gap in understanding their comparative burden. **To address this gap, the aim of the chapter five was to compare QoL between patients with chronic UVH and those with BVP, using a set of validated PROMs.**

Existing PROMs were not specifically designed for chronic UVH, which may limit their ability to capture all relevant symptoms and functional issues. The Bilateral Vestibulopathy Questionnaire (BVQ), developed specifically for bilateral vestibulopathy, assesses a broad range of physical, cognitive, and emotional symptoms, along with their impact on daily life (60, 61). Given the symptomatic overlap and comparable QoL challenges between BVP and chronic UVH, the preliminary version of the BVQ might serve as a starting point, as it encompasses a broad range of symptoms also relevant to chronic UVH. Therefore, the aim of Chapter 6 was to investigate the construct validity and reliability of the preliminary version of the BVQ in patients with chronic UVH, as a first step toward the development of a condition-specific questionnaire for this population.

1.7 Vestibular implants as potential future management of chronic UVH

Although this thesis does not include data on any interventions, addressing the management of chronic UVH remains essential. Management strategies vary depending on the etiology and associated conditions, and typically include three key approaches: treatment of the primary disorder (e.g., Mé-enière's Disease), treatment of secondary

conditions (e.g., PPPD), and direct treatment of vestibular hypofunction itself. In recent years, several novel treatment options have been explored for conditions such as Menière's disease (62), vestibular migraine (63) and PPPD (64). For chronic UVH specifically, vestibular rehabilitation remains the first-line intervention (65). However, a subset of patients with chronic UVH does not respond adequately to vestibular rehabilitation. For these patients, emerging technologies such as the use of a vestibular implant may offer promising alternatives in the future (66, 67). **Accordingly, the aim of the chapter seven was to review the present status and future prospects of the vestibular implant.**

1.8 Outline of this thesis

Chapter two: *Chronic symptoms in patients with unilateral vestibular hypofunction: A systematic review and meta-analysis*

This study systematically reviews chronic symptoms in patients with chronic UVH and evaluates the impact of various interventions on these symptoms through a meta-analysis.

Chapter three: *Chronic unilateral vestibular hypofunction: A qualitative study exploring the full spectrum of symptoms and impacts through the ICF framework*

Due to the limitations of self-report measures in capturing the full range of symptoms experienced by patients with chronic UVH, a qualitative concept elicitation study was conducted using semi-structured interviews. Fifteen patients with chronic UVH were interviewed to evaluate the complete spectrum of symptoms and their impact on daily functioning. Furthermore, the extent to which these symptoms and impacts are adequately represented by existing patient-reported outcome measures (PROMs), was assessed using an objective classification system based on the International Classification of Functioning, Disability and Health (ICF) framework.

Chapter four: *Chronic unilateral vestibular hypofunction: Insights into etiologies, clinical subtypes, diagnostics and quality of life*

Chronic UVH is associated with a significant reduction in QoL across multiple domains. In this chapter, etiologies, clinical subtypes, secondary diagnoses, and co-morbidities were retrospectively analyzed in a cohort of 251 patients with chronic UVH. In addition, potential predictors influencing QoL outcomes were identified.

Chapter five: *Comparison of quality of life between patients with chronic unilateral vestibular hypofunction and bilateral vestibulopathy*

In this study, a total of 100 patients with chronic UVH and 148 patients with BVP completed the same set of PROMs, including both disease-specific and generic instruments. In addition, normative health data from the general population were retrieved from the literature. This chapter compares QoL outcomes between the two patient groups and healthy controls, to determine the extent to which QoL is affected in patients with chronic UVH.

Chapter six: *Construct validity and reliability of the preliminary version of the Bilateral Vestibulopathy Questionnaire (BVQ) in patients with chronic unilateral vestibular hypofunction*

The BVQ was originally developed to assess symptoms and their impact on quality of life in patients with BVP. Given the considerable overlap in symptomatology and reduced quality of life in both BVP and chronic UVH, this chapter aims to evaluate the construct validity and reliability of the preliminary version of the BVQ as a first step toward the development of a condition-specific questionnaire for patients with chronic UVH.

Chapter seven: *Vestibular implants: The present status and future prospects*

This chapter provides an overview of the current state of vestibular implantation, including the fundamentals of vestibular implants, candidacy criteria, surgical approaches, intraoperative measures, and clinical outcomes in patient with BVP. Additionally, future directions are discussed, with particular attention to the potential candidacy of patients with chronic UVH for vestibular implantation.

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2

CHAPTER 2

Chronic symptoms in patients with unilateral vestibular hypofunction: systematic review and meta-analysis

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ABSTRACT

Objective

To systematically evaluate the full spectrum of self-reported chronic symptoms in patients with unilateral vestibular hypofunction (UVH) and to investigate the effect of interventions on these symptoms.

Methods

A systematic review was conducted following the guidelines of the Preferred Reporting Items for Systematic Review and Meta-Analysis Statement (PRISMA). A literature search was performed in Pubmed, Web of Science, Embase, and Scopus to investigate self-reported symptoms and self-report questionnaires in patients with UVH. All original studies ranging from full-text clinical trials to case reports, written in English, German, and French, were included. The frequency of self-reported symptoms was presented. For self-report questionnaires, a meta-analysis was carried out to synthesize scale means by the pre- and post-intervention means and mean changes for studies that investigated interventions.

Results

A total of 2,110 studies were retrieved. Forty-seven studies were included after title-abstract selection and full-text selection by two independent reviewers. The symptoms of UVH patients included chronic dizziness (98%), imbalance (81%), symptoms worsened by head movements (75%), visually induced dizziness (61%), symptoms worsened in darkness (51%), and oscillopsia (22%). Additionally, UVH could be accompanied by recurrent vertigo (77%), tiredness (68%), cognitive symptoms (58%), and autonomic symptoms (46%). Regarding self-report questionnaires, UVH resulted on average in a moderate handicap, with an estimated mean total score on the Dizziness Handicap Inventory (DHI) and the Vertigo Symptom Scale (VSS) of 46.31 (95% CI: 41.17–51.44) and 15.50 (95% CI: 12.59–18.41), respectively. In studies that investigated the effect of vestibular intervention, a significant decrease in the estimated mean total DHI scores from 51.79 (95% CI: 46.61–56.97) (pre-intervention) to 27.39 (95% CI: 23.16–31.62) (post intervention) was found ($p < 0.0001$). In three studies, the estimated mean total Visual Analog Scale (VAS) scores were 7.05 (95% CI, 5.64–8.46) (pre-intervention) and 2.56 (95% CI, 1.15–3.97) (post-intervention). Finally, a subgroup of patients (≥32%) persists with at least a moderate handicap, despite vestibular rehabilitation.

Conclusion

A spectrum of symptoms is associated with UVH, of which chronic dizziness and imbalance are most frequently reported. However, semi-structured interviews should be conducted

to define the whole spectrum of UVH symptoms more precisely, in order to establish a validated patient-reported outcome measure (PROM) for UVH patients. Furthermore, vestibular interventions can significantly decrease self-reported handicap, although this is insufficient for a subgroup of patients. It could therefore be considered for this subgroup of patients to explore new intervention strategies like vibrotactile feedback or the vestibular implant.

1 INTRODUCTION

Unilateral vestibular hypofunction (UVH) is a heterogeneous disorder in which a partial or complete loss of one of the vestibular organs and/or nerves is present (1, 2). UVH occurs either suddenly or gradually, depending on the etiology. The reported vestibular symptoms of UVH include, among others, dizziness, imbalance, and oscillopsia (an illusion of an unstable vision) and the time course and impact of these symptoms can vary between patients (3–5). They can occur both in static conditions (no body/head movements) and in dynamic conditions (with body/head movements). In case UVH symptoms occur, a neurological process called vestibular compensation can decrease these symptoms (6, 7). However, vestibular compensation is most effective for symptoms in static conditions (8), and less effective for dynamic conditions: approximately 29–66% of UVH patients remain to have vestibular symptoms in dynamic conditions, despite vestibular rehabilitation (9–12). This can cause chronicity and results in a bunch of chronic symptoms in patients with UVH. It was previously demonstrated that a whole spectrum of additional symptoms can be related to UVH, varying from visually induced dizziness (13, 14), impaired spatial navigation and motion perception (14–17), to cognitive complaints (14, 18), autonomic complaints (14, 19), and increased tiredness (14). UVH can therefore significantly affect quality of life (20).

In the literature, different methods are used to capture chronic UVH symptoms (i.e., ≥3 months (21)): history taking (22); questionnaires like the Dizziness Handicap Inventory (DHI) (23) and Vertigo Symptom Scale (VSS) (24); scales like the Visual Analog Scale (VAS) (25); and semi-structured interviews (26). Regarding questionnaires, the DHI and VSS are commonly used patient-reported outcome measures (PROMs) in this patient population. The DHI is a validated, self-reported questionnaire composed of 25 questions to quantify the impact of dizziness on daily life. For each question, “yes,” “sometimes,” or “no” (that correspond to four, two, or zero points) are answered by patients. The DHI scores categorize the self-perception of dizziness as mild (0–30); moderate (31–60); and severe (61–100) (23, 27). The VSS, consisting of 15 items, reflects severity and frequency of dizziness symptoms within the last month. Each item is scored on a 5-point scale (range 0–4) and hence the total scale score ranges from 0 to 60. Severe dizziness is defined as ≥12 points on the total scale (28). The VAS, which can be used to assess different aspects (e.g., dizzines intensity, dizziness frequency, visual vertigo), subjectively evaluates the perception of vestibular symptoms related to vertigo, dizziness, imbalance, and oscillopsia. In the VAS, dizziness severity is categorized as none (1); slight (2–3); mild (4–5); moderate (6–7); severe (8–9); and extreme (10) (29). A semi-structured interview, which is a combination of a structured and unstructured interview, can also be performed to evaluate symptoms related to UVH. It comprises open-ended questions to facilitate subjects freely expressing their own experiences, opinions, and attitudes (30).

Each method has its pros and cons. For example, questionnaires reflect patients' subjective experiences. This might be an advantage since it avoids interpretation by the clinician and they facilitate quantification of symptoms. On the other hand, it could be a disadvantage since a clinician might ask relevant questions which go beyond the focus of the questionnaire (31). This indicates that no method is perfect to reliably capture the whole spectrum of chronic UVH symptoms, and a combination of these methods might be preferred. In addition, various intervention methods such as vestibular rehabilitation therapy, medical management, surgery, and psychotherapy are applied to see if there is any effect on chronic symptoms in patients with UVH. Depending on the etiology, and prognosis of the disease, the method to be used varies. The effect of interventions on symptoms is mostly provided through patient-reported outcome measures.

Although many symptoms related to UVH have been described in the literature, a structured overview of chronic symptoms related to UVH is currently lacking. Therefore, the objective of this study was to systematically review the full spectrum of chronic UVH symptoms. In addition, the effect (or lack of effect) of interventions on these symptoms was evaluated. These findings could serve as the first step to establish a validated PROM specifically for patients with UVH.

2 METHODS

2.1 Registration and protocol

This systematic review was carried out following the guidelines of the Preferred Reporting Items for Systematic Review and Meta-Analysis Statement (PRISMA) (32). The protocol was registered by the International Prospective Register of Systematic Reviews (PROSPERO) (www.crd.york.ac.uk/prospero; registration no. CRD42021260512).

2.2 Data sources and searches

The last systematic search was conducted on November 4, 2022, in the following databases: Pubmed, Web of Science, Embase, and Scopus. "Unilateral Vestibular Hypofunction" (Population), "Chronic Symptoms, ≥3 months (Outcome)." Specific search queries were used (see Supplementary Tables S1, S2). The search queries were developed by three of the authors (MK, LVL, RvdB), in cooperation with an independent librarian at Maastricht University. No filters were applied.

2.3 Study selection

Using predefined inclusion and exclusion criteria (see below), possibly relevant articles were selected. All publications were first exported to EndNote X9 software. After that,

the option “Find Duplicates” was applied in order to remove the publications appearing in more than one database. Two independent reviewers (MK, LVL) screened the articles first on title and abstract (stage 1) and subsequently, a complete reading of the full-text articles was performed (stage 2). Following each phase, inconsistencies regarding inclusion and exclusion criteria between the reviewers were discussed in consensus meetings. Consensus was reached for all cases. Eventually, to ensure that no relevant articles were missed, the references of the articles included after phase 2, were screened and included if eligible.

2.4 In- and exclusion criteria

The in-and exclusion criteria can be found in the Supplementary Table S3. Regarding study design, all original studies ranging from full text clinical trials to case reports, written in English, German, and French were included. Conference abstracts/−reports, letters, abstracts only, animal studies, editorials, (systematic) reviews, and meta-analysis were excluded. Regarding the study population, only studies were selected which included adult UVH patients (≥18 years) with etiologies that could possibly lead to chronic UVH (e.g., acute unilateral vestibulopathy/vestibular neuritis, Menière’s disease, vestibular schwannoma, labyrinthitis, etc.). UVH was defined as a unilateral vestibular deficit, which could vary from (relatively) mild hypofunction to areflexia. UVH needed to be demonstrated by caloric test and/or, rotatory chair test, and/or (video) head impulse test. Therefore, studies were excluded in case none of these vestibular tests were performed. Studies investigating animals and/or patients with central vestibular pathologies and bilateral vestibulopathy were also excluded. Regarding outcomes, only studies with chronic UVH symptoms were selected. Chronic symptoms were defined as symptoms that lasted ≥3 months, according to the clinical practice guideline from the academy of neurologic physical therapy of the American physical therapy association (33). Both self-reported symptoms and self-report questionnaires were included for analysis.

2.5 Quality assessment

The Quality in Prognosis Studies (QUIPS) tool was used to assess risk of bias. The level of evidence was graded using the EBRO-platform (Evidence-Based Guideline Development) (34). Level A1, A2, B, C, or D could be given, based on different items such as the number of participants and statistical power (Supplementary Table S4). Both reviewers independently assessed the risk of bias and level of evidence assessment and discussed the results during a consensus meeting. A total risk of bias score for each study was determined based on the guideline of the checklists: “low risk of bias,” “uncertain risk of bias,” or “high risk of bias.” Four types of biases were taken into consideration:

- Selection bias: “Low risk of bias” in case diagnostic criteria were clearly reported, “uncertain risk of bias” in case diagnostic criteria were not clearly reported.

- Attrition bias: “Low risk of bias” in case the drop-out rate was below 20%, “uncertain risk of bias” in case the drop-out rate was not reported, and “high risk of bias” in case the drop-out rate was above 20%.
- Detection bias: “Low risk of bias” in case valid questionnaires were reported, “uncertain risk of bias” in case questionnaires and self-reported symptoms were reported, “high risk of bias” in case only self-reported symptoms were reported.
- Publication bias: “Low risk of bias” in case the statistical analysis was clearly reported, “uncertain risk of bias” in case the statistical analysis was not clearly reported, “high risk of bias” in case the statistical analysis was not appropriate for the design of the study.

Interrater reliability was evaluated based on Cohen’s kappa. Cohen indicated that the kappa statistic can be categorized as no agreement (values <0), none to slight (0.01–0.20), fair (0.21–0.40), moderate (0.41–0.60), substantial (0.61–0.80), and almost perfect agreement (0.81–1.00). Four different questions indicating four different biases were assessed by Cohen’s kappa: Selection, attrition, detection, and publication bias.

2.6 Data extraction

The relevant data were extracted from the included articles by both reviewers (see Supplementary Tables S5, S6, for further details). First, patient characteristics were extracted, which comprised: total number of patients, age, distribution of gender, etiology, diagnosis, and duration of symptoms. Secondly, all symptoms possibly related to UVH were extracted (self-reported and self-report questionnaires). However, symptoms clearly not related to the vestibular deficit, but related to etiology (e.g., hearing loss after intratympanic gentamicin) were not selected. Thirdly, diagnostic tests and their criteria used for diagnosing UVH (caloric test, rotatory chair test, (video) head impulse test), were extracted. Finally, for self-reported questionnaires, means and standard deviations were extracted (for pre-and post-intervention assessment in studies investigating interventions) where possible.

2.7 Data synthesis

The main outcome measure of this systematic review was a detailed overview of chronic symptoms related to UVH, as reported in the literature. This included self-reported symptoms and self-report questionnaires. The self-reported symptoms were reviewed by three authors (MK, LVL, RvdB). In consensus, these self-reported descriptions were categorized using the universal symptom classification established by Lucieer et al. in patients with a bilateral vestibulopathy (35). The self-report questionnaires DHI, VSS, and VAS were included in the analysis, since these questionnaires were most frequently used in the selected studies. For description of patient characteristics, it was found that

etiologies were defined differently between studies. Etiologies were therefore categorized into different entities, e.g., infectious/inflammatory, neoplasm, iatrogenic, vascular, and trauma (see Supplementary Table S5, 5th and 6th column). In case etiologies were not mentioned in a study, it was categorized as "missing."

2.8 Statistical analysis

Regarding self-reported symptoms, descriptive statistics (number and percentage) were used to show the frequency of each self-reported symptom. The percentage of each self-reported symptom was calculated by the total number of patients who reported the specific symptom (summed over all studies that assessed this symptom), divided by the number of patients that were included in the same studies, multiplied by 100%. It was decided to not divide by the total number of patients included in all studies, since patients did not have the opportunity to report on specific symptoms in all studies. Regarding the self-reported questionnaires, the means for each questionnaire (i.e., DHI, VSS, and VAS) were synthesized via meta-analysis using random-effects models fitted via restricted maximum-likelihood estimation. Based on the estimated pooled means and amount of heterogeneity as estimated from the random-effects models, we also estimated the percentage of true means for the DHI and VAS that are expected to fall above 30 and 3, respectively. For studies examining interventions, mean changes between the pre-and post-intervention assessment regarding the DHI and VAS scores were computed and were also synthesized using random-effects models. The correlation coefficient between the pre-and post-intervention assessments (which is needed to compute the sampling variances of the mean changes, but which is typically not reported) was approximated as 0.5, which could be considered a moderate correlation coefficient. For each model, we report the estimated pooled mean and mean change with a corresponding 95% confidence interval (CI). Besides, heterogeneity was analyzed using Cochran's Q statistic, its degrees of freedom (df) and its corresponding value of p. Higgins' I2 (%) was measured to assess the amount of heterogeneity that could be explained by true, i.e., between study variation. The interpretation of the amount of observed heterogeneity in Higgins' bench-marking values was performed as around 25% (low heterogeneity), around 50% (moderate heterogeneity) and around or above 75% (high heterogeneity). Forest plots were used to visualize the results. The statistical analyses were carried out using R (version 4.2.2) (36) and the metafor package (version 3.8.1) (37).

3 RESULTS

3.1 Study selection

A total of 2,110 articles were retrieved. After removing duplications (1,268 studies) via Endnote, a total of 842 citations were screened on title and abstract. After the second screening phase, 47 articles (2, 14, 16, 17, 24, 38–79) met the in-and exclusion criteria (Figure 1).

3.2 Patient characteristics

A total of 1,478 adults, 799 females (54%) and 679 males (46%), were described, with study sample sizes ranging from 1 to 174. Study participants were between 18 and 84 years of age. The duration of symptoms ranged from at least 3 months to 42 years. A more detailed overview of patient characteristics can be found in Supplementary Table S5.

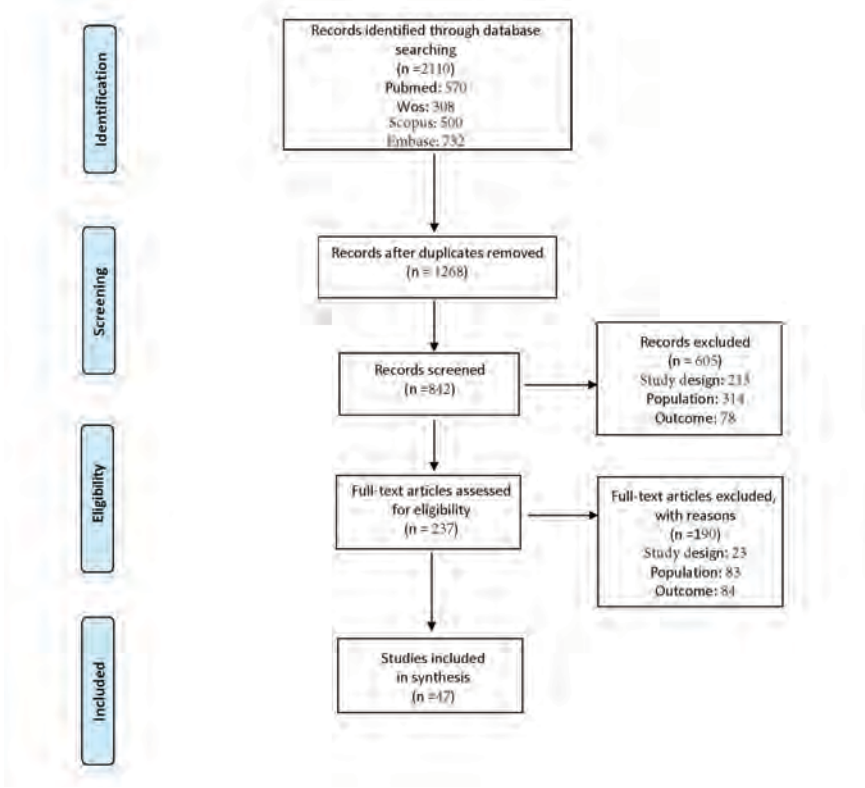


Figure 1. Flow chart of the study selection

3.3 Etiologies

Eight different etiology categories were identified in this systematic review, which could lead to UVH. The most frequent etiologies were Menière's disease (38%) and infectious/inflammatory (16%). In 33% of the patients, the etiology was not described and therefore labeled as "missing" (Table 1).

Table 1. Etiologies of unilateral vestibular hypofunction reported in the studies included in this systematic review

Etiologies (n=1461 patients)	Percentage
Menière's Disease	38%
Infectious/Inflammatory	16%
Neoplasm	3%
Idiopathic	3%
Iatrogenic	2%
Vestibular migraine	2%
Vascular	2%
Trauma	1%
Missing	33%

3.4 Self-reported symptoms

A spectrum of self-reported symptoms related to UVH was reported in 37 studies. Chronic dizziness and imbalance were most reported. The self-reported chronic UVH symptoms were: chronic dizziness (98%), imbalance (81%), symptoms worsened by head movements (75%), visually induced dizziness (61%), symptoms worsened in darkness (51%), and oscillopsia (22%). Together with these symptoms, UVH could be accompanied by recurrent vertigo (77%), tiredness (68%), cognitive symptoms (58%), and autonomic symptoms (46%). Four studies reported additional symptoms beyond vestibular and hearing deficits such as headaches, ear/neck/back pain, limited social activities, and reduced quality of life (Table 1; Supplementary Table S6).

Table 2. Symptoms of patients with Unilateral Vestibular Hypofunction, as reported in the studies included in this review

Symptoms	Number of patients included for analysis	Reported (%)
Chronic dizziness	528	98%
Imbalance	606	81%
Recurrent vertigo	572	77%
Head movements worsen symptoms	144	75%
Tiredness	149	68%
Visually induced dizziness	144	61%
Cognitive complaints	145	58%
Darkness worsens symptoms	161	51%
Autonomic complaints	165	46%
Oscillopsia	151	22%

3.5 Symptoms in self-report questionnaires

Self-report questionnaires were administered in studies without and with interventions (different types of vestibular rehabilitation). Sixteen studies[1] (2, 17, 24, 38–40, 43, 48, 62–65, 69, 74, 78, 79) investigated the total scores of the DHI and six studies (see footnote 1) (16, 24, 40, 64, 65, 69) investigated the total scores of the VSS in patients without (or before) intervention. The estimated mean total scores of the DHI and VSS were 46.31 (95% CI: 41.17–51.44) and 15.50 (95% CI: 12.59–18.41), respectively. These mean scores indicated a moderate handicap. The distributions of the means suggest that subgroups exist with little to no handicap, as well as with a severe handicap (see Figure 2).[2] Additionally, while high and statistically significant heterogeneity was obtained between the studies that evaluated DHI ($Q = 110.31$; $p < 0.001$; $I2 = 86.7\%$), moderate and statistically significant heterogeneity was found between the studies that evaluated VSS ($Q = 19.17$; $p = 0.004$; $I2 = 70.3\%$).

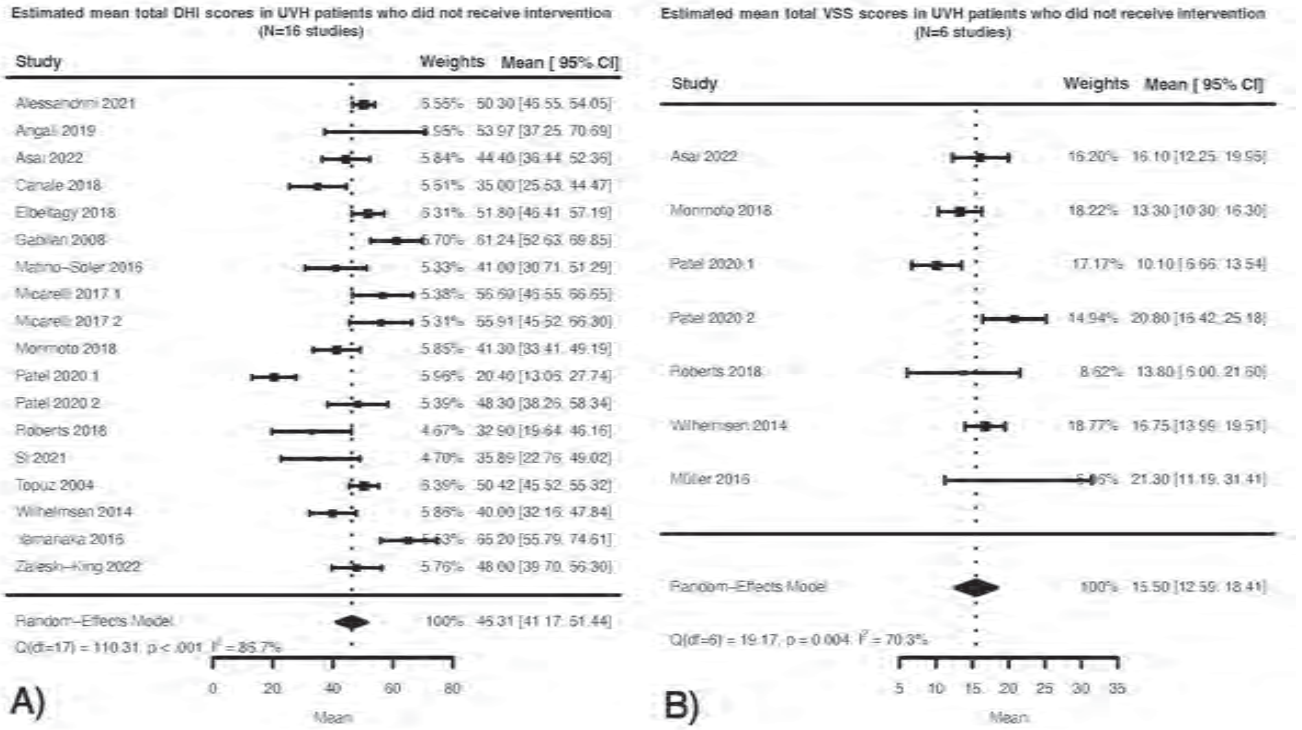
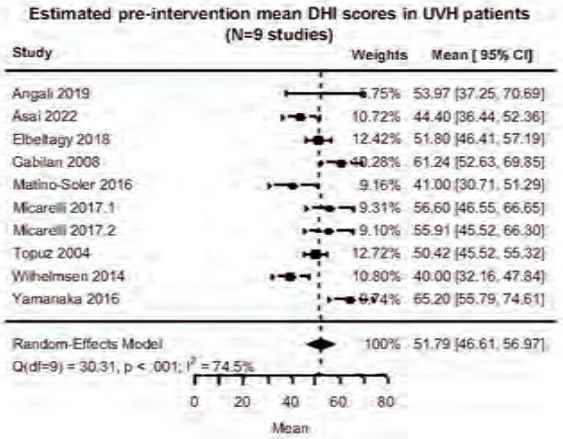
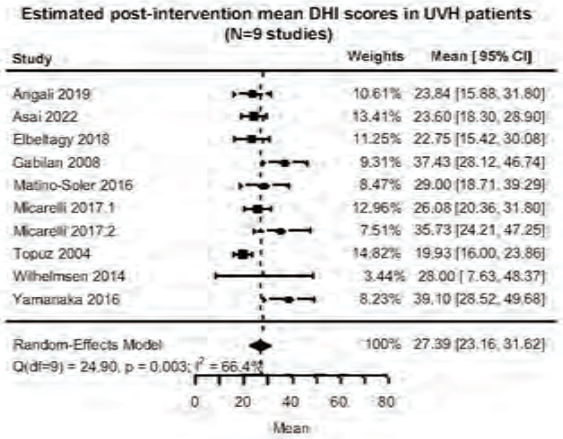


Figure 2. (A,B) Estimated mean total DHI and VSS scores in unilateral vestibulopathy patients who did not receive intervention. This includes DHI and VSS scores from studies without an intervention, as well as pre-intervention DHI and VSS scores from interventional studies. The dashed lines on the forest plots represent the overall pooled estimates. The black squares indicate the mean scores of each study and horizontal lines represent their 95% confidence intervals. The size of the black squares represents the weight contributed by each study in the meta-analysis. The black diamonds refer to the pooled odds ratio and their 95% confidence intervals. DHI, dizziness handicap inventory; VSS, vertigo symptom scale; Q, Cochran's Q statistic; df, degrees of freedom; I2, Higgins' calculation; CI, confidence interval.

Nine studies (see footnote 1) (2, 24, 39, 40, 48, 62, 63, 74, 78) evaluated total DHI scores before and after an intervention. Interventions included vestibular rehabilitation therapy aiming to improve gaze stabilization, postural control, gait, and balance (N = 8 studies) as well as providing coordination of sensorimotor strategies with active body control (N = 1 study) (Supplementary Table S6). The estimated pooled pre-and post-intervention means on the DHI were 51.79 (95% CI: 46.61–56.97) and 27.39 (95% CI: 23.16–31.62), respectively. Heterogeneity between studies that evaluated DHI pre-intervention and post-intervention was moderate, respectively ($Q = 30.31$, $I2 = 74.5\%$, $p < 0.001$; $Q = 24.90$, $I2 = 66.4\%$, $p = 0.003$). The estimated pooled mean change based on the random-effects model was −24.70 (95% CI: −20.69 to −28.71). The percentage of true means that are expected to fall above 30 was estimated to be 32% in the post-intervention studies. A forest plot showing the observed outcomes and the estimate of the pooled mean DHI based on the random-effects model is shown in Figure 3A. Total VAS scores were compared in three studies (2, 38, 74) and the estimated pooled mean total VAS score decreased from 7.05 (95% CI: 5.64–8.46) (pre-intervention) to 2.56 (95% CI: 1.15–3.97) (post-intervention). The percentage of true means expected to fall above 3 was estimated to be 37% in the post-intervention studies. Only three studies evaluated VAS during pre-intervention and post-intervention, therefore heterogeneity assessments were not applied. A forest plot showing the observed outcomes and the estimate of the mean VAS based on the random-effects model is shown in Figure 3B.





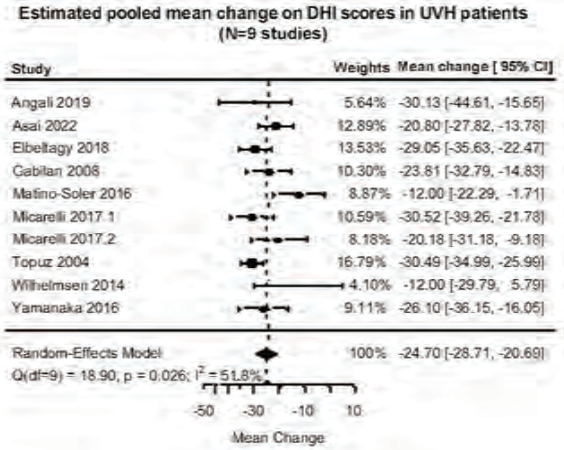


Figure 3. *Continued*

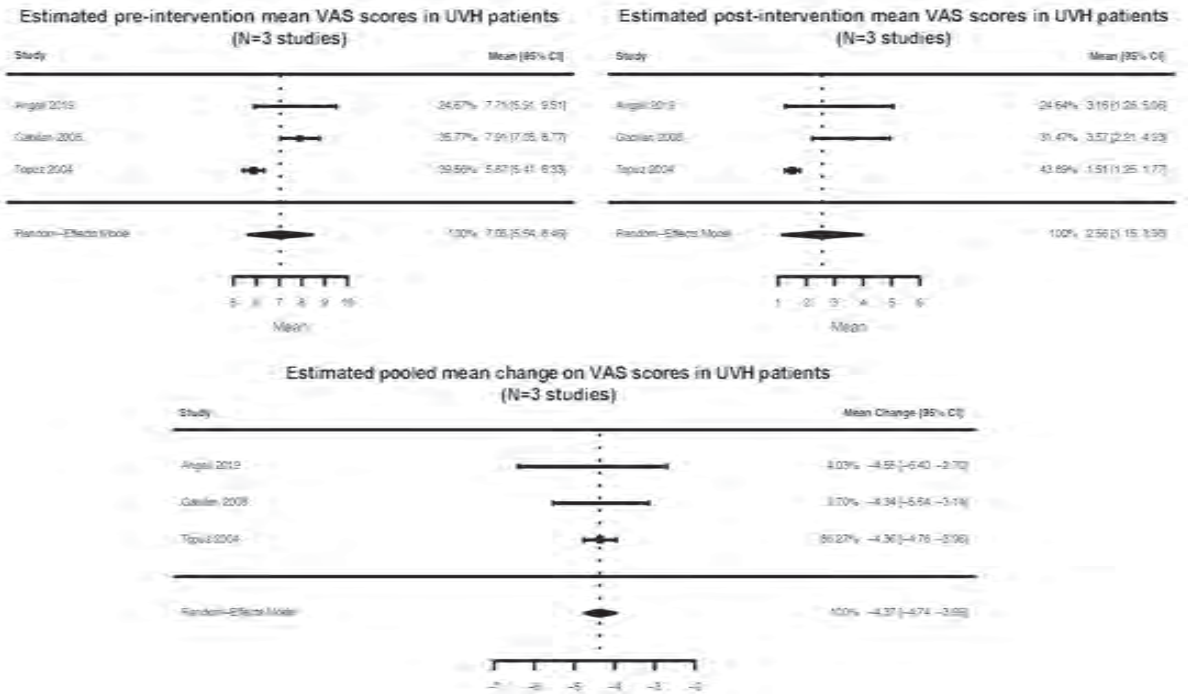


Figure 3. (A) Estimated mean DHI scores pre-intervention and post-intervention in patients with unilateral vestibulopathy (N = 9 studies). Interventions included vestibular rehabilitation therapy aiming to improve gaze stabilization and postural control, as well as providing coordination of sensorimotor strategies with active body control. The dashed line on the forest plots represents the overall pooled estimates. The black squares indicate the mean scores of each study and horizontal lines represent their 95% confidence intervals. The size of the black squares represents the weight contributed by each study in the meta-analysis. The black diamonds refer to the pooled odds ratio's and their 95% confidence intervals. DHI, dizziness handicap inventory; Q, Cochran's Q statistic; df, degrees of freedom; I2, Higgins' calculation; CI, confidence interval. **(B)** Estimated mean VAS scores pre-intervention and post-intervention in patients with unilateral vestibulopathy (N = 3 studies). Interventions included vestibular rehabilitation therapy aiming to improve gaze stabilization and postural control as well as providing coordination of sensorimotor strategies with active body control. The dashed line on the forest plot represents the overall pooled estimate. The black squares indicate the mean scores of each study and horizontal lines represent their 95% confidence intervals. The size of the black squares represents the weight contributed by each study in the meta-analysis. The black diamonds refer to the pooled odds ratio and their 95% confidence intervals. VAS, visual analog scale; CI, confidence interval; RE, random-effects.

3.6 Risk of bias and level of evidence

Twenty-four out of the 47 articles were graded with a "low risk of bias," while the remaining 23 were graded with an "unclear risk of bias." The two main reasons for assigning an unclear risk of bias were uncertainty about vestibular testing diagnostic criteria and/or a dropout rate that was higher than 20%. No study seemed to have a high risk of bias. Regarding level of evidence, all interventional cross-sectional studies were graded with level of evidence B (n = 39) due to the type of study design. Only seven studies were considered as a level of evidence C, mostly due to the small sample size in these articles (See Supplementary Table S7). One study was classified as A2 due to the large sample size. The Cohen's kappa analysis revealed a substantial level of interrater reliability on all four risk of bias sections: selection bias (0.759), attrition bias (0.773), detection bias (0.709), and publication bias (0.754).

4 DISCUSSION

The aim of this systematic review was to investigate the full spectrum of chronic symptoms and the effects of interventions on these symptoms in patients with UVH. It was found that UVH can lead to a spectrum of symptoms, of which chronic dizziness (98%) and imbalance (81%) are most prevalent. Furthermore, vestibular rehabilitation can significantly decrease self-reported handicap in patients with chronic symptoms, but a subgroup of patients (≥32%) persists with at least a moderate handicap, despite vestibular rehabilitation.

Chronic dizziness and imbalance were most frequently reported and might be considered the main symptoms of UVH. Additionally, the spectrum of other symptoms related to UVH varied from, e.g., visually induced dizziness and oscillopsia, to tiredness and cognitive impairment. Oscillopsia was reported in 22% of the patients, which is lower than in patients with bilateral vestibulopathy (50–70%) (35). This indicates that one vestibular organ might often be sufficient to enable gaze stabilization and maintain dynamic visual acuity, but it can still fail in a subgroup of UVH patients. This again illustrates that maintaining dynamic visual acuity is a multifactorial process, in which the visual, oculomotor, and vestibular system are all involved: some systems might (partially) compensate for the unilateral loss of vestibulo-ocular reflex (80). Additionally, many of the self-reported symptoms are not specific for UVH. For instance, visually induced dizziness can be related to Persistent Postural Perceptional Dizziness (PPPD) (81). Furthermore, the high percentage of patients with head movement induced worsening of symptoms should be noted. After all in clinical practice, this symptom of hypofunction might often lead to a misdiagnosis of Benign Paroxysmal Positional Vertigo or cervical vertigo (82).

The additional symptoms of cognitive impairment, autonomic symptoms, and tiredness were only reported in six out of 46 studies. These symptoms were most likely underreported. After all, it could be hypothesized that in many studies these additional symptoms were not part of the standard history taking process and questionnaires, and patients might find it challenging to precisely describe their symptoms and to understand the interrelation of these symptoms with their vestibular deficit (82). In addition, acute (e.g., acute unilateral vestibulopathy/vestibular neuritis), episodic (e.g., Menière's disease), and chronic vestibular disorders (e.g., vestibular schwannoma) might all lead to UVH symptoms. This complicates further history taking, since vertigo attacks can co-exist with UVH symptoms. Therefore, it could be advised to perform structured history taking in patients with UVH (22). Acronyms like SO STONED (83) and DISCOHAT (14) may be used to improve history taking and capture the symptoms related to UVH. For research purposes, semi-structured interviews should be conducted to define the whole spectrum of UVH symptoms more precisely. This should include a structural evaluation of DISCOHAT symptoms. In addition, open ended-questions and respondent-driven topics could be used to evaluate other symptoms related to UVH. This would facilitate the development of a validated PROM for UVH patients.

The high prevalence of chronic dizziness and imbalance, and the self-reported handicaps in UVH patients, illustrate that vestibular compensation and vestibular rehabilitation in the (sub) acute phase are not always sufficient to decrease symptoms, as previously described (9–12). After all, vestibular compensation is often sufficient for symptoms in static conditions, but not for symptoms in dynamic conditions (7). Unfortunately, current laboratory tests are not (yet) adequate to precisely determine the state of vestibular compensation (84). Therefore, it remains difficult to predict which UVH patients will keep on having (disabling) symptoms related to vestibular hypofunction. Nevertheless, vestibular rehabilitation still provides a substantial benefit in many patients, even though it is not globally unified, and a placebo-effect cannot always be ruled out. Depending on the type of program (office versus home-based), duration of intervention, protocol, applied equipment, and the provider of the training (ENT, physiotherapist, audiologist, etc.), as well as patient commitment, the outcomes might differ. However, vestibular rehabilitation should be offered to adults with UVH who present with symptoms, activity limitations, and participation restrictions as a result from UVH (21, 85, 86). According to the results found in this systematic review, a subgroup of patients does not sufficiently benefit from vestibular rehabilitation and maintains a moderate level of disability. In case the disability of these patients results from UVH and not from the primary and/or secondary pathology (e.g., Menière's disease or Persistent Postural Perceptional Dizziness), not many additional interventions are currently clinically available. Therefore, it could be considered to explore new intervention strategies like noisy galvanic vestibular stimulation (87), vibrotactile feedback (88) or a vestibular implant (89). Especially for vestibular implantation, patient selection should be carefully investigated: not all UVH patients with remaining symptoms after vestibular rehabilitation would be eligible for implantation (90).

Finally, it should be noted that emotional and environmental factors can influence the experienced symptoms of UVH (91, 92). This also (partially) explains why objective vestibular findings (e.g., laboratory test results) do not perfectly match with subjective vestibular complaints (e.g., symptoms captured with history taking and/or questionnaires) (93, 94). Therefore, it would be advised to screen patients with chronic symptoms of UVH for underlying psychological/psychiatric/functional disorders which might negatively influence their vestibular symptoms (22). Eventually, treatment of these co-morbidities might improve their experienced burden of disease.

4.1 Limitations

Five limitations were identified when performing this systematic review. First, different diagnostic criteria were used to define UVH (e.g., different cut-off values for vestibular tests), which led to a relatively heterogeneous study population, varying from mild to severe UVH. Second, UVH symptoms were collected differently (e.g., history taking, self-report questionnaires) which could induce a selection bias, especially risking underreporting of symptoms (see above). Third, since patients find it difficult to reliably describe their symptoms (82), the same symptom type might be described differently by different patients (e.g., vertigo and dizziness may be used interchangeably in some languages). This could have resulted in the same symptom being classified into different symptom categories (Table 2). Fourth, vestibular compensation can take up to 1 year (7) and this systematic review included studies with UVH symptoms lasting (only) 3 months or longer. This might imply that the prevalence and reported burden of some UVH symptoms could be different after full vestibular compensation. However, since many studies included patients with symptoms lasting more than 1 year, this effect is not expected to be substantial. Finally, in this systematic review, patients with UVH were included who could also have recurrent vertigo attacks and/or psychological comorbidities. This may have resulted in moderate to high heterogeneity in studies that evaluated self-reported questionnaires. It should be pointed out that not only UVH influences questionnaire scores or duration of symptoms, but also the primary pathology (e.g., Menière's disease) and/or secondary pathology (e.g., Persistent Postural Perceptional Dizziness). It is therefore imperative to treat the presence of current attacks and/or psychological comorbidity together with UVH symptoms (22).

5 CONCLUSION

A spectrum of symptoms is associated with UVH, of which chronic dizziness and imbalance are most frequently reported. Other symptoms include, among others, visually induced dizziness, oscillopsia, autonomic complaints, cognitive complaints, and tiredness. However, semi-structured interviews should be conducted to define the whole spectrum of UVH symptoms

more precisely, in order to establish a validated PROM for UVH patients. Furthermore, vestibular rehabilitation can significantly decrease self-reported handicap, but a subgroup of patients (≥32%) persists with at least a moderate handicap, despite vestibular rehabilitation. For this subgroup, it could be considered to explore new intervention strategies like noisy galvanic vestibular stimulation (87), vibrotactile feedback (88) or the vestibular implant (89).

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SUPPLEMENTARY MATERIALS

Table S1. P(IC)O-strategy using search terms based on Medical Subject Headings keywords

Population		Outcome
OR		**OR**
Unilateral vestibular hypofunction		Chronic symptoms
Unilateral vestibular loss		Chronic signs
Unilateral vestibular failure		Chronic complaints
Unilateral vestibular dysfunction	**AND**	Terms referring to chronicity: - Persistent - Enduring - Permanent - Uncompensated - Continuous - Recurrent
Unilateral vestibulopathy		
Unilateral vestibular deafferentation		
Unilateral vestibular disease		
Unilateral vestibular disorder		
Unilateral vestibular syndrome		

Table S2. Search queries for each database

WEB OF SCIENCE N: 342 hits on 19th of February 2024 ((((ALL=(Symptom* OR Sign* OR Complaint*)) AND ALL=(Chronic OR Uncompensated OR Persistent OR Enduring OR Permanent OR Recurrent OR Continuous)) AND ALL=(Unilateral)) AND ALL=(Vestibular)) AND ALL=(Hypofunction OR Failure OR Loss OR Deafferentation OR Disease OR Disorder OR Syndrome OR Impairment OR Dysfunction OR Vestibulopathy)
EMBASE N: 829 hits on 19th of February 2024 (((symptom OR sign OR complaint)) AND (((chronic OR uncompensated OR persistent OR enduring OR permanent OR recurrent OR continuous)) AND ((unilateral) AND (((vestibular) AND ((hypofunction OR failure OR loss OR deafferentation OR disease OR disorder OR syndrome OR ımpairment OR dysfunction))) OR (vestibulopathy)))))
PUBMED N:614 hits on 19th of February 2024 (((Symptom[All Fields] OR Sign[All Fields] OR Complaint[All Fields])) AND (((Chronic[All Fields] OR Uncompensated[All Fields] OR Persistent[All Fields] OR Enduring[All Fields] OR Permanent[All Fields] OR Recurrent[All Fields] OR Continuous[All Fields])) AND ((Unilateral[All Fields]) AND (((Vestibular[All Fields]) AND ((Hypofunction[All Fields] OR Failure[All Fields] OR Loss[All Fields] OR Deafferentation[All Fields] OR Disease[All Fields] OR Disorder[All Fields] OR Syndrome[All Fields] OR Impairment[All Fields] OR Dysfunction[All Fields])) OR (Vestibulopathy[All Fields]))))
SCOPUS N: 554 hits on 19th of February 2024 TITLE-ABS-KEY ((symptom* OR sign* OR complaint*) AND ((chronic OR uncompensated OR persistent OR enduring OR permanent OR recurrent OR continuous) AND (unilateral) AND ((vestibular) AND (hypofunction OR failure OR loss OR deafferentation OR disease OR disorder OR syndrome OR impairment OR dysfunction OR vestibulopathy))))

Table S3. Inclusion and exclusion criteria

	Inclusion criteria	Exclusion criteria
Study design	– Randomized controlled trials (RCTs) – Cohort studies – Case control studies – Case reports Language: English, French, German	– Systematic reviews – Meta-analyses – Editorials – Conference proceedings – Letter to editors – Abstract only – Other languages
Population	– Unilateral Vestibular Hypofunction (UVH) Vestibular testing to determine UVH • Caloric test and/or • Rotatory chair test and/or • (Video) head impulse test **Age: ≥ 18 years old**	– Healthy subjects – Bilateral vestibulopathy – Central vestibular disorders – Animal Studies **Age: < 18 years old**
Outcome	– Self-reported Symptoms – Patient-reported Questionnaires • Dizziness Handicap Inventory (DHI) • Vertigo Symptom Scale (VSS) • Visual Analogue Scale (VAS) – **Duration of symptoms ≥3 months**	– Only assessing physical signs and quality of life, no symptoms – **Duration of symptoms < 3 months**

Table S4. Level of evidence, Evidence Guideline Development platform (EBRO platform (28))

Level of evidence	**Interventional studies**	**Diagnostic accuracy studies**	**Harm, side effects, etiology and prognosis**
Level A1	Systematic review/meta-analysis of at least two independently conducted studies of A2 level		
Level A2	Randomized, double blind trial with good study quality and an adequate number of study participants	*Index test compared to reference test (reference standard); cut-offs were defined a priori; independent interpretation of test results; an adequate number of consecutive patients were enrolled; all patients received both tests*	*Prospective cohort study of sufficient magnitude and follow-up, adequately controlled for 'confounding' and no selective follow-up*
Level B	Clinical trial, but without all the features mentioned for level A2 (including case-control study, cohort study)	*Index test compared to reference test, but without all the features mentioned for level A2*	*Prospective cohort study, but without all the features mentioned for level A2 or retrospective cohort study or case-control study*
Level C	Non-comparative studies		
Level D	Expert opinion		

Table S5. Data extraction: Patient characteristics of the studies included in this systematic review

Authors	Total Number of Patients	Gender	Age (Years)	Diagnosis/ Etiology/ N			Duration of Symptoms
Alessandrini 2021	46	19 Female 27 Male	Mean±SD: 51.7±9.3	Acute unilateral vestibulopathy/ Vestibular neuritis Vestibular schwannoma Previous otological surgery Ramsay hunt syndrome	Infectious/ Inflammatory Neoplasm Iatrogenic Infectious/ Inflammatory	23 13 8 2	Mean±SD: 16.3±7 (months)
Angali 2019	31	15 Female 16 Male	Range: 24-59 Mean±SD: 39.48±10.96	Unilateral vestibular hypofunction	Missing	31	Mean±SD: 4.58±2.28 (years)
Asai 2022	21	15 Female 6 Male	Mean±SD: 60.9±13.7	Unilateral vestibular hypofunction	Missing	21	Mean±SD: 17.9±14.2 (months)
Bamiou 2000	44	23 Female 21 Male	Range: 20-65 Median (IQR): 48.5 (39.25-57.5)	Idiopathic Migraine Vascular inner ear disease Viral labyrinthitis Inner ear infection Head trauma Ramsay hunt syndrome	Idiopathic Vestibular migraine Vascular Infectious/ Inflammatory Infectious/ Inflammatory Trauma Infectious/ Inflammatory	13 9 6 5 4 4 3	Range: 6 months- 5 years
Binetti 2017	1	1 Female	30	Acute unilateral vestibulopathy/ Vestibular neuritis	Infectious/ Inflammatory	1	>9 months

Authors	Total Number of Patients	Gender	Age (Years)	Diagnosis/ Etiology/ N			Duration of Symptoms
Canale 2018	15	8 Female 7 Male	Range: 24-65 Mean: 50.8	Menière's Disease (Vestibular Neurectomy)	Menière's Disease	15	Range: 3-12 years Mean:6.7 years
Casani 2005	26	13 Female 13 Male	Range: 38-80 Mean: 58	Menière's Disease (Chemical labyrinthectomy)	Menière's Disease	26	Range: 20-151 months Mean: 49 months
Cohen 2017	20	6 Female 14 Male	Mean± SD: 62.5±7	Unilateral vestibular hypofunction	Missing	20	≥3 months
Corna 2003	14	7 Female 7 Male	Mean±SD: 58.9±12.9	Vascular inner ear disease	Vascular	7	≥3 months
				Vestibular schwannoma	Neoplasm	3	
				Idiopathic	Idiopathic	2	
				Menière's Disease	Menière's Disease	1	
				Head trauma	Trauma	1	
Crane 2017	4	3 Female 1 Male	Range: 31-74 Mean: 51	Vestibular schwannoma	Neoplasm	2	Range: 3-17 months
				Acute unilateral vestibulopathy/ Vestibular neuritis	Infectious/ Inflammatory	1	
				Labyrinthitis	Infectious/ Inflammatory	1	
Elbeltagy 2018	20	12 Female 8 Male	Range: 20-60 Mean±SD: 41.25±6.47	Unilateral vestibular hypofunction	Missing	20	Range: 3-12 months: 13 >12 months: 7
Foster 1994	6	3 Female 3 Male	Range: 36-67 Mean±SD: 50.83±1.41	Menière's Disease (Vestibular neurectomy: 4 Labyrinthectomy: 1)	Menière's Disease	5	Range: 4 months -9 years Mean: 5.3 years
				Vestibular schwannoma	Neoplasm	1	

Table S5. *Continued*

Authors	Total Number of Patients	Gender	Age (Years)	Diagnosis/ Etiology/ N			Duration of Symptoms
Fujimoto 2012	16	8 Female 8 Male	Range: 36-77 Mean±SD: 57.2±12.6	Vestibular schwannoma	Neoplasm	8	Range: 3-6 months: 6 6-12 months: 3 ≥12 months: 7
				Acute unilateral vestibulopathy/ Vestibular neuritis	Infectious/ Inflammatory	5	
				Labyrinthitis	Infectious/ Inflammatory	2	
				Previous otological surgery	Iatrogenic	1	
Fujimoto 2013	1	1 Male	43	Unilateral vestibular hypofunction	Missing	1	7 months
Gabilan 2008	21	18 Female 3 Male	Range: 20-63	Menière's Disease	Menière's Disease	7	Range: 3 months-1 year:3 1-10 years: 13 10-20 years: 4 >20 years: 1
				Vascular inner ear disease	Vascular	5	
				Acute unilateral vestibulopathy/ Vestibular neuritis	Infectious/ Inflammatory	2	
				Labyrinthitis	Infectious/ Inflammatory	2	
				Vestibular schwannoma surgery	Neoplasm	2	
				Head trauma	Trauma	2	
				Idiopathic	Idiopathic	1	
Gamba 2022	48	24 Female 24 Male	Range: 58-87 Mean: 71	Unilateral vestibular hypofunction	Missing	48	≥6 months
Ghulyan-Bedikian 2013	43	25 Female 18 Male	Range: 38-84	Unilateral vestibular hypofunction	Missing	26	>1 year
				Menière's Disease (Vestibular Neurectomy)	Menière's Disease	14	
				Vestibular schwannoma	Neoplasm	3	

Authors	Total Number of Patients	Gender	Age (Years)	Diagnosis/ Etiology/ N			Duration of Symptoms
Gill-Body 1994	1	1 Female	62	Acute unilateral vestibulopathy/ Vestibular neuritis	Infectious/ Inflammatory	1	6 months
Giray 2009	20	14 Female 6 Male	Range: 26-78	Unilateral vestibular hypofunction	Missing	20	≥3 months
Henriksson 2011	14	10 Female 4 Male	Mean±SD: 73.6±1.6	Acute unilateral vestibulopathy/ Vestibular neuritis	Infectious/ Inflammatory	9	>1 year
				Labyrinthitis	Infectious/ Inflammatory	3	
				Menière's Disease	Menière's Disease	2	
Kirazli 2020	10	6 Female 4 Male	Range: 34-65 Mean±SD: 50.30± 10.02	Menière's Disease	Menière's Disease	7	Range: 4-120 months Mean±SD: 45.5±38.95 months
				Acute unilateral vestibulopathy/ Vestibular neuritis	Infectious/ Inflammatory	3	
Kitahara 2018	60	34 Female 26 Male	Mean±SD: 46.2±15.1	Menière's Disease	Menière's Disease	60	Mean±SD: 48.8±30.6 months
Lazaro 2008	1	1 Male	48	Menière's Disease	Menière's Disease	1	3 years
Lopez 2007	40	20 Female 20 Male	Range: 22-74 Mean±SD: 48±13	Menière's Disease	Menière's Disease	40	Range: 1-22 years Mean±SD: 6±6 years
Martin 2003	71	35 Female 36 Male	Mean: 53.6	Menière's Disease (Chemical labyrinthectomy)	Menière's Disease	71	Mean: 12.6 months

Table S5. *Continued*

Authors	Total Number of Patients	Gender	Age (Years)	Diagnosis/ Etiology/ N			Duration of Symptoms
Matino-Soler 2016	16	9 Female 7 Male	Range: 32-79 Mean±SD: 55±13	Acute unilateral vestibulopathy/ Vestibular neuritis	Infectious/ Inflammatory	9	Range: 6-15 month Mean±SD: 9.2±4.6 months
				Vestibular schwannoma	Neoplasm	4	
				Menière's Disease (Chemical labyrinthectomy)	Menière's Disease	3	
Micarelli 2017	47	20 Female 27 Male	Head mounted display (HMD) +Vestibular Rehabilitation (VR) Group: Mean±SD: 49.72±10.34	Acute unilateral vestibulopathy/ Vestibular neuritis	Infectious/ Inflammatory	14	Mean±SD: 9.91±2.15 months
				Vestibular schwannoma	Neoplasm	4	
				Previous otological surgery	Iatrogenic	4	
				Ramsay hunt syndrome	Infectious/ Inflammatory	1	
			Only VR group: Mean±SD: 50.48±9.12	Acute unilateral vestibulopathy/ Vestibular neuritis	Infectious/ Inflammatory	13	Mean±SD: 9.37±1.55 months
				Vestibular schwannoma	Neoplasm	5	
				Previous otological surgery	Iatrogenic	4	
				Ramsay hunt syndrome	Infectious/ Inflammatory	2	
Morimoto 2018	28	16 Female 12 Male	Mean±SD: 63.5±15.6	Unilateral vestibular hypofunction	Missing	28	Mean±SD: 18.1±14.6 months
Müller 2016	13	4 Female 9 Male	Range: 29-70 Mean±SD: 54.6±12.5	Acute unilateral vestibulopathy/ Vestibular neuritis	Infectious/ Inflammatory	13	Range: 3-60 months Mean±SD: 16.5±15.1

Authors	Total Number of Patients	Gender	Age (Years)	Diagnosis/ Etiology/ N			Duration of Symptoms
Paredis 2021	143	86 Female 58 Male	Range: 18-84 Mean:59	Menière's Disease	Menière's Disease	50	Range: 1-42 years Mean±SD: 7±8 years
				Acute unilateral vestibulopathy/ Vestibular neuritis	Infectious/ Inflammatory	31	
				Idiopathic	Idiopathic	22	
				Vestibular migraine	Vestibular migraine	13	
				Previous otological surgery	Iatrogenic	8	
				Vascular inner ear disease	Vascular	6	
				Labyrinthitis	Infectious/ Inflammatory	4	
				Head trauma	Trauma	4	
				Vestibular schwannoma	Neoplasm	3	
				Scleroderma	Auto-immune	1	
				Other	Other	1	
Patel 2020	35	10 Female 25 Male	Vestibular Neuritis Mean±SD: 54.8±14.4 Menière's Disease Mean±SD: 48.9±12.3	Acute unilateral vestibulopathy/ Vestibular neuritis	Infectious/ Inflammatory	20	Range: 6-40 months
				Menière's Disease	Menière's Disease	15	>6 months
Perez 2003	71	35 Female 36 Male	Mean: 53.6	Menière's Disease (Chemical labyrinthectomy)	Menière's Disease	71	Mean: 6.9 years

Table S5. *Continued*

Authors	Total Number of Patients	Gender	Age (Years)	Diagnosis/ Etiology/ N			Duration of Symptoms
Quaglieri 2014	174	82 Female 92 Male	Mean±SD: 53.8±13.1	Menière's Disease (Chemical labyrinthectomy)	Menière's Disease	174	Range: 6-90 months Mean: 24 months
Rinaudo 2019	1	1 Female	58	Labyrinthitis	Infectious/ Inflammatory	1	>3 years
Roberts 2018	17	9 Female 8 Male	Mean±SD: 58.8±17.3	Acute unilateral vestibulopathy/ Vestibular neuritis	Infectious/ Inflammatory	17	>6 months
Sadeghi 2019	16	5 Female 11 Male	Range: 25-64 Mean±SD: 43.2±17.0	Unilateral vestibular hypofunction	Missing	16	Range: 1-8 years Mean±SD: 3.5±2
Shotton 1989	6	5 Female 1 Male	Range: 33-66 Mean: 49.9	Menière's Disease (Vestibular neurectomy)	Menière's Disease	6	Range: 2.7-5 years
Si 2021	18	12 Female 6 Male	Mean±SD: 47.94±11.01	Acute unilateral vestibulopathy/ Vestibular neuritis	Infectious/ Inflammatory	18	Range: 5-72 months Mean±SD: 18.61±2.82
Smółka 2020	58	43 Female 15 Male	Range: 40-64	Unilateral vestibular hypofunction	Missing	58	Range: >4 months
Tekin Dal 2021	75	40 Female 35 Male	**Group 1:** Median (IQR): 38 (33-52) **Group 2:** Median (IQR): 42 (32-56) **Group 3**: Median (IQR): 43 (33-56)	Unilateral vestibular hypofunction	Missing	75	≥3 months

Authors	Total Number of Patients	Gender	Age (Years)	Diagnosis/ Etiology/ N			Duration of Symptoms
Topuz 2004	93	61 Female 32 Male	Range: 18–75 Mean±SD: 44.08±14.30	Unilateral vestibular hypofunction	Missing	93	Range: 6-46 months Mean±SD: 15.76 ± 7.67
Ushio 2007	13	7 Female 6 Male	Range: 32-90	Acute unilateral vestibulopathy/ Vestibular neuritis	Infectious/ Inflammatory	9	>6 months
			Mean: 73.3	Unilateral vestibular hypofunction	Missing	4	
Waterston 2004	3	3 Female	Range: 45-49 Mean±SD: 47±2.82	Unilateral vestibular hypofunction	Missing	3	Range: 6-12 months
Wilhelmsen 2014	3	2 Female 1 Male	Range: 56-73	Acute unilateral vestibulopathy/ Vestibular neuritis	Infectious/ Inflammatory	3	Range: 9-29 months
Yagi 2021	10	3 Female 7 Male	Mean±SD: 65.7±8.1	Unilateral vestibular hypofunction	Missing	10	≥3 months
Yamanaka 2016	16	11 Female 5 Male	Range: 29-79 Mean: 59.8	Acute unilateral vestibulopathy/ Vestibular neuritis	Infectious/ Inflammatory	NR	>5 years
				Ramsay hunt syndrome	Infectious/ Inflammatory	NR	
				Labyrinthitis	Infectious/ Inflammatory	NR	
				Vestibular schwannoma surgery	Neoplasm	NR	

Table S5. *Continued*

Authors	Total Number of Patients	Gender	Age (Years)	Diagnosis/ Etiology/ N			Duration of Symptoms
Zaleski-King 2022	27	15 Female 12 Male	Range: 18-70 Mean±SD: 48±0.05	Acute unilateral vestibulopathy/ Vestibular neuritis	Infectious/ Inflammatory	10	≥3 months
				Persistent postural perceptional dizziness		8	
				Vestibular migraine	Vestibular migraine	6	
				Bening paroxysmal positional dizziness (BPPV)		4	
				Other (intracranial hypertension, Chiari, idiopathic)	Idiopathic	4	
				Menière's Disease	Menière's Disease	3	
				Vestibular schwannoma	Neoplasm	1	
				Subjects may have had more than one diagnosis			

Abbreviations: IQR: Interquartile range, NR: Not reported, SD: Standart Deviation

Table S6. Data extraction: Patient-reported questionnaire scores, self reported symptoms, and vestibular tests of the articles included in this systematic review

Authors	Method of collecting symptoms	Questionnaire Scores	Intervention	Self-reported vestibular symptoms (N/ N_{total})	Caloric Test	Rotatory Chair test	(v)HIT
Alessandrini 2021	Questionnaire-based	**DHI** (Total score: Mean±SD) 50.3±12.98 (No intervention)	N/A	N/A	Bithermal caloric test: ≥25% asymmetry rate in maximum slow phase velocity between two ears	N/A	N/A
Angali 2019	Questionnaire-based	**DHI** (Total score: Mean±SD) 53.97±8.53 (Pre-intervention) 23.84±4.06 (Post-intervention) **VAS** (Mean±SD) 7.71±0.92 (Pre-intervention) 3.16±0.97 (Post-intervention)	VRT	N/A	Caloric test: >25% asymmetry rate in maximum slow phase velocity between two ears	N/A	HIT: Positive clinical HIT
Asai 2022	Questionnaire-based	**DHI** (Total score: Mean±SD) 44.4±18.6 (Pre-intervention) 23.6±12.4 (Post-intervention) **VSS** (Mean±SD) 16.1±9.0 (Pre-intervention) 10.8±6.7 (Post-intervention)	Gait exercises	N/A	Bithermal caloric test: ≥25% asymmetry rate in maximum slow phase velocity between two ears	N/A	N/A
Bamiou 2000	Self reported Questionnaire-based	**DHI** (Total score:Median±IQR) 36 (19-65.5) (No intervention)	N/A	Chronic dizziness (39/44)	Bithermal caloric test: >10% asymmetry rate in maximum slow phase velocity between two ears	Rotatory chair test: Directional preponderance in velocity stepping test	N/A
Binetti 2017	Self Reported Questionnaire-based	**DHI** (Total score: Mean) 66 (Pre-intervention) 12 (Post-intervention)	VRT	Imbalance (1/1) Oscillopsia (1/1) Chronic dizziness (1/1) Darkness (1/1)	Caloric test: 78% asymmetry rate in maximum slow phase velocity between two ears	N/A	vHIT: Unilateral horizontal canal gain< 0.8 The presence of compensatory saccades including covert and overt

Table S6. *Continued*

Authors	Method of collecting symptoms	Questionnaire Scores	Intervention	Self-reported vestibular symptoms (N/ N_{total})	Caloric Test	Rotatory Chair test	(v)HIT
Canale 2018	Questionnaire-based	**DHI** (Total score: Mean±SD) 35±18.72 (No intervention)	N/A	N/A	Bithermal caloric test: ≥20 % asymmetry rate in maximum slow phase velocity between two ears	N/A	vHIT: Unilateral horizontal canal gain< 0.8 Unilateral vertical canal gain< 0.7
Casani 2005	Self reported	N/A	N/A	Recurrent vertigo (26/26)	Bithermal caloric test: >20% asymmetry rate in maximum slow phase velocity between two ears	N/A	N/A
Cohen 2017	Self reported	N/A	N/A	Chronic dizziness (20/20)	Caloric test: >60% asymmetry rate in maximum slow phase velocity between two ears	N/A	N/A
Corna 2003	Self reported	N/A	N/A	Imbalance (14/14)	Monothermal caloric test: >20% asymmetry rate in maximum slow phase velocity between two ears (I looked at the reference of this article)	N/A	N/A
Crane 2017	Self reported Questionnaire-based	**DHI** (Total score: Mean) 42 (Pre-intervention) 11.5 (Post intervention)	VRT	Chronic dizziness (1/4) Imbalance (1/4)	Caloric test: Caloric areflexia on one side. Ice water caloric: Caloric areflexia on one side.	N/A	N/A
Elbeltagy 2018	Self-reported Questionnaire-based	**DHI** (Total score: Mean±SD) 51.80±2.75 (Pre-intervention) 22.75±3.74 (Post intervention)	VRT	Chronic dizziness (20/20)	Bithermal caloric test: >25% asymmetry rate in maximum slow phase velocity between two ears	N/A	N/A

Authors	Method of collecting symptoms	Questionnaire Scores	Intervention	Self-reported vestibular symptoms (N/ N_{total})	Caloric Test	Rotatory Chair test	(v)HIT
Foster 1994	Self-reported	N/A	N/A	Oscillopsia (6/6) Recurrent vertigo (2/6)	Ice caloric test: Caloric areflexia on one side.	N/A	N/A
Fujimoto 2012	Self-reported	N/A	N/A	Recurrent vertigo (16/16)	Ice caloric test: Caloric areflexia on one side.	N/A	N/A
Fujimoto 2013	Self-reported	N/A	N/A	Imbalance (1/1)	Ice caloric test: >20% asymmetry rate in maximum slow phase velocity between two ears	N/A	N/A
Gabilan 2008	Questionnaire-based	**DHI** (Total score: Mean±SD) 61.24±20.12 (Pre-intervention) 37.43±21.77 (Post-intervention) **VAS** (Total score:Mean±SD) 7.91±2.02 (Pre-intervention) 3.57±3.19 (Post-intervention)	VRT	N/A	Bithermal caloric test: >25% asymmetry rate in maximum slow phase velocity between two ears	N/A	N/A
Gamba 2022	Self-reported	N/A	N/A	Chronic dizziness (48/48) Imbalance (48/48)	N/A	N/A	vHIT: Unilateral horizontal canal gain< 0.8
Ghulyan-Bedikian 2013	Self-reported Questionnaire-based	**DHI** N/A	N/A	Chronic dizziness (43/43) Imbalance (43/43)	Bithermal cloric test: ≥34 asymmetry rate in maximum slow phase velocity between two ears	Rotatory chair test: VOR gain≥ 0.4 at 0.25 Hz	N/A
Gill-Body 1994	Self-reported Questionnaire-based	**DHI** (Total score:Mean) 14 (Pre-intervention) NR (Post-intervention) **VAS** (Total score:Mean) 4 (Pre-intervention) 3 (Post-intervention)	VRT	Imbalance (1/1)	Bithermal cloric test: 87% asymmetry rate in maximum slow phase velocity between two ears	Rotatory chair test: Mildly decreased VOR gain at frequencies from 0.01 to 0.1 Hz	N/A

Table S6. *Continued*

Authors	Method of collecting symptoms	Questionnaire Scores	Intervention	Self-reported vestibular symptoms (N/ N_{total})	Caloric Test	Rotatory Chair test	(v)HIT
Giray 2009	Questionnaire-based	**DHI** (Total score:Median±IQR) 64.00 (30-92) (Pre-intervention) 22.00 (0-84) (Post-intervention) **VAS** (Total score:Median±IQR) 4.45 (1.0-9.2)(Pre-intervention) 1.35 (0-7.1) (Post-intervention)	VRT	N/A	Bithermal caloric test: >25% asymmetry rate in maximum slow phase velocity between two ears	N/A	N/A
Henriksson 2011	Self-reported	N/A	N/A	Imbalance (14/14)	Caloric test: Reduced caloric response from the SCC on one side/ear.	N/A	HIT: The lack of gaze stabilization indicating reduced vestibular function for the ear ipsilateral to the head thrust
Kirazli 2020	Self-reported	N/A	N/A	Imbalance (10/10)	Bithermal caloric test: Caloric areflexia on one side.	N/A	N/A
Kitahara 2018	Self-reported	N/A	N/A	Chronic dizziness (60/60)	Monothermal caloric test: Unilateral maximum slow phase eye velocity ≤10 degrees/second	N/A	N/A
Lazaro 2008	Self-reported	N/A	N/A	Recurrent vertigo (1/1) Imbalance (1/1) Chronic dizziness (1/1) Autonomic symptoms (1/1)	Bithermal caloric test: 88% asymmetry rate in maximum slow phase velocity between two ears	Rotatory chair test: Decreased VOR gain at frequencies from 0.01 to 0.16 Hz	N/A

Authors	Method of collecting symptoms	Questionnaire Scores	Intervention	Self-reported vestibular symptoms (N/ N_{total})	Caloric Test	Rotatory Chair test	(v)HIT
Lopez 2007	Self-reported	N/A	N/A	Recurrent vertigo (40/40)	Bithermal caloric test: ≥22% asymmetry rate in maximum slow phase velocity between two ears	N/A	N/A
Martin 2003	Self-reported	N/A	N/A	Recurrent vertigo (17/71)	Bithermal caloric test: No specific criteria described Ice caloric test: Caloric areflexia on one side.	Rotatory chair test: No specific criteria described	N/A
Matino-Soler 2016	Self-reported Questionnaire-based	**DHI** (Total score:Mean±SD) 41±21(Pre-intervention) 29±21(Post-intervention)	VRT	Imbalance (16/16)	N/A	N/A	vHIT: Horizontal canal gain< 0.8 The presence of compensatory saccades including covert and overt
Micarelli 2017	Questionnaire-based	**DHI** (Total score:Mean±SD) <u>HMD+VR group</u> 56.6±5.13 (Pre-intervention) 26.08±2.92 (Post-intervention) <u>Only VR group</u> 55.91±5.3 (Pre-intervention) 35.73±5.88 (Post-intervention)	VRT	N/A	Bithermal caloric test: >25% asymmetry rate in maximum slow phase velocity between two ears	N/A	N/A
Morimoto 2018	Self-reported Questionnaire-based	**DHI** (Total score:Mean±SD) 41.3±21.3 (No intervention) **VSS** (Total score:Mean±SD) 13.3±8.1 (No intervention)	N/A	Chronic dizziness (28/28)	Bithermal caloric test: >40% asymmetry rate in maximum slow phase velocity between two ears	N/A	N/A

Table S6. *Continued*

Authors	Method of collecting symptoms	Questionnaire Scores	Intervention	Self-reported vestibular symptoms (N/ N_{total})	Caloric Test	Rotatory Chair test	(v)HIT
Müller 2016	Questionnaire-based	**VSS** (Total score:Mean±SD) 21.3± 18.6 (No intervention)	N/A	N/A	N/A	N/A	vHIT: Unilateral horizontal canal gain< 0.8 Unilateral vertical canal gain< 0.7 The presence of compensatory saccades including covert and overt
Paredis 2021	Self-reported	N/A	N/A	Darkness (79/144) Imbalance (99/144) Supermarket effect (88/144) Cognitive deficits (83/144) Oscillopsia (26/144) Head movements (108/144) Autonomic symptoms (65/144) Tiredness (99/144)	Bithermal caloric test: >25% asymmetry rate in maximum slow phase velocity between two ears	N/A	N/A
Patel 2020	Questionnaire-based	**DHI** (Total score:Mean±SD) Vestibular Neuritis: 20.4±14.5 (No intervention) Menière's Disease: 48.3±22.9 (No intervention) **VSS** (Total score:Mean±SD) Vestibular Neuritis: 10.1±6.8 (No intervention) Menière's Disease: 20.8±10 (No intervention)	N/A	N/A	Bithermal caloric test: >25% asymmetry rate in maximum slow phase velocity between two ears	N/A	N/A

Authors	Method of collecting symptoms	Questionnaire Scores	Intervention	Self-reported vestibular symptoms (N/ N_{total})	Caloric Test	Rotatory Chair test	(v)HIT
Perez 2003	Self-reported Questionnaire-based	**DHI** (Total score:Mean) 56.25 (Pre-intervention) 29.42 (Post-intervention)	N/A	Imbalance (17/71) Recurrent vertigo (17/71)	Bithermal caloric test: >20% asymmetry rate in maximum slow phase velocity between two ears	Rotatory chair test: Sinusoidal harmonic acceleration and velocity stepping tests were performed.	N/A
Quaglieri 2014	Self-reported	N/A	N/A	Recurrent vertigo (174/174)	Caloric test: ≥30% asymmetry rate in maximum slow phase velocity between two ears Ice water caloric test: Caloric areflexia on one side.	N/A	N/A
Rinaudo 2019	Self-reported Questionnaire-based	**DHI** (Total score:Mean) 52 (Pre-intervention) 40 (Post-intervention)	VRT	Imbalance (1/1) Tiredness (1/1) Cognitive deficit (1/1) Chronic dizziness (1/1)	Bithermal caloric test: 59% asymmetry rate in maximum slow phase velocity between two ears	N/A	N/A
Roberts 2018	Questionnaire-based	**DHI** (Total score:Mean±SD) 32.9±27.9 (No intervention) **VSS** (Total score:Mean±SD) 13.8±16.4 (No intervention)	N/A	N/A	Bithermal caloric test: ≥20% asymmetry rate in maximum slow phase velocity between two ears	N/A	N/A
Sadeghi 2019	Self-reported	N/A	N/A	Imbalance (8/16) Darkness (2/16) Autonomic symptoms (8/16)	N/A	Rotatory chair test: Directional preponderance > 10% at 0.2 Hz	N/A
Shotton 1989	Self-reported	N/A	N/A	Imbalance (1/6)	Bithermal Caloric test: No specific criteria described	N/A	N/A

Table S6. *Continued*

Authors	Method of collecting symptoms	Questionnaire Scores	Intervention	Self-reported vestibular symptoms (N/ N_{total})	Caloric Test	Rotatory Chair test	(v)HIT
Si 2021	Self-reported Questionnaire-based	**DHI** (Total score:Mean±SD) 35.89 ± 6.70 (No intervention)	N/A	Chronic dizziness (18/18) Imbalance (18/18)	Bithermal caloric test: >25% asymmetry rate in maximum slow phase velocity between two ears	N/A	N/A
Smółka 2020	Self-reported	N/A	N/A	Recurrent vertigo (58/58) Imbalance (58/58)	Bithermal caloric test: No specific criteria described	N/A	N/A
Tekin Dal 2021	Self-reported Questionnaire-based	**VAS** (Total score: Median±IQR) Group I 6 (6-7) (Pre-intervention) 5 (5-6) (Post-intervention) **Group 2** 7 (6-7) (Pre-intervention) 6 (5-6) (Post-intervention)	Activity-based exercises Cawthorne-Cooksey exercises	Chronic dizziness (75/75)	Bithermal caloric test: >24% asymmetry rate in maximum slow phase velocity between two ears	N/A	N/A
Topuz 2004	Self-reported Questionnaire-based	**DHI** (Total score:Mean±SD) 50.42 ± 24.124 (Pre-intervention) 19.93 ± 19.33 (Post-intervention) **VAS** (Total score:Mean±SD) 5.87 ± 2.27 (Pre-intervention) 1.51± 1.29 (Post-intervention)	VRT	Chronic dizziness (93/93) Imbalance (93/93) Recurrent vertigo (93/93)	Bithermal caloric test: >25% asymmetry rate in maximum slow phase velocity between two ears	N/A	N/A
Ushio 2007	Self-reported	N/A	N/A	Recurrent vertigo (13/13) Chronic dizziness (13/13)	Monothermal caloric test: >20% asymmetry rate in maximum slow phase velocity between two ears	N/A	N/A
Waterston 2004	Self-reported	N/A	N/A	Headache (3/3) Autonomic symptoms (1/3) Imbalance (1/3) Recurrent vertigo (1/3) Chronic dizziness (3/3)	Bithermal caloric test: >25% asymmetry rate in maximum slow phase velocity between two ears Directional preponderance >30%	Rotatory chair test: Decreased VOR gain at frequencies from 0.1 to 0.4 Hz	N/A

Authors	Method of collecting symptoms	Questionnaire Scores	Intervention	Self-reported vestibular symptoms (N/ N_{total})	Caloric Test	Rotatory Chair test	(v)HIT
Wilhelmsen 2014	Self-reported Questionnaire-based	**DHI** (Total score: Mean±SD) 40.65±5.65 (Pre-intervention) 27.25±12.72 (Post-intervention) **VSS** (Total score:Mean±SD) 16.75±1.41 (Pre-intervention) 10.25±10.60 (Post-intervention)	VRT	Headache (2/3) Tiredness (1/3) Cognitive symptoms (1/3) Neck and back pain (1/3) Ear pain (1/3) Chronic dizziness (3/3) Concentration difficulties (1/3)	Bithermal caloric test: >25% asymmetry rate in maximum slow phase velocity between two ears	N/A	N/A
Yagi 2021	Self-reported	N/A	N/A	Chronic dizziness (10/10)	Bithermal caloric test: >20% asymmetry rate in maximum slow phase velocity between two ears	N/A	vHIT: Unilateral borizontal canal gain< 0.8 The presence of compensatory saccades including covert and overt
Yamanaka 2016	Self-reported Questionnaire-based	**DHI** (Total score:Mean±SD) 65.2 ± 4.8 (Pre-intervention) 39.1 ± 5.4 (Post-intervention)	Vibrotactile stimulation Substitution	Chronic dizziness (16/16) Imbalance (16/16)	Ice water caloric test: Maximum slow phase velocity <3 degree/ second.	N/A	N/A
Zaleski-King 2022	Self-reported Questionnaire-based	**DHI** (Total score:Mean±SD) 48±22 (No intervention)	N/A	Chronic dizziness (27/27) Imbalance (27/27)	Bithermal caloric test: ≥20% asymmetry rate in maximum slow phase velocity between two ears	Sinusoidal harmonic acceleration: Presence of low frequency phase lead at 0,01, 0,32 and 0.64 Hz	vHIT: Unilateral borizontal canal gain< 0.8 The presence of overt saccades

Abbreviations: VRT: Vestibular Rehabilitation Therapy, vHIT: Video Head Impulse Test, DHI: Dizziness Handicap Inventory, VAS: Visual Analog Scale, VSS: Vertigo Symptom Scale, N/A: Not applicable, NR: Not reported

Table S7. Risk of Bias evaluation with the 'Quality in Prognostic Studies tool' and the level of evidence

Authors	Selection Bias	Attrition Bias	Detection Bias	Publication Bias	Risk of Bias	Level of Evidence
Alessandrini 2021	+	+	+	+	Low RoB	B
Angali 2019	+	+	+	+	Low RoB	B
Asai 2022	+	+	+	+	Low RoB	B
Bamiou 2000	+	+	+	+	Low RoB	B
Binetti 2017	+	−	−	−	Unclear RoB	C
Canale 2018	+	+	+	+	Low RoB	B
Casani 2005	+	+	?	−	Unclear RoB	B
Cohen 2017	+	?	−	?	Unclear RoB	B
Coma 2003	+	+	?	+	Low RoB	B

Authors	Selection Bias	Attrition Bias	Detection Bias	Publication Bias	Risk of Bias	Level of Evidence
Crane 2017					Unclear RoB	B
Elbeltagy 2018					Low RoB	B
Foster 1994					Unclear RoB	C
Fujimoto 2012					Unclear RoB	B
Fujimoto 2013					Unclear RoB	B
Gabilan 2008					Low RoB	B
Gamba 2022					Unclear RoB	B
Ghulyan-Bedikian 2013					Unclear RoB	B
Gill-Body 1994					Unclear RoB	B
Giray 2009					Low RoB	B

Table S7. *Continued*

Authors	Selection Bias	Attrition Bias	Detection Bias	Publication Bias	Risk of Bias	Level of Evidence
Guidetti 2008					Low RoB	B
Henriksson 2011					Unclear RoB	B
Kirazli 2020					Low RoB	B
Kitahara 2018					Low RoB	B
Lazaro 2008					Unclear RoB	C
Lee 2019					Unclear RoB	B
Lopez 2007					Unclear RoB	B
Martin 2003					Unclear RoB	B
Matino-Soler 2016					Low RoB	B

Authors	Selection Bias	Attrition Bias	Detection Bias	Publication Bias	Risk of Bias	Level of Evidence
Micarelli 2017	+	+	+	+	Low RoB	B
Morimoto 2018	+	+	?	+	Low RoB	B
Müller 2016	+	+	+	+	Low RoB	B
Patel 2020	+	+	+	?	Low RoB	B
Paredis 2021	+	+	+	+	Low RoB	A2
Perez 2003	+	−	?	?	Unclear RoB	C
Quaglieri 2014	+	+	−	?	Low RoB	C
Rinaudo 2019	+	+	?	−	Low RoB	C
Roberts 2018	+	+	+	?	Low RoB	B
Sadeghi 2019	+	?	?	?	Unclear RoB	B

Table S7. *Continued*

Authors	Selection Bias	Attrition Bias	Detection Bias	Publication Bias	Risk of Bias	Level of Evidence
Shotton 1989					Unclear RoB	B
Smółka 2020					Low RoB	B
Tekin Dal 2021					Unclear RoB	B
Topuz 2004					Low RoB	B
Ushio 2007					Unclear RoB	B
Waterston 2004					Unclear RoB	B
Wilhelmsen 2014					Unclear RoB	C
Yamanaka 2016					Unclear RoB	B
Zaleski-King 2022					Low RoB	B

3

CHAPTER 3

Chronic unilateral vestibular hypofunction: A qualitative study exploring the full spectrum of symptoms and impacts through the ICF framework

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ABSTRACT

Objective

To explore the full spectrum of symptoms and impacts associated with chronic unilateral vestibular hypofunction (UVH), and to assess whether these symptoms and impacts are fully covered by patient-reported outcome measures (PROMs) within the International Classification of Functioning, Disability and Health (ICF) framework.

Methods

A qualitative study was conducted using semi-structured interviews, which were recorded, transcribed, and analyzed by two independent reviewers through a consensus approach. Data collection continued until thematic saturation was reached. Domains were then identified from interviews and PROMs (Dizziness Handicap Inventory, Hospital Anxiety and Depression Scale, EQ-5D-5L) using the ICF linking process. The analysis comprised three stages: (1), documenting the full spectrum of UVH symptoms and impacts from interviews, (2) reporting domains and constructs based on interviews, (3) comparing domains identified from interviews with those from PROMs (DHI, HADS, EQ-5D-5L, analyzed separately).

Results

Fifteen patients with chronic UVH were interviewed. Reported symptoms revealed 16 physical symptoms, four cognitive symptoms, and five emotions. Key challenges included driving difficulties, darkness, sleep problems, fear of falling, and discomfort in crowded environments. Patients adapted certain behaviors, such as moving slowly, using supports, and avoiding sudden movements. Regarding the ICF framework, the most frequently reported construct was Body functions, with key domains including emotional, vestibular, and hearing-related functions. Activities and participation focused on maintaining body position and family relationships, while environmental factors highlighted the impact of light and sound. Interviews identified key domains related to vision, memory, multitasking, and activities impacting quality of life that were often overlooked by the PROMs.

Conclusion

Patients with chronic UVH experience a wide spectrum of physical, cognitive, and emotional symptoms, resulting in significant limitations in daily life. The frequently used PROMs (DHI, HADS, and EQ-5D-5L) do not fully cover these symptoms and their impacts, which leave many aspects underrepresented. A tailored PROM for UVH may be needed, to better reflect the specific symptoms, behaviors and functional limitations related to chronic UVH.

1 INTRODUCTION

Unilateral vestibular hypofunction (UVH) is a complex disorder in which vestibular function in one ear is partially or completely absent (1). The onset of UVH may occur suddenly or gradually, depending on the underlying etiology (2). UVH symptoms include e.g. dizziness, unsteadiness and oscillopsia. These symptoms can occur in both static and dynamic conditions (3). When UVH occurs, a neurological process known as vestibular compensation, can (partially) mitigate these symptoms. Vestibular compensation targets both static and dynamic conditions. Static conditions refer to situations without head movements. Dynamic conditions refer to situations with head movements (4, 5). While vestibular compensation addresses both conditions, symptoms in static conditions (e.g. spontaneous nystagmus) typically resolve more quickly and completely (6, 7). However, 29-66% of patients continue to experience symptoms in dynamic conditions, often resulting in a chronic disorder (8-11).

Multiple etiologies can result in UVH, including Menière's Disease, infection/inflammation, vestibular migraine, vascular conditions, or iatrogenic factors (2, 12, 13). This implies that patients with chronic UVH might experience symptoms related to different disorders. For example in patients with Menière's disease, 'vertigo attacks' would be related to Menière's disease, and 'unsteadiness in between attacks' would be related to UVH resulting from Menière's disease (14). Previously, it was found that UVH can result in a spectrum of symptoms, beyond dizziness and unsteadiness (2, 12). Evaluation of therapeutic interventions (e.g. rehabilitation (15), the vestibular implant (16)) should therefore incorporate this spectrum of symptoms, to better estimate the effects of interventions.

Several techniques are used to collect UVH-related symptoms, in clinical setting and in research setting. These techniques include, for example, history taking (14), patient-reported outcome measures (PROMs) (e.g., Dizziness Handicap Inventory (DHI) (17), Hospital Anxiety and Depression Scale (HADS) (18)), and interviews (19). Each method has its own strengths and limitations. For instance, PROMs provide valuable insights and allow for symptom quantification, but they may fail to assess less common symptoms (20). In previous studies, including a systematic review and a retrospective study, symptoms were collected through PROMs and self-reports; however, a full representation of UVH symptoms was still not achieved (2, 12). Therefore, conducting interviews with patients would be essential to more accurately define the entire range of UVH symptoms. The findings of these interviews could indicate whether existing PROMs would be sufficient to cover the relevant UVH symptoms. If not, a new PROM might be needed to evaluate effects of therapeutic interventions in chronic UVH patients.

Symptom definitions are crucial for effective communication in both clinical practice and research (21). Patients and clinicians might not always be on the same page when describing symptoms, which can create gaps in understanding the full impact of the condition (22-24). For example, patients may use terms like vertigo and dizziness interchangeably. Beyond symptom descriptions, it is equally important to examine patients' behaviors, challenges, and coping strategies to fully understand their experiences. Here, the International Classification of Functioning, Disability, and Health (ICF) framework provides a structured framework to assess these aspects. It uses a standardized language to describe interactions between health conditions and the environment (25). Its universal language enhances inter- and multidisciplinary communication in both clinical and research settings and enables the comparison of health states across countries and disciplines. The ICF framework covers four key constructs: body functions, body structures, activities and participation, and environmental factors (26). This framework can allow for a clear evaluation of how UVH affects physical, social, and environmental functioning. Furthermore, linking PROMs data and findings from qualitative research to the ICF, helps capturing the broader impact of UVH on daily life, while providing a standardized language for evaluation (27). As a result, this approach enables clearer insights into patient needs. This supports a more accurate interpretation of UVH symptoms and their effects on quality of life.

Overall, the aim of this study was to identify the full spectrum of symptoms and their impact in patients with chronic UVH. Additionally, this study also aimed to determine whether symptoms and impacts are fully covered by PROMs within the ICF framework.

2 MATERIALS AND METHODS

Patients

Potential participants were first identified through the Bayındır Hospital database (Ankara, Türkiye), based on prior video head impulse test (vHIT) results. VHIT results had to comply with the following criteria: a reduced VOR gain on the affected side (<0.7), normal gain values on the healthy side (VOR gain between ≥0.8 and ≤1.2), and an asymmetry of at least 18% between the two ears. Patients who met these vHIT criteria were then contacted by phone to assess whether they experienced at least one of the following chronic symptoms: dizziness, unsteadiness, oscillopsia, or symptoms worsening with head movements. To be eligible, symptoms had to persist ≥3 months. Only patients who fulfilled both the criteria for vHIT and chronic UVH symptoms, were able to participate in the study. After providing informed consent, all participants underwent a second vHIT to confirm that they still met the diagnostic criteria. Patients who did not meet the criteria upon re-testing, or who did not report any of the required symptoms during the in-person interview, were

excluded from the final sample. Other exclusion criteria included a medical history of neurological disorders (e.g., multiple sclerosis, stroke, Parkinson's disease). Additionally, patients who were not able (e.g., mentally disabled) or willing to discuss certain topics (e.g., psychology/psychiatry, health care utilization), unable to discontinue medication for anxiety or depression (due to the vestibulo-suppressive effect), or refusing to undergo vHIT, were excluded from the study. As this study employed a qualitative approach, the goal was to explore a wide range of symptoms and their impacts, rather than their frequency. In other words, the type of symptoms was more important than how often they occurred. Therefore, patients from different ages and genders were included to reflect a diverse UVH population. All patients underwent vHIT by an experienced vestibular clinican (E.Y.), and were interviewed by the first author (M.K.).

Vestibular testing

The vHIT was performed using the Ulmer system (Synapsis, Marseille, France). The procedure was previously described (28). In brief, the patient was seated in a chair and instructed to fixate on a target on the wall, positioned 1.5 m away. Head impulses were performed in the plane of both horizontal semicircular canals, with a velocity between 150°/s- 250°/s. The amplitudes were low (± 20°). A minimum of ten impulses were administered in each direction. The Synapsis system calculated the VOR gain from 40 ms before to 80 ms after peak head acceleration for each impulse. In cases with covert saccades, the 80-ms window was adjusted accordingly, and stopped at time of onset of the covert saccade (29). However, the specific method used by the Synapsis system for gain calculation is not disclosed by the manufacturer. Regarding the vHIT criteria, no standardized diagnostic criteria are currently available for chronic UVH. The Bárány Society's recommendations for acute unilateral vestibulopathy suggest a VOR gain <0.7 on the affected side and/or a side difference of >0.3 between ears. However, this side difference of 0.3 is only considered relevant when the affected side has a gain >0.7 (e.g., the affected side 0.25 and the healthy side 0.55, indicating bilateral vestibulopathy). Thus, using an asymmetry of 18% consistently corresponds to a side difference of >0.3 between the healthy and the affected side. As a result, a more conservative approach was used in our study: a gain <0.7 on the affected side and an asymmetry ≥18%.

Research paradigm

A post-positivist approach was used to combine results of PROMs with patient interviews. An objective reality was acknowledged (vHIT demonstrated vestibular hypofunction), with a focus on how individual perspectives and social contexts shape its effects (30). The principle of 'modified objectivity' was used. This requires the researcher to critically reflect on, and address, their own biases and assumptions (31). Other factors were also explored, like societal norms, that might have influenced patients' experiences (32).

By incorporating these elements, this approach could offer valuable insights into how patients understand and cope with UVH (30).

Patient interviews

Individual semi-structured interviews were conducted. Patients with chronic UVH were asked open-ended questions regarding the types of symptoms they encounter: the most frequently occurring symptoms, the symptoms that disrupt their daily lives, situations in which these symptoms are noticeable, coping strategies, and the impact of UVH on their relationships. The questions are provided in the Supplementary Materials Table S1. The interviews were conducted in person (14 patients) and online (1 patient). The protocol was reviewed by co-authors (HA, EY, ONÖ, RvdB) to optimize the interview guide. Every interview was recorded and transcribed word-for-word, without the use of any software.

Each interview was then analyzed using thematic analysis via ATLAS.ti software (33). This analysis used a "coding" process, wherein the first and second author (M.K. and H.A.) independently extracted keywords and statements from the transcriptions. These data were reviewed and discussed, which led to a consensus-based categorization into primary codes (e.g., imbalance, forgetfulness, sadness). Following this, the same authors independently developed main themes (e.g., physical symptoms, emotions, challenging tasks, etc) based on the primary codes, which were then labeled accordingly. Additionally, emotions were coded using Parrot's classification of emotions, which included primary, secondary, and tertiary levels (34) (Supplementary Materials Table S2). In case the two authors disagreed, the original data was reassessed to reach consensus. All interviews and transcriptions were conducted in Turkish, and the coding process was subsequently carried out in English. Analyses continued until saturation was reached (35-37). Mindmaps were used to visually illustrate the full spectrum of reported symptoms and impacts, created by Mindomo (9.2.4).

Content analysis: Patient-reported outcome measures

The Dizziness Handicap Inventory (DHI) (38), the Hospital Anxiety and Depression Scale (HADS) (39), and the EuroQol-5D-5L (EQ-5D-5L) (40) were used for data collection. These tools were selected since they represent different symptom domains affected by UVH, and are widely recognized and validated tools in clinical and research contexts. Specifically, the DHI is designed to assess the self-perceived impact of dizziness and/or unsteadiness on daily life across physical, functional, and emotional subdomains. The HADS examines anxiety and depression, and the EQ-5D-5L evaluates overall health status and quality of life, including pain/discomfort, mobility, self-care, usual activities, and mental well-being. These tools were also previously validated in Turkish populations (41-43).

In this study, the content analysis was conducted for each PROM. Content analysis is a systematic research method used to categorize and interpret textual data by linking it to predefined frameworks or themes (44). The purpose of including PROMs was to compare their assessed domains with those identified in patient interviews. This comparison aimed to explore potential gaps and overlaps between interviews and PROMs. In this stage, each item from PROMs was systematically evaluated and linked to its corresponding ICF constructs and domains. These terms and ICF linking procedure is described in detail below.

ICF Linking

The ICF linking procedure includes several terms: items, concepts, constructs, and domains. An item is a measurable element that captures specific aspects of a domain or construct, either as structured questions in PROMs or as interview quotations from participant-driven insights. For example, a PROM item might ask, “How often do you experience difficulty walking a short distance?”, while an interview quotation item might state, “I can no longer walk to the grocery store without holding onto something.” A concept is a variable created to represent the general meaning of an item, typically summarized in 2-3 words for clarity and categorization. For instance, the concept for the above items might be labeled as "Walking Difficulty." A construct is a broad concept defining major areas of health, functioning, or context, such as Body Functions or Activities and Participation. A domain is a specific subcategory within a construct, grouping related aspects of health or functioning. For example, the Mobility domain, under the construct of Activities and Participation, includes tasks such as walking or climbing stairs (45).

In this study, the items from semi-structured interviews and all PROMs were organized into standardized domains and constructs within ICF. Initially, the items from these measures were obtained. Each item was examined to identify its main and additional concepts. The main concept referred to the primary focus of the item, while additional concepts included any supplementary information. These identified concepts were then linked to the most appropriate ICF domain and construct. Items not covered by the ICF were labeled as "Not covered (Nc)" and those with insufficient information to determine an ICF code were marked as "Not definable (Nd)"(27). Annotations were noted if necessary. The first and second reviewers independently conducted the linking of items from semi-structured interviews and all PROMs. Any inconsistencies in applying the ICF linking procedure between the reviewers were discussed in consensus meetings, and agreement was reached in all cases. The linking details are available in the Supplementary Materials Tables S3 and S4.

ICF Linking analysis

The ICF framework includes four main constructs: Body Functions (denoted by "b"), Activities and Participation ("d"), Environmental Factors ("e"), and Body Structures ("s"). These constructs are organized into a hierarchical structure with domains ranging from the first to the fourth level, and in some cases, a fifth level. The level of each domain is identified by the number of digits following the corresponding alphabet. For instance, “b2351-Vestibular function of balance” represents a fourth-level domain, while “b235-Vestibular functions” is a third-level domain. The second-level domain is “Hearing and vestibular functions”, and the first-level domain is “Sensory functions and pain”. First- and second-level domains in the ICF are presented without numerical codes. In this study, certain items were specifically linked to fourth-level domain (e.g., “Dizziness” (b2401)) since they could be directly linked to specific ICF codes. Others were linked to the third-level domain (e.g., “Sensations associated with hearing and vestibular functions” (b240)) in case a direct code linkage was not feasible. To maintain consistency during analysis, items initially categorized at the fourth-level domain, were standardized to the third-level domain. Following this, second and first-level domains, along with the constructs, were created to provide a comprehensive framework for the analysis.

Two distinct analyses were conducted. First, the frequencies of each domain and construct were analyzed using interview data and visualized through PieDonuts graph based on second-level domains. Second, domains identified from interviews were compared with those identified from PROMs (DHI, HADS, EQ-5D-5L, analyzed separately), illustrated by a heatmap. These comparisons used third-level domains to demonstrate the more detailed aspects of the data. The flowchart of the study design is shown in Figure 1.

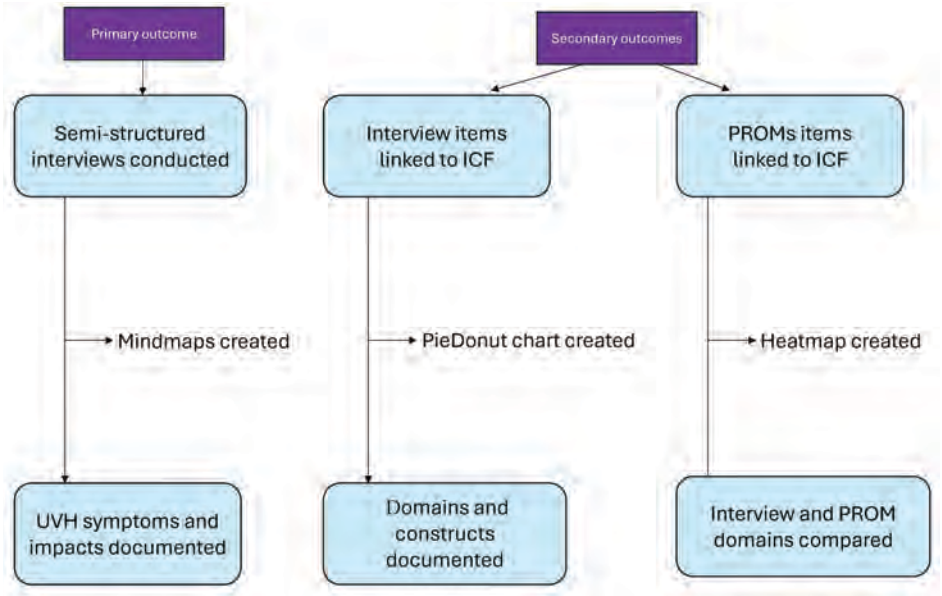


Figure 1. Flowchart of the study design

Ethical considerations

This study adhered to the legislation and ethical standards on human experimentation in Türkiye, as well as the principles outlined in the Declaration of Helsinki. The medical ethical committee of Bayındır Söğütözü Hospital approved this study (BTEDK-03/23 date: 02.02.2023), and written informed consent was obtained from all patients.

3 RESULTS

Patient characteristics

Fifteen chronic UVH patients (9 women, 6 men) with a mean age of 64 years (range 38–75 years), were included for the qualitative analysis. The duration of symptoms ranged from 7 months to 24 years. The diagnoses of UVH in these patients were: Acute unilateral vestibulopathy/vestibular neuritis (n=6); Menière's disease (n=5); idiopathic (n=3) and vestibular schwannoma (n=1). Based on vHIT results, 6 patients had a right sided UVH and 9 patients had a left sided UVH. The mean VOR gain on the pathological side was 0.33 (SD ±0.21), while the healthy side showed a mean value of 0.86 (SD ±0.06). The average asymmetry (%) between the two sides was 48 (SD ±25.8). Regarding co-morbidities, more than half of the patients (53%) had hypertension (n=8). Additionally, patients reported migraine headache, non-migraine headache, anxiety, or autoimmune disorders (each

n=3). The least reported co-morbidities were diabetes and depression (13%, n=2). Table 1. presents the results of each PROM (DHI, HADS and EQ-5D-5L) administered to 15 chronic UVH patients. The DHI showed a mean score of 49.2±16.5, indicating a moderate handicap, with scores ranging from mild to severe handicap (range 28-80). The physical subscale revealed the highest score (18.6±5.9) out of max. 28 points). The HADS indicated borderline anxiety levels (7.5±3.9) and normal depression levels (6.3±4.0). The EQ-5D-5L showed a mean index value of 0.580±0.19, which is lower than the Dutch age-adjusted reference value of 0.839 (60–70 years). Among the five dimensions of the EQ-5D-5L, the "anxiety/depression" dimension was most affected, with a mean score of 2.9±1.0 out of 5.

Table 1. Results from the DHI, HADS and EQ-5D-5L obtained in 15 chronic UVH patients

Questionnaire	Mean (SD) (Median, range)
DHI	
Physical	18.6 (SD=5.9) (20, 8-28)
Functional	16.6 (SD=7.4) (14, 6-29)
Emotional	14.0 (SD=7.3) (14, 2-28)
Total	49.2 (SD=16.5) (46, 28-80)
HADS	
Anxiety	7.5 (SD=3.9) (7, 1-16)
Depression	6.3 (SD=4.0) (6, 1-13)
EQ-5D-5L	
VAS	62.7 (SD=14.43) (60, 25-80)
Index value	0.580 (SD=0.19) (0.620, 0.213-0.883)

Reference values of questionnaires:
DHI: subscales: physical (max 28), functional (max 36), and emotional (max 36). Total score (range 0–100): ≤ 16 no handicap, 16–34 mild handicap, 36–52 moderate handicap, ≥ 54 severe handicap
HADS: 0–7 normal, 8–10 borderline, 11–21 abnormal
EQ-5D-5L: VAS = visual analog scale (0—100%), Mean index value score for age 50–60 years 0.857 and 60–70 years: 0.839
SD= Standard deviation

Patient interviews

After fifteen interviews, no new information was obtained and transcription was discontinued. The average duration of the interviews was 31 min (range 21–52 min) and resulted on average in 2739 words (range 2166– 4413 words). Through thematic analysis of participants' responses, four main categories were identified: symptoms (physical, cognitive, emotions), challenging tasks, coping strategies and behavior. While the interview questions broadly reflected these areas, the final categorization resulted

from the individual interview data. The associated frequencies of occurrence can be found in the Supplementary materials Table S5.

Physical symptoms

Chronic dizziness and unsteadiness were among the most frequently reported symptoms, affecting the majority of patients. Many reported unsteadiness while walking, when bending over, and with fast body movements. Moreover, some noted that darkness exacerbated their symptoms, requiring to turn on lights while walking or standing. To maintain stability, patients indicated the need of support or a reference point, such as holding onto an object.

Another commonly described symptom was visually-induced dizziness, also known as 'the supermarket effect', often triggered in environments with complex visual stimuli. More than half of patients described difficulties when looking at fast-moving objects, car headlights, certain patterns, colors, or objects that move like flowing water. Many also struggled with the inability to perform fast head movements during activities such as walking through pedestrian crossings or looking in mirrors while driving.

Some patients reported autonomic complaints/orthostatic dizziness, experiencing short-term dizziness when making sudden movements from sitting to standing or lying down to standing, requiring them to wait for a moment. Tiredness was also reported by several patients in a way that fatigue occurred in the absence of physical or mental effort, with increased frequency and intensity since UVH onset.

Only few patients mentioned oscillopsia, who described a moving horizon or environment during movements, and difficulty reading signs while walking. Additionally, participants reported other symptoms such as recurrent vertigo, tinnitus, headache, hearing loss, brain fog, neck pain, sweating, and aural fullness. Figure 2 presents a mind map illustrating the physical symptoms. The patient quotations related to cognitive symptoms are presented in Supplementary Materials Table S3.

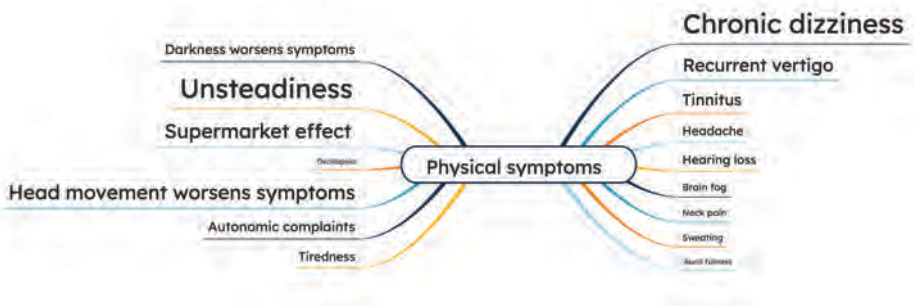


Figure 2. Mind map of physical symptoms, as reported by chronic UVH patients (n = 15) during semi-structured interviews. The larger the font size of a specific symptom, the more often this symptom was addressed during the interviews.

Cognitive symptoms

The majority of patients reported difficulties with concentration, describing struggles with following long conversations, the need to re-read passages for comprehension, and difficulty to repeatedly perform familiar tasks. More than half of patients also noted increased forgetfulness, which was reflected in challenges with recalling familiar information, confusion during routine activities, and forgetting daily tasks. Several patients experienced difficulties with dual tasking, such as walking while reading on their smartphone, or generally trying to do two things at the same time. The least reported cognitive symptom was spatial orientation, which was further categorized into two types: disorientation and misjudging distances. Misjudging distances was illustrated by examples such as bumping into objects or struggling with spatial awareness while driving. Figure 3 presents a mind map illustrating the cognitive symptoms. The patient quotations related to cognitive symptoms are presented in Supplementary Material Table S3.

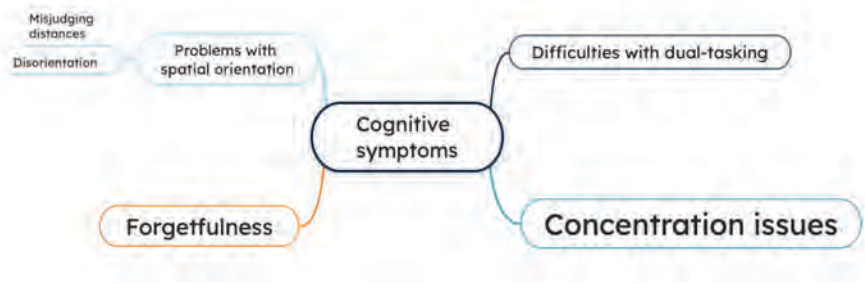


Figure 3. Mind map of cognitive symptoms, as reported by chronic UVH patients (n = 15) during semi-structured interviews. The larger the font size of a specific symptom, the more often this symptom was addressed during the interviews.

Emotions

Parrot's classification of emotions was used to categorize the emotions into primary, secondary, and tertiary emotions. All patients reported negative emotions, and some mentioned positive emotional experiences.

Sadness was often described. It was categorized into disappointment, neglect, sadness, and suffering. Disappointment reflected unmet expectations (e.g., "I didn't expect to have this illness" [UVH-6]). Neglect included embarrassment, insecurity, and isolation (e.g., "I feel concerned if others notice when I stumble" [UVH-3], "This condition (UVH) makes me feel trapped" [UVH-7]). Sadness encompassed depression, despair, sadness, and woe (e.g., "Constant dizziness makes me feel I've lost control" [UVH-8], "I asked the doctor if I could drive a car again" [UVH-11]). Lastly, suffering was characterized by an overwhelming emotion of suffering ("It feels like my mind is constantly heavy, and I can't find any relief."[UVH-10]).

Fear was also frequently mentioned, categorized into nervousness and horror. Nervousness included anxiety, distress, and worry with patients fearing daily activities (e.g., "I'm afraid of going out alone, feel anxious about facing the same challenges" [UVH-1], and "I'm worried about falling or hurting myself" [UVH-7]. Horror involved fear and panic, such as, "I try to avoid darkness; it terrifies me" [UVH-5], " I suddenly feel overwhelmed, like my heart is racing and I can't catch my breath." [UVH-2].

More than half of patients expressed anger, primarily in the form of frustration, irritation and exasperation. Frustration included statements like "I can react sharply to the smallest things" [UVH-1]. Irritation was reflected in a comment such as "Restricted movements irritate me" [UVH-10].

Several patients also reported positive emotions, including joy and love. Joy, expressed as cheerfulness, contentment, and optimism, included statements as "At least I'm happy that this disease is gradually getting better." [UVH-8], and "I have learned to appreciate life and be content with what I have" [UVH-9]. Love was reflected in the form of affection such as "I care for my family; their company brings me joy" [UVH-4] and "Support from my close family keeps me going" [UVH-6]. Figure 4 presents a mind map illustrating the emotions. The patient quotations related to emotions are presented in Supplementary Material Table S3.



Figure 4. Mind map of cognitive symptoms, as reported by chronic UVH patients (n = 15) during semi-structured interviews. The larger the font size of a specific symptom, the more often this symptom was addressed during the interviews.

Challenging tasks, coping strategies, and behavior

Driving was challenging for several patients due to various factors: visually-induced dizziness [UVH-12], difficulty turning their heads [UVH 5,7], worsening symptoms on uneven ground, sharp turns, or sudden head movements triggered by the vehicle's swaying motion [UVH-2,6,8,15]. Some patients experienced sleeping problems, and several patients described a fear of falling particularly in darkness, on stairs, or when dual tasking. Discomfort in crowded situations was also noted, with patients finding it difficult to navigate busy environments. A few patients struggled with reading, particularly with subtitles on television.

Patients adopted various coping strategies to manage symptoms. Many emphasized moving slowly and cautiously, such as waiting before walking, or holding onto railings when using stairs (e.g. "I now think that I will do everything without rushing, taking slow steps" [UVH-2]). Patients reported to avoid sudden movements, overexertion, and crowded environments: "I try to protect myself as much as possible, avoiding rushing, overexertion, and crowded environments" [UVH-2]. At night, patients often used walls for support when moving: "At night, I support myself by holding onto walls" [UVH-10]. Others described modifying tasks to prevent discomfort, such as avoiding certain head movements: "I never lie on my left side, and when I need to look to the left, I turn my whole body" [UVH-15].

Regarding behavior, several patients expressed acceptance of their condition, linking challenges to age or medical history, with comments such as "I accept that as I get older, certain difficulties will arise" [UVH-8], or "I have learned to live with it" [UVH-11]. A few noted reduced family interaction, such as "Even the time I spend with my child has changed" [UVH-2]. Limitations in daily life were also reported, affecting work, travel, and

social activities. One described "This illness made life feel empty, like being imprisoned." [UVH-7], while another mentioned reduced socializing: "I used to meet neighbors often, but this condition has affected me" [UVH-12]. Figure 5 presents a mind map illustrating the challenges, coping strategies and behaviors. The patient quotations related to challenges, behaviors and coping strategies are presented in Supplementary Material Table S3.

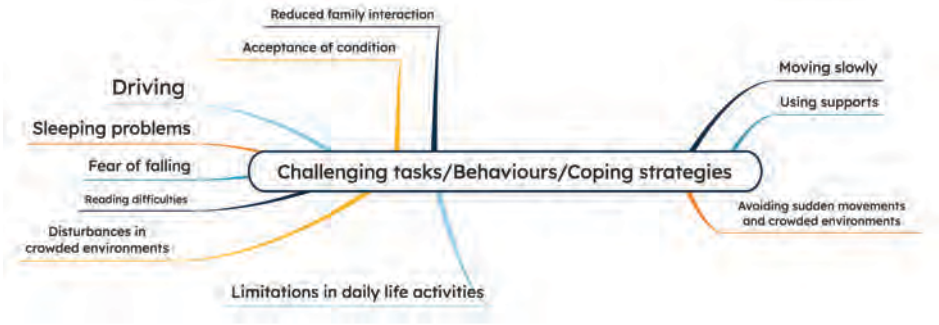


Figure 5. Mind map of challenging tasks, behaviors and coping strategies, as reported by chronic UVH patients (n = 15) during semi-structured interviews. The larger the font size of a specific symptom, the more often this symptom was addressed during the interviews.

Table 2. shows the overview of key themes identified from semi-structured interviews with 15 chronic UVH patients.

Table 2. Semi-structured interview results of the 15 UVH patients

Patients	Semi-structured interview					
	Physical symptoms	**Cognitive symptoms**	**Emotions**	**Challenging tasks**	**Coping strategies**	**Behaviors**
UVH-1	Chronic dizziness Unsteadiness Tiredness	Forgetfulness	Sadness (Sadness) Anger (Exasperation) Fear (Nervousness)		Avoid going outside alone Limit the duration of standing upright	
UVH-2	Chronic dizziness Unsteadiness Supermarket effect Head movement worsens symptoms Oscillopsia	Concentration issues Forgetfulness	Sadness (Sadness, disappointment, neglect) Fear (Nervousness, horror)	Driving Discomfort in crowded situations Reading difficulty	Move slowly Avoid crowded environments	Reduced family interaction Limitations in daily life activities
UVH-3	Chronic dizziness Supermarket effect Head movement worsens symptoms Autonomic complaints Tiredness	Concentration issues Difficulties in dual-tasks Disorientation	Sadness (Sadness, disappointment, neglect) Anger (Exasperation, Irritation) Fear (Nervousness)		Move slowly	Reduced family interaction
UVH-4	Unsteadiness Supermarket effect Head movement worsens symptoms Darkness worsens symptoms Autonomic complaints Tiredness	Concentration issues Difficulties in dual-tasks	Sadness (Sadness, disappointment) Anger (Exasperation) Joy (Optimism) Love (Affection)	Reading difficulty	Move slowly and cautiously, pausing before walking Use railings for support when using stairs	
UVH-5	Chronic dizziness Unsteadiness Supermarket effect Head movement worsens symptoms Darkness worsens symptoms	Forgetfulness, Difficulties in dual-tasks Disorientation Misjudging distance	Anger (Exasperation) Fear (Nervousness, horror)	Driving Sleep problem	Avoid dark environments Seek support by holding onto nearby objects when needed	Limitations in daily life activities

Table 2. *Continued*

Patients	Semi-structured interview					
	Physical symptoms	**Cognitive symptoms**	**Emotions**	**Challenging tasks**	**Coping strategies**	**Behaviors**
UVH-6	Chronic dizziness Tiredness	Concentration issues	Sadness (Disappointment) Anger (Exasperation) Love (Affection)	Driving Sleep problem		
UVH-7	Chronic dizziness Unsteadiness Supermarket effect Head movement worsens symptoms Autonomic complaints Tiredness	Concentration issues Misjudging distance	Sadness (Sadness, disappointment) Fear (Nervousness) Joy (Optimism)	Driving Sleep problem	Move slowly Use railings for support when using stairs	Limitations in daily life activities
UVH-8	Chronic dizziness Unsteadiness Supermarket effect Head movement worsens symptoms Darkness worsens symptoms	Concentration issues Difficulties in dual-tasks	Anger (Exasperation) Joy (Cheerfulness, Contentment)	Driving Fear of falling Discomfort in crowded situations	Avoid crowded environments	Acceptance of condition
UVH-9	Chronic dizziness Supermarket effect Darkness worsens symptoms	Forgetfulness	Sadness (Disappointment) Fear (Nervousness) Joy (Contentment)	Sleep problem Fear of falling	Move slowly and cautiously, pausing before walking Avoid sudden movements	
UVH-10	Chronic dizziness Unsteadiness Head movement worsens symptoms	Concentration issues Forgetfulness	Sadness (Suffering, disappointment) Anger (Exasperation, Irritation) Fear (Nervousness) Love (Affection)	Sleep problem Fear of falling	Use railings for support when using stairs Avoid sudden head movements	Limitations in daily life activities

Patients	Semi-structured interview					
	Physical symptoms	**Cognitive symptoms**	**Emotions**	**Challenging tasks**	**Coping strategies**	**Behaviors**
UVH-11	Unsteadiness Head movement worsens symptoms Darkness worsens symptoms		Sadness (Sadness)	Sleep problem Discomfort in crowded situations	Move slowly and cautiously Use railings for support when using stairs	Acceptance of condition
UVH-12	Chronic dizziness Unsteadiness Supermarket effect Head movement worsens symptoms Autonomic complaints	Concentration issues	Sadness (Sadness, disappointment)	Driving	Use railings for support when using stairs Avoid from light	Limitations in daily life activities
UVH-13	Unsteadiness Supermarket effect		Sadness (Disappointment) Fear (Nervousness)		Limit the duration of standing upright	
UVH-14	Chronic dizziness Unsteadiness Supermarket effect Head movement worsens symptoms Darkness worsens symptoms Autonomic complaints Oscillopsia	Concentration issues Forgetfulness	Fear (Nervousness)	Fear of falling Discomfort in crowded situations Reading difficulty	Move slowly and cautiously Use railings for support when using stairs Avoid sudden movements	Reduced family interaction
UVH-15	Chronic dizziness Unsteadiness Supermarket effect Head movement worsens symptoms Autonomic complaints	Concentration issues	Anger (Irritation)	Driving Fear of falling	Avoid certain head movements	Acceptance of condition

ICF Linking

Figure 6 illustrates the frequencies of each construct and domain identified from interviews. Body functions was the most frequently reported construct (60%). Within this construct, the most commonly reported domains were “Specific mental functions” and “Hearing and vestibular functions”, with specific items “b152-Emotional functions”, “b235- Vestibular functions”, “b240 Sensations associated with hearing and vestibular functions”. Patients reported items covering 5 out of 8 first-level domains in the ICF framework, excluding “Voice and speech functions”, “Functions of the digestive, metabolic and endocrine systems” and “Genitourinary and reproductive functions”.

Activities and participation was the secondly most reported construct (31%). The most frequently noted domains were “Changing and maintaining body position” and “Particular interpersonal relationships”, with specific items such as “d4105-Bending”, “d415-Maintaining body position”, and “d760-Family relationships”. Patients mentioned items covering 7 of the 9 first-level domains in the ICF framework, excluding “Self-care” and “Domestic life”.

Environmental factors was the least reported construct (9%). The most commonly reported domain was “Natural environment and human-made changes to environment”, including specific items such as “e240- Light”, “e250-Sound”. Patients referred to items covering 4 of the 5 first-level domains in the ICF framework, excluding “Services, systems and policies”. No items related to the body structure construct were identified in the interviews.

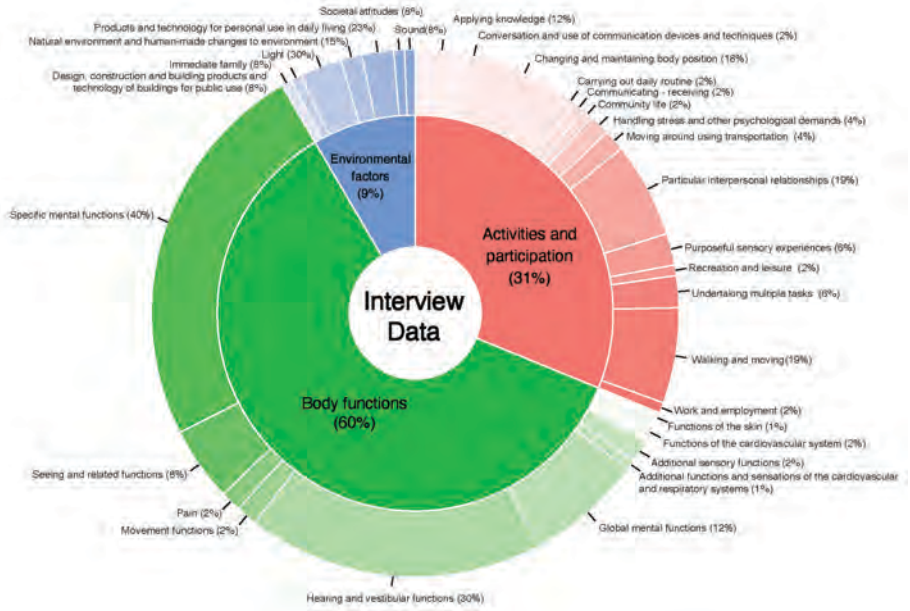


Figure 6. The frequencies of each construct and domain identified from semi-structured interviews.

Figure 7 compares domains identified in the patient interviews, with domains covered by the DHI, HADS, and EQ-5D-5L. The DHI does not include critical cognitive domains, such as memory and thought functions, and activities like undertaking multiple tasks. Physical limitations, including seeing function, blood pressure functions, and maintaining body position, were also absent. The HADS, which focuses on emotional aspects, does not assess physical symptoms, which limits its ability to fully represent the multidimensional impact of UVH. The EQ-5D-5L, despite providing a general overview of quality of life, does not cover key cognitive and physical domains, such as proprioception and vestibular-related challenges, making it less comprehensive in capturing the full impact of UVH on patients. The interviews, however, revealed important domains not addressed in the PROMs, including consciousness, proprioceptive, sleep, blood pressure, exercise tolerance, and hearing functions, along with community life.

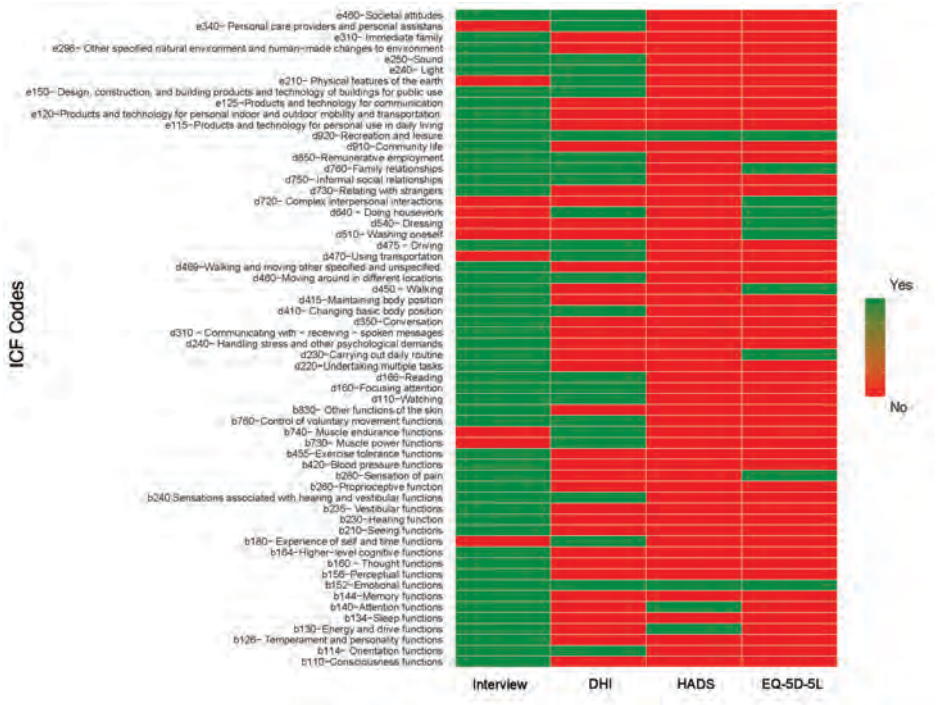


Figure 7. Comparative analysis of domains identified through semi-structured patient interviews versus those covered by the DHI, HADS, and EQ-5D-5L instruments.

4 DISCUSSION

This qualitative study demonstrated the diverse symptoms of chronic UVH, across physical, cognitive, and emotional domains. To manage symptoms, patients adopted strategies like moving slowly, using support like walls or railings, and avoiding sudden movements. However, despite these strategies, significant functional limitations in daily life, social interactions, and family relationships were found. The frequently used PROMs (DHI, HADS, and EQ-5D-5L) did not fully cover these symptoms and their impacts. This left many domains underrepresented such as vision, memory, multitasking, and daily activities impacting quality of life.

Symptoms

Chronic dizziness and unsteadiness were among the most frequently reported symptoms in this study, which corresponds with previous research (2, 12, 46, 47). More than half of the interviewed patients reported that symptoms worsened with head movements or visual triggers. These findings may be influenced by selection bias, as patients with severe symptoms are more likely to seek medical care and participate in research. Only a

few patients experienced oscillopsia, which is also congruent with previous studies (2, 3, 12, 48). Input from the remaining vestibular organ, and central vestibular compensation mechanisms, may support gaze stabilization and dynamic visual acuity but can still fail in dynamic conditions. Symptoms like recurrent vertigo and hearing loss may be linked to the underlying cause of UVH rather than UVH itself (e.g. Menière's disease) (2, 49). Furthermore, problems with spatial orientation issues may be partially linked to hippocampal atrophy resulting from UVH (50, 51). Overall, this qualitative study supports the findings of previous studies. It prospectively confirmed that the spectrum of UVH symptoms extends beyond chronic dizziness and unsteadiness.

Some reported symptoms, for example those related to cognition and emotions, may not be exclusively due to UVH. These could be linked to other chronic conditions such as migraine, diabetes, and anxiety disorders. However, it is well established that vestibular disorders and anxiety/depression symptoms often co-exist and can mutually influence one another (52). Therefore, such symptoms were considered as part of the chronic UVH-related symptoms. Chronic conditions can heighten psychological distress and increase the need for psychosocial support. This may exacerbate negative emotional states and cognitive difficulties, such as impaired concentration and forgetfulness (53, 54). Additionally, UVH alters connectivity in cortical and subcortical brain structures, which can affect bodily self-awareness, emotional regulation, and cognitive processes (55, 56). Therefore, these symptoms likely have a multifactorial origin, reflecting both the direct effects of UVH and the broader impact of other chronic conditions.

Challenges, coping strategies and behaviors

Patients identified several triggers that worsened their symptoms, such as overexertion, stress, and activities like bending or standing. Driving, exposure to complex visual stimuli, and crowded environments were particularly challenging, often resulting in fear of falling, heightened caution, and avoidance behaviors (57, 58). It should be noted that some triggers (e.g. exposure to complex visual stimuli and crowded environments) can also be present in other disorders than UVH, like PPPD (59). Therefore, these findings might not exclusively be related to UVH. Patients also adopted coping strategies like slowing down movements, using supports like walls or railings, and avoiding sudden movements. While these strategies may provide short-term relief, they can also reinforce maladaptive behaviors linked to PPPD, such as over-reliance on caution and hypervigilance (60). Furthermore, the significant social and emotional impacts emphasize the multifactorial nature of UVH, with common reports of frustration, isolation, and changes in family dynamics, which reflect the burden of persistent symptoms on daily life. These findings highlight the need to address both the vestibular hypofunction and the psychosocial adaptations to prevent the maladaptive behaviors and improve long-term outcomes (61). Integrating targeted

interventions that consider the potential overlap with PPPD could support both functional recovery and emotional well-being (62).

Comparison between interview and content analysis of PROMs

The interviews in this study provided detailed information, as these allowed for follow-up questions to clarify responses, reducing ambiguity caused by fixed questionnaire formats. It was demonstrated that the interviews identified several key domains which were not reflected by the DHI, HADS, and EQ-5D-5L. These domains included vision, hearing, memory, sleep, consciousness, proprioceptive, blood pressure, and multitasking.

The DHI, HADS, and EQ-5D-5L were selected for their reliability and widespread use in assessing chronic UVH. The findings of this study imply that these PROMs not fully represent the wide spectrum of symptoms experienced by UVH patients. In addition to these PROMs, a large number of other PROMs (n=48) were developed for patients with vestibular symptoms (63). However, the majority of these PROMS were designed for a heterogeneous patient population, and focus on single domains such as dizziness or emotional distress. (63). Furthermore, a previous qualitative study in vestibular patients found that around one-quarter of interview items raised by patients, were not reflected by existing PROMs (64). Given these limitations, it can be concluded that current PROMs not fully reflect UVH-related symptoms and their impact on daily life. Therefore, it might be preferred to develop a tailored PROM specifically designed for UVH, which takes all the relevant symptoms, behaviors and functional limitations into account (65-67).

The role of the ICF framework

The ICF framework was not used to identify symptoms or functional limitations, but rather to systematically classify and organize them. Since the interviews provided a wide range of patient experiences, the ICF served as a structured model to categorize these findings into well-defined domains and constructs. This helped to ensure that the results were presented in a way that allows for comparison with existing health models and other conditions. In line with this, previous studies used the ICF to identify relevant domains of functioning, to develop standardized Core Sets for dizziness and balance disorders, and to explore the influence of environmental triggers on symptom severity (68-70). These efforts demonstrate the value of using a standardized recognized classification system to understand the broader impact of vestibular disorders on daily life. Following previous studies, this study applies the ICF framework to both interview data and PROMs in chronic UVH, which offered an integrated perspective on how physical, emotional, and cognitive challenges can be categorized and communicated within a standardized health model. Additionally, using the ICF framework makes it easier to communicate the impact of UVH to healthcare professionals, researchers, and policymakers by placing patient experiences

within a standardized classification system. This system supports cross-study and cross-population comparisons, which can therefore aid in the identification of both common patterns and unique challenges.

This qualitative study, along with a previous systematic review and retrospective study on chronic UVH (2, 12), identified symptoms, daily life impact, and functional limitations that closely aligned with those reported in patients with bilateral vestibulopathy (BVP) (71-73). Both disorders share similar symptoms such as unsteadiness, visually-induced dizziness, oscillopsia, cognitive complaints, autonomic dysfunction, tiredness, and spatial disorientation, although their severity and impact may vary. To address these challenges in BVP, the Bilateral Vestibulopathy Questionnaire (BVQ) was developed as a PROM to evaluate the full spectrum of symptoms and their impact on daily life (74, 75). Given the substantial overlap in symptomatology and functional consequences between chronic UVH and BVP, the BVQ is currently being evaluated for validity in patients with chronic UVH.

Limitations

Several limitations were identified in this study. First, there might be selection bias because patients were chosen using purposive sampling. This means that those who agreed to participate could have different symptoms or psychological traits compared to those who did not participate. Secondly, even though the protocol was checked by three different co-authors, there was no pilot study to test the interview questions beforehand, which could imply that important aspects of patients' experiences may have been missed. Thirdly, no standardized diagnostic criteria for chronic UVH are currently available. Diagnosis of UVH was therefore based on horizontal vHIT in this study, which is consistent with the Bárány Society's criteria for bilateral vestibulopathy. Horizontal vHIT was also selected due to its higher specificity, reduced susceptibility to artifacts compared to vertical vHIT or the caloric test, and its relevance to natural head movement frequencies (76, 77). While this approach may have limited sensitivity, it minimized false positives and aligned with available standards. Lastly, this study was limited to a Turkish population, which may affect its relevance to other cultures due to differences in symptom perception.

5 CONCLUSION

Patients with chronic UVH experience a wide spectrum of physical, cognitive, and emotional symptoms, resulting in significant limitations in daily life. The frequently used PROMs (DHI, HADS, and EQ-5D-5L) do not fully cover these symptoms and their impacts, which leaves many aspects underrepresented. A tailored PROM for UVH may be needed, to better reflect the specific symptoms, behaviors and functional limitations related to chronic UVH.

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SUPPLEMENTARY MATERIALS

Table S1. Interview questions

1. Could you share your experiences related to your condition? • How/When did it happen? • Was it sudden/gradual? • What symptoms did you experience? • What do you believe are the causes?
2. How long have you had your complaints/symptoms?
3. What complaints/symptoms related to your balance system do you currently experience? • Physical/Cognitive/Emotional
4. What complaints/symptoms do you experience most frequently?
5. Which complaints/symptoms interfere most with your daily life?
6. When or in what situations do your complaints/symptoms worsen or appear?
7. How do you cope with these symptoms? • How do you feel about managing this condition? How has it impacted you?
8. How do these complaints/symptoms affect your relationships with your partner/family/friends/work colleagues?
9. What treatment processes have you undergone (medical treatment, vestibular rehabilitation, surgical procedures)? • How long was each treatment? • What was your experience?
10. Do you have any other additional health conditions?

Table S2. Parrot's Classification of Emotions (2001)

Primary emotion	Secondary emotion	Tertiary emotion
Love	Affection	Adoration, affection, love, fondness, liking, attraction, caring, tenderness, compassion, sentimentality
	Lust	Arousal, desire, lust, passion, infatuation
	Longing	Longing
Joy	Cheerfulness	Amusement, bliss, cheerfulness, gaiety, glee, jolliness, joviality, joy, delight, enjoyment, gladness, happiness, jubilation, elation, satisfaction, ecstasy, euphoria
	Zest	Enthusiasm, zeal, zest, excitement, thrill, exhilaration
	Contentment	Contentment, pleasure
	Pride	Pride, triumph
	Optimisim	Eagerness, hope, optimism
	Enthrallment	Enthrallment, rapture
	Relief	Relief
Anger	Irritation	Aggravation, irritation, agitation, annoyance, grouchiness, grumpiness
	Exasperation	Exasperation, frustration
	Rage	Anger, rage, outrage, fury, wrath, hostility, ferocity, bitterness, hate, loathing, scorn, spite, vengefulness, dislike, resentment
	Disgust	Disgust, revulsion, contempt
	Envy	Envy, jealousy
	Torment	Torment

Primary emotion	Secondary emotion	Tertiary emotion
Sadness	Suffering	Agony, suffering, hurt, anguish
	Sadness	Depression, despair, hopelessness, gloom, glumness, sadness, unhappiness, grief, sorrow, woe, misery, melancholy
	Disappointment	Dismay, disappointment, displeasure
	Shame	Guilt, shame, regret, remorse
	Neglect	Alienation, isolation, neglect, loneliness, rejection, homesickness, defeat, dejection, insecurity, embarrassment, humiliation, insult
	Symphaty	Pity, sympathy
Fear	Horror	Alarm, shock, fear, fright, horror, terror, panic, hysteria, mortification
	Nervousness	Anxiety, nervousness, tenseness, uneasiness, apprehension, worry, distress, dread

Table S3. The extracted data and linking details from semi-structured interviews

Name of symptoms	Verbatim health information	Perspective adopted in information	Response options	Classification of response options
PHYSICAL SYMPTOMS				
Chronic dizziness	"It feels like I am walking on clouds." [UVH-1] "It's like a momentary slow-motion film strip, like I'm moving slowly." [UVH-2] "I experience brief dizzy, but it also feels like I am groggy." [UVH-7] "Does it feel like the environment is spinning? Or is it something else? I feel weak." [UVH-9] "It feels like one of my feet is in the air, not touching the ground, and when it does touch, it feels like I'm about to fly away." [UVH-14]	Descriptive-Performance	--	Qualitative attributes
Unsteadiness	"When I go on bumpy roads, I feel a sense of imbalance, and it feels like I might turn over at any moment." [UVH-2] "I constantly felt like I was going to fall. I couldn't stay balanced." [UVH-4] "It always feels like I am leaning to one side. When I was receiving treatment, I tried walking on a straight line, but I would slide to one side." [UVH-10] "The worst thing I experience is occasional imbalance. I especially feel it more when I am very tired or have not had enough sleep." [UVH-13]	Descriptive-Performance	--	Qualitative attributes
Supermarket effect	"For example, colorful objects. Fluid-like things. For instance, black and white things, sliding things." [UVH-2] "While using my phone, sometimes when scrolling, I get tired and can't follow. It feels like things are coming towards me." [UVH-4] "When I look at colorful products on the shelves, my balance gets disrupted." [UVH-7] "When I stir the soup, my eyes spin as the soup spins. My head spins too." [UVH-12]	Descriptive; Performance	--	Qualitative attributes

Main concepts: What is this information about?	Additional concepts contained in the information	ICF category of main concept	ICF category of other concepts	Annotation
Perception of walking on an unstable surface Grogginess Perception of foot not touching the ground Sensation of swaying Perception of moving in slow motion	Consciousness Body position Proprioception Energy	**b2351**-Vestibular function of balance **b2401**-Dizziness	**b110-**Consciousness functions **b260**-Proprioceptive function **b130**-Energy and drive functions **d469**-Walking and moving other specified and unspecified. **d415**-Maintaning body position **b156**-Perceptual functions	
Unsteadiness on uneven surfaces Persistent feeling of falling Loss of balance while walking Leaning to one side	Fatigue Lack of sleep	**b2351-**Vestibular function of balance **b2402**-Sensation of falling **b2409**-Sensations associated with hearing and vestibular functions, unspecified	**b130**-Energy and drive functions **b134**-Sleep functions **d410**-Changing basic body positions **d460**-Moving around in different locations **d415**-Maintaining body position **e298**-Natural environment and human-made changes to environment	Chronic dizziness is more about a subjective feeling of altered spatial orientation, while imbalance is a physical difficulty in maintaining stability.
Sensitivity to visual stimuli Difficulty following moving objects on phone Sensitivity to fluid-like moving objects Balance disruption by colorful objects		**b210-**Seeing functions **b2351-**Vestibular function of balance **b2409**-Sensations associated with hearing and vestibular functions, unspecified **b2402**-Sensation of falling	**e240-**Light **b260**-Proprioceptive function **d110**-Watching **d160**-Focusing attention **e120**-Products and technology for personal indoor and outdoor mobility and transportation.	This is called visually-induced dizziness. So, it is unspecified.

Table S3. *Continued*

Name of symptoms	Verbatim health information	Perspective adopted in information	Response options	Classification of response options
Head movements worsen symptoms	"When I turn quickly my head, I experience sense of losing balance." [UVH-2] "When I bend over or change my position, for instance, if I bend over to do something and then stand up, if I'm not careful, I might fall." [UVH-5] "I try to be careful with sudden head movements because I'm afraid I might lose my balance suddenly." [UVH-8] "I can't look up. Or I try to turn my whole body to look right or left. I can't just turn my neck. Even if I do, I can't see clearly." [UVH-14] "When I enter a curve quickly, with a quick head movement, my dizziness starts." [UVH-15]	Descriptive; Performance	--	Qualitative attributes
Darkness worsens symptoms	"I struggle to walk in the dark. I think to myself, 'Let me turn on the light ahead before I go,' otherwise I can't find my way in the darkness." [UVH-4] "I absolutely have to turn on a flashlight or use my phone in the dark. I'm not like I used to be. I have to turn on a light or keep one on in the corridor." [UVH-14]	Descriptive; Performance	--	Qualitative attributes
Autonomic complaints	"When I get up suddenly, I experience a loss of balance. To manage this, I try to slow down and control myself." [UVH-12] "When I stand up quickly, it feels like my blood pressure rises or drops. There's this sudden pressure in my head. I don't know if it's going up or down, but something happens. Then it passes." [UVH-15]	Descriptive; Performance	--	Qualitative attributes
Tiredness	"Sometimes, even if I'm not doing any activity or exerting myself, I find myself feeling tired. I don't know how to prevent this." [UVH-4] "But I get tired very quickly. I wasn't like this before. I used to go up and down without getting tired. But especially after this dizziness started, it feels like my fatigue has increased." [UVH-6]	Descriptive; Performance	--	Qualitative attributes

Main concepts: What is this information about?	Additional concepts contained in the information	ICF category of main concept	ICF category of other concepts	Annotation
Loss of balance with quick movements Discomfort with head tilting Restriction in head movement	Precautionary behavior, anxiety Fear of falling	**b2351**-Vestibular function of balance **b2409**-Sensations associated with hearing and vestibular functions, unspecified **d410**-Changing basic body positions **d110**-Watching **b760**-Control of voluntary movement functions	**b152**-Emotional functions **b2402**-Sensation of falling **d4105-**Bending **d450**-Walking **b210-**Seeing functions **d160**-Focusing attention	This type of symptom is related to dizziness and unsteadiness. However, this is also different entity that specifically the head movements worsen the balance.
Difficulty walking in the dark	Dependence on external light sources	**d450**- Walking **b210**- Seeing function **d460**-Moving around in different locations **b2351**-Vestibular function of balance **b21020**-Light sensitivity	**e240**- Light **d220**- Undertaking multiple tasks	
Loss of balance when standing up quickly	Perception of head pressure	**b2351**- Vestibular function of balance **d410**- Changing basic body position **b420**-Blood pressure functions		The sensation of pressure around neck or head does not take place in ICF. Therefore, it is called not covered (Nc). But it is related to hearing and vestibular functions which is not specified.
Fatigue without exertion	Increased fatigue, particularly after dizziness onset	**b4552**- Fatiguability **b1300**- Energy level	**b2401-** Dizziness	

Table S3. *Continued*

Name of symptoms	Verbatim health information	Perspective adopted in information	Response options	Classification of response options
Oscillopsia	"For example, when I'm moving or walking, the objects around me seem to be shaking." [UVH-2] "When I'm walking, I notice it, and oddly enough, I kind of enjoy it. Sometimes I even try to enjoy it when I move my head. But it really happens; the things around me seem to be shaking." [UVH-14]	Descriptive; Performance	--	Qualitative attributes
Tinnitus	"In the morning, I wake up with a ringing in my ears." [UVH-2] "My right ear constantly rings, and it's always there." [UVH-5]	Descriptive; Performance	--	Qualitative attributes
Recurrent vertigo	"After my first episode, I didn't have another attack for three years. Then, three years later, I had another one." [UVH-12] "It always comes in episodes like this. The first one happened seven years ago." [UVH-13]	Descriptive; Performance	--	Qualitative attributes
Headache	"About a week to ten days before the attack, I had a headache where one side was pulling forward, and the other was pulling backward. My head felt like a drum." [UVH-14] "Recently, in the last few years, I've been getting headaches. For example, I had one this winter." [UVH-15]	Descriptive; Performance	--	Qualitative attributes
Hearing loss	"Now, if I want to listen, I turn my hearing side towards the sound. Otherwise, if someone comes and talks on my other side, I don't hear them at all." [UVH-9] "I realized later that my right ear wasn't hearing." [UVH-12]	Descriptive; Performance	--	Qualitative attributes
Brain fog	"One of my biggest symptoms is when a sudden heaviness and drowsiness comes over me. If I don't sleep at that moment, I know an attack is coming. I start feeling like I'm in a daze." [UVH-2] "It's just like I suddenly feel dazed, like I'm in a fog." [UVH-6]	Descriptive; Performance	--	Qualitative attributes
Neck pain	"Especially after that period, about 1 or 2 months later, a dull pain remained at the back of my head. It's like the kind of stiffness you feel in some organs." [UVH-3]	Descriptive; Performance	--	Qualitative attributes
Sweating	"Even if I don't move much, I sweat. My sweating has become more frequent." [UVH-5]	Descriptive; Performance	--	Qualitative attributes
Aural fullness	"But I also feel like there's a sense of fullness in my right ear." [UVH-6]	Descriptive; Performance	--	Qualitative attributes
COGNITIVE SYMPTOMS				

Main concepts: What is this information about?	Additional concepts contained in the information	ICF category of main concept	ICF category of other concepts	Annotation
Perception of objects shaking while moving		**b2100** Visual acuity functions **d450**-Walking **b235**- Vestibular functions	**b2401**-Dizziness	
Sensation of ringing in the ear.		**b2400** Ringing in ears or tinnitus		
Vertigo attacks occur more than once		**b240** Sensations associated with hearing and vestibular functions		
The sensation of headache		**b280**-Sensation of pain		
Hearing loss Hearing fluctuation		**b230**- Hearing functions		
Lack of mental clarity and a feeling of being mentally disoriented.		**b144**-Memory functions		
Neck pain		**b28010** Pain in head and neck		
		b830- Other functions of the skin		This category includes the functions of sweating in ICF.
		b2405- Aural pressure		

Table S3. *Continued*

Name of symptoms	Verbatim health information	Perspective adopted in information	Response options	Classification of response options
Difficulties with dual tasks	"I usually focus on one task first, finish it, and then move on to the next activity. It takes more time this way, but if I try to do both at the same time, everything ends up a mess." [UVH-4] "For example, when my wife is talking to me, I can't do something else at the same time. I need to focus on listening to her." [UVH-5] “I can't exactly figure out where to focus when I have two tasks at once. For example, I can't concentrate on my phone while I'm walking” [UVH-8]	Descriptive; Performance	--	Qualitative attributes
Disorientation	"I often find myself getting confused about directions, like not knowing which way to turn in familiar places." [UVH-5]	Descriptive; Performance	--	Qualitative attributes
Misjudging distances	"When I'm driving—I try to line up the car while overtaking, but I still end up touching the car" [UVH-5] "I've had a few issues like occasionally bumping into the elevator door while walking or hitting my arm while passing through a doorway." [UVH-7]	Descriptive; Performance	--	Qualitative attributes
Concentration problems	"I can't keep up with long conversations after a while. They start to bore and tire me out." [UVH-8] "Sometimes, while reading, I find myself not understanding, like my mind is elsewhere. I often have to read things twice or struggle to fully concentrate" [UVH-10] "Even with something I'm familiar with, I often find myself having to repeat the same task or process." [UVH-14]	Descriptive; Performance	--	Qualitative attributes
Forgetfulness	"My memory used to be excellent; I never forgot a face or a voice. Now, I forget things easily and often have to repeat what I read to understand it." [UVH-2] "While praying, I used to never forget the verses, but in the past couple of years, I've found myself mixing up which ones I've recited or which part of the prayer I'm on." [UVH-5] "Sometimes I forget tasks I need to do during the day, even when I'm not busy. When I remember later, I get frustrated with myself for forgetting." [UVH-9]	Descriptive; Performance	--	Qualitative attributes
EMOTIONS				
Disappointment	"I didn't expect to have this illness" [UVH-6]	Descriptive; Performance	--	Qualitative attributes

Main concepts: What is this information about?	Additional concepts contained in the information	ICF category of main concept	ICF category of other concepts	Annotation
Difficulty with multitasking Distraction Lack of focus		**b140** Attention functions **d220**-Undertaking multiple tasks	**d310** - Communicating with - receiving - spoken messages **d450** - Walking	
Confusion Navigation issues		**b114**-Orientation functions		
Difficulty with driving		**b164**-Higher-level cognitive functions		
Fatigue Disinterest Repetition		**b140**-Attention functions **b144-**Memory functions **b160-**Thought functions	**d350-** Conversation **d166-**Reading	
Repetition Memory lapses Confusion		**b144-**Memory functions	**d230-**Carrying out daily routine	
Disappointment		**b152** - Emotional functions		

Table S3. *Continued*

Name of symptoms	Verbatim health information	Perspective adopted in information	Response options	Classification of response options
Displeasure	"My wife never leaves me alone due to my balance issues; it makes me feel dependent" [UVH-4]	Descriptive; Performance	--	Qualitative attributes
Embarrasment	"I feel concerned if others notice when I stumble" [UVH-3]	Descriptive; Performance	--	Qualitative attributes
Insecurity	"I feel unsure of myself, what if something happens spontaneously?" [UVH-2]	Descriptive; Performance	--	Qualitative attributes
Isolation	"This condition makes me feel trapped" [UVH-7]	Descriptive; Performance	--	Qualitative attributes
Sadness	"Family issues make me sad" [UVH-12]	Descriptive; Performance	--	Qualitative attributes
Depression	"A sudden heaviness and drowsiness overwhelms me" [UVH-2]	Descriptive; Performance	--	Qualitative attributes
Despair	"I asked the doctor if I could drive a car again" [UVH-11]	Descriptive; Performance	--	Qualitative attributes
Woe	"Constant dizziness makes me feel I've lost control" [UVH-8]	Descriptive; Performance	--	Qualitative attributes
Suffering	"It feels like my mind is constantly heavy, and I can't find any relief." [UVH-10]	Descriptive; Performance	--	Qualitative attributes
Anxiety	"I'm afraid of going out alone, anxious about facing the same challenges" [UVH-1]	Descriptive; Performance	--	Qualitative attributes
Distress	"I have to focus on my condition because my quality of life deteriorates" [UVH-2]	Descriptive; Performance	--	Qualitative attributes
Worry	"I'm worried about falling or hurting myself" [UVH-7]	Descriptive; Performance	--	Qualitative attributes
Fear	"I try to avoid darkness; it terrifies me" [UVH-5]	Descriptive; Performance	--	Qualitative attributes
Panic	"Sometimes, I suddenly feel overwhelmed, like my heart is racing and I can't catch my breath." [UVH-2].	Descriptive; Performance	--	Qualitative attributes
Frustration	"My tolerance level has decreased, and I react strongly to situations" [UVH-4].	Descriptive; Performance	--	Qualitative attributes

Main concepts: What is this information about?	Additional concepts contained in the information	ICF category of main concept	ICF category of other concepts	Annotation
Feeling dependent		**b152 -** Emotional functions	**d760** - Family relationships	
Concern about judgment		**b152 -** Emotional functions **e460**- Societal attitudes	**d730** Relating with strangers	
Insecurity		**b152 -** Emotional functions **b126**-Temperament and personality functions		
Feeling trapped		**b152 -** Emotional functions **d240**-Handling stress and other psychological demands		
Sadness		**b152 -** Emotional functions	**d760** - Family relationships	
Depression		**b152 -** Emotional functions		
Despair		**b152 -** Emotional functions	**d475** - Driving	
Feeling of loss of control		**b152 -** Emotional functions	**b235**-Vestibular functions	
Mental suffering		**b152 -** Emotional functions **b130**-Energy and drive functions		
Anxiety		**b152 -** Emotional functions	**d460** - Moving around in different locations	
Distress		**b152 -** Emotional functions	**b160** - Thought functions	
Worry		**b152 -** Emotional functions	**b2402** Sensation of falling	
Fear of darkness		**b152 -** Emotional functions	**e240** - Light	
Overwhelming fear		**b152 -** Emotional functions	**b420** Blood pressure functions	
Frustration		**b152 -** Emotional functions		

Table S3. *Continued*

Name of symptoms	Verbatim health information	Perspective adopted in information	Response options	Classification of response options
Irritation	"Having my movements restricted irritates me" [UVH-10]	Descriptive; Performance	--	Qualitative attributes
Happiness	"At least I'm happy that this disease is gradually getting better." [UVH-8]	Descriptive; Performance	--	Qualitative attributes
Contentment	"I've learned to appreciate life and be content with what I have" [UVH-9]	Descriptive; Performance	--	Qualitative attributes
Optimism	"I comfort myself by believing this illness will eventually improve" [UVH-7]	Descriptive; Performance	--	Qualitative attributes
Fondness	"I care for my family; their company brings me joy" [UVH-4]	Descriptive; Performance	--	Qualitative attributes
Sentimentality	"Support from my close family keeps me going" [UVH-6]	Descriptive; Performance	--	Qualitative attributes
CHALLENGING TASKS				
Driving	"I get dizzy when I turn my head suddenly while driving." [UVH-7] "Sometimes it feels like my vision becomes distorted or unusual when I'm driving a car." [UVH-12] "I have trouble with sharp turns while driving; they seem to trigger me." [UVH-15]	Descriptive; Performance	--	Qualitative attributes
Sleeping problem	"Sometimes I wake up very often during the night. Sometimes I can sleep comfortably until the morning. As I said, there is a lack of consistency." [UVH-9] "I have a very hard time falling asleep, unfortunately. It's very interrupted, I jump at even the slightest sound. I can't remember a time when I had a deep, uninterrupted sleep." [UVH-11]	Descriptive; Performance	--	Qualitative attributes
Fear of falling	"When there are two tasks at the same time, I can't fully decide what to focus on. I have fears that I might lose my balance." [UVH-8] "I already don't like the dark at all. And when I get up in the dark, I have this fear of falling." [UVH-14] "I can go down, but probably a bit slowly. I can go down, but I might be scared. I can go up without holding on, but when going down, it might feel like I'm about to fall." [UVH-15]	Descriptive; Performance	--	Qualitative attributes

Main concepts: What is this information about?	Additional concepts contained in the information	ICF category of main concept	ICF category of other concepts	Annotation
Irritation		**b152 -** Emotional functions	**d415**-Maintaning a body position	
Happiness		**b152 -** Emotional functions		
Contentment		**b152 -** Emotional functions		
Optimism		**b152 -** Emotional functions		
Fondness		**b152 -** Emotional functions	**d760** - Family relationships	
Sentimentality		**b152 -** Emotional functions	**d760** - Family relationships **e310**-Immediate family	
Difficulty when turning head Visual vertigo Worsening symptoms on uneven ground, sharp turns		**d475**- Driving **b210-** Seeing function **b2401-** Dizziness		
Difficulty maintaining consistent sleep Difficulty falling asleep		**b1341-** Onset of sleep **b1342-** Maintenance of sleep		
Dual-task difficulty Fear of falling Needing light	Dual-task Light Scared	**b140** Attention functions **b2402** Sensation of falling **b235**-Vestibular functions	**e240-** Light **d410-** Changing basic body positions **b152**-Emotinal functions **d220**-Undertaking multiple tasks	

Table S3. *Continued*

Name of symptoms	Verbatim health information	Perspective adopted in information	Response options	Classification of response options
Disturbance in crowded environments	"We are in a crowded group setting, you are talking, the other person is talking, and another person is talking. That triggers an attack for me." [UVH-2] "I can enter the supermarket comfortably, but when there are a lot of people, that disturbs me a little." [UVH-8] "Let me put it this way, sounds that I don't like bother me. For example, the constant honking in traffic, or even music I don't want to hear can be disturbing." [UVH-9] "Because of my ear, since I have trouble hearing, noise also affects me." [UVH-12]	Descriptive; Performance	--	Qualitative attributes
Reading difficulties	"When I'm watching TV at home, I especially have a hard time reading the subtitles when they appear." [UVH-2]	Descriptive; Performance	--	Qualitative attributes
BEHAVIORS				
Acceptance of condition	"I accept that as I get older, there will be some difficulties in life. After all, I've reached a certain age." [UVH-8] "I think a lot about the ear issue myself. I handled it very calmly. I mean, all the bad things that happened, the surgeries, the deafness, I accepted it. I have learned to live with it." [UVH-11] "Well, maybe it used to happen in the beginning, but now because I've accepted it. I've accepted myself this way. Therefore, I know what I need to do for myself, or what I shouldn't do." [UVH-15]	Descriptive; Performance	--	Qualitative attributes
Less interaction	"Even the time I spend with my child has changed" [UVH-2].	Descriptive; Performance	--	Qualitative attributes
Limitations in daily life activities	"If there's something tiring, I don't enter that environment. If there's an event happening or tasks to be done together, I'm involved in the least part of it." [UVH-2] "I don't have my old activities and movements anymore. I used to work a lot, but I can't work the way I used to." [UVH-5] "After this illness, whether it's traveling, my work environment, or evening dinners... Of course, it has been a hindrance. Suddenly, I felt like I was in a void. Like, as they say, I became like someone in prison." [UVH-7] "I used to meet with my neighbors more often, but this condition has affected me." [UVH-12]	Descriptive; Performance	--	Qualitative attributes

Main concepts: What is this information about?	Additional concepts contained in the information	ICF category of main concept	ICF category of other concepts	Annotation
Discomfort in crowded places Hearing difficulties and sensitivity to noise	Sound Disturbing	**b230** Hearing functions **b240** Sensations associated with hearing and vestibular functions **d750**- Informal social relationships	**e250**-Sound **b152**-Emotional functions	
Difficulty reading subtitles on TV		**d166**-Reading **b210**-Seeing function	**d110**-Watching **e125**-Products and technology	
Acceptance of condition (related to ear issue) Demonstration of emotion related to condition		**b126**-Temperament and personality functions **b152**-Emotional functions	**d240**-Handling stress and other psychological demands	
Reduced interaction with family		**d760**-Family relationships		
Avoidance of overwhelming activities Reduced capacity for work and physical activities Reduced social interactions due to health condition		**d910**-Community life **b130**-Energy and drive functions **d920**-Recreation and leisure **b152**-Emotional functions **d750**-Informal social relationships **d760**-Family relationships	**d850**-Remunerative employment	

Table S3. *Continued*

Name of symptoms	Verbatim health information	Perspective adopted in information	Response options	Classification of response options
COPING STRATEGIES				
Coping strategies	"I now think that I will do everything without rushing, taking slow steps." [UVH-2] "I try to protect myself as much as possible, avoiding rushing, overexertion, and noisy environments." [UVH-2] "When I stand up, I wait a few seconds before walking. I hold the railing when using stairs, watch my diet, go for walks, and swim." [UVH-4] "When praying, I keep a chair nearby for support when standing up." [UVH-5] "I've developed strategies like moving slowly, getting up carefully, and taking my time." [UVH-7] "When going up and down stairs, I make sure to hold onto something for support." [UVH-7] "I remind myself to walk cautiously after getting up, and to sit for a moment before moving." [UVH-9] "At night, I support myself by holding onto walls when moving around." [UVH-10] "I completely avoid sudden movements and always hold onto something when using stairs." [UVH-11] "If I go out for a long time, I try not to go alone and avoid standing too long." [UVH-1] "I always hold onto something when going up or down stairs." [UVH-12] "When I see a lot of movement, I lose balance. I sit down and focus on a single point until I feel stable." [UVH-13] "I never lie on my left side, and when I need to look to the left, I turn my whole body. I avoid looking up. I try to do tasks like changing light bulbs without raising my head." [UVH-15]	Descriptive; Performance	--	Qualitative attributes

Main concepts: What is this information about?	Additional concepts contained in the information	ICF category of main concept	ICF category of other concepts	Annotation
Moving slowly to prevent symptoms Self-protection Cautious movement and support use when standing or using stairs Using walls for support at night	Prevention of falls on stairs Avoiding prolonged standing alone Noisy environment	**b760-**Control of voluntary movement functions **d410-**Changing body position **d460-**Moving around in different locations **b2351-**Vestibular functions of balance **d160-**Focusing attention	**e298-**Natural environment and human-made changes to environment **e150-**Design, construction, and building products and technology of buildings for public use **e115**-Products and technology for personal use in daily living	

Table S4. The extracted data and linking details from PROMs (DHI, HADS and EQ-5D-5L)

Name of symptoms	Verbatim health information	Perspective adopted in information	Response options	Classification of response options
Dizziness Handicap Inventory (DHI)				
DHI	1-Does looking up increase your problem?	Descriptive-Capacity	Yes, Sometimes, No	Intensity
DHI	2- Because of your problem, do you feel frustrated?	Appraisal	Yes, Sometimes, No	Intensity
DHI	3-Because of your problem, do you restrict your travel for business or recreation?	Descriptive-Capacity	Yes, Sometimes, No	Intensity
DHI	4-Does walking down the aisle of a supermarket increase your problems?	Descriptive-Performance	Yes, Sometimes, No	Intensity
DHI	5-Because of your problem, do you have difficulty getting into or out of bed?	Descriptive-Capacity	Yes, Sometimes, No	Intensity
DHI	6-Does your problem significantly restrict your participation in social activities, such as going out to dinner, going to the movies, dancing, or going to parties?	Descriptive-Performance	Yes, Sometimes, No	Intensity
DHI	7-Because of your problem, do you have difficulty reading?	Descriptive-Capacity	Yes, Sometimes, No	Intensity
DHI	8-Does performing more ambitious activities such as sports, dancing, household chores (sweeping or putting dishes away) increase your problems?	Descriptive-Performance	Yes, Sometimes, No	Intensity
DHI	9-Because of your problem, are you afraid to leave your home without having someone accompany you?	Descriptive-Capacity	Yes, Sometimes, No	Intensity
DHI	10-Because of your problem have you been embarrassed in front of others?	Appraisal	Yes, Sometimes, No	Intensity
DHI	11-Do quick movements of your head increase your problem?	Descriptive-Capacity	Yes, Sometimes, No	Intensity

	Main concepts: What is this information about?	Additional concepts contained in the information	ICF category of main concept	ICF category of other concepts	Annotation
	Looking up Change head position	Dizziness	**d110-** Watching **d410-** Changing body positions	**b2401-** Dizziness	Problem means already dizziness
	Feeling frustrated	Dizziness	**b152**- Emotional functions	**b2401**- Dizziness	
	Restriction in travel	Dizziness	**d470**-Using transportation **d475**- Driving	**b2401**- Dizziness	
	Walking in a supermarket	Dizziness	**d4601**- Moving around within buildings other than home	**e150**- Design, construction and building products and technology of buildings for public use b2401- Dizziness	
	Difficulty getting into or out of bed	Dizziness	**d410**-Changing body position	**b2401**- Dizziness	
	Restriction in social participation	Dizziness	**d920**- Recreation and leisure	**b2401**- Dizziness	
	Difficulty reading	Dizziness	**d166**- Reading	**b2401**- Dizziness	
	Difficulty with ambitious activities	Dizziness	**d9201**- Sports **d640**- Doing housework	**b7602**- Coordination of voluntary movement **b730**- Muscle power functions **b2401**- Dizziness	
	Fear of leaving home alone	Dizziness	**b152**- Emotional functions **e340**- Personal care providers and personal assistans	**b2401**- Dizziness	
	Embarrassment	Dizziness	**b152**- Emotional functions **e460**- Societal attitudes	**b2401**- Dizziness	
	Quick head movements	Dizziness	**b760**- Control of voluntary movement functions	**b2401**- Dizziness	

Table S4. *Continued*

Name of symptoms	Verbatim health information	Perspective adopted in information	Response options	Classification of response options
DHI	12-Because of your problem, do you avoid heights?	Descriptive-Performance	Yes, Sometimes, No	Intensity
DHI	13-Does turning over in bed increase your problem?	Descriptive-Capacity	Yes, Sometimes, No	Intensity
DHI	14-Because of your problem, is it difficult for you to do strenuous homework or yard work?	Descriptive-Performance	Yes, Sometimes, No	Intensity
DHI	15- Because of your problem, are you afraid people may think you are intoxicated?	Descriptive-Capacity	Yes, Sometimes, No	Intensity
DHI	16-Because of your problem, is it difficult for you to go for a walk by yourself?	Appraisal	Yes, Sometimes, No	Intensity
DHI	17-Does walking down a sidewalk increase your problem?	Descriptive-Capacity	Yes, Sometimes, No	Intensity
DHI	18-Because of your problem, is it difficult for you to concentrate?	Descriptive-Performance	Yes, Sometimes, No	Intensity
DHI	19-Because of your problem, is it difficult for you to walk around your house in the dark?	Descriptive-Capacity	Yes, Sometimes, No	Intensity
DHI	20-Because of your problem, are you afraid to stay home alone?	Descriptive-Performance	Yes, Sometimes, No	Intensity
DHI	21-Because of your problem, do you feel handicapped?	Descriptive-Capacity	Yes, Sometimes, No	Intensity

	Main concepts: What is this information about?	Additional concepts contained in the information	ICF category of main concept	ICF category of other concepts	Annotation
	Avoidance of heights	Dizziness	**e2100**-Land forms	**e150**- Design, construction and building products and technology of buildings for public use b2401- Dizziness	
	Turning over in bed	Dizziness	**d410**- Changing body position	**b2401**- Dizziness	
	Difficulty with strenuous work	Dizziness	**d640**- Doing houseworks	**b730**- Muscle power functions **b740**- Muscle endurance functions **b2401**- Dizziness	
	Fear of being judged	Dizziness	**b152**- Emotional functions **e460**- Societal attitudes	**b2401**- Dizziness	
	Difficulty walking alone	Dizziness	**d4602**- Moving around outside the home and other buildings **e340**- Personal assistants	**b2401**- Dizziness	
	Walking on a sidewalk	Dizziness	**d4602**- Moving around outside the home and other buildings	**e298**- Natural environment and human-made changes to environment **b2401**- Dizziness	
	Difficulty concentrating	Dizziness	**d160**- Focusing attention	**b2401**- Dizziness	
	Walking in the dark	Dizziness	**d4600**- Moving around within the home	**e240**- Light **b2401**- Dizziness	
	Fear of staying home alone	Dizziness	**b152**- Emotional functions **e340**- Personal care providers and personal assistans	**b2401**- Dizziness	
	Feeling handicapped	Dizziness	**b11420**- Orientation to self **b180**- Experience of self and time functions	**b2401**- Dizziness	

Table S4. *Continued*

Name of symptoms	Verbatim health information	Perspective adopted in information	Response options	Classification of response options
DHI	22-Has the problem placed stress on your relationships with members of your family or friends?	Appraisal	Yes, Sometimes, No	Intensity
DHI	23-Because of your problem, are you depressed?	Descriptive-Capacity	Yes, Sometimes, No	Intensity
DHI	24-Does your problem interfere with your job or household responsibilities?	Descriptive-Performance	Yes, Sometimes, No	Intensity
DHI	25- Does bending over increase your problem?	Descriptive-Capacity	Yes, Sometimes, No	Intensity
Hospital Anxiety and Depression Scale (HADS)				
HADS	1-I feel tense or 'wound up'	Appraisal	Most of the time, A lot of the time, From time to time, occasionally, Not at all	Intensity
HADS	2-I still enjoy the things I used to enjoy	Appraisal	Definitely as much, Not quite so much, Only a little, Hardly at all	Intensity
HADS	3-I get a sort of frightened feeling as if something awful is about to happen	Appraisal	Very definitely and quite badly, Yes but not too badly, A little but it doesn't worry me, Not at all	Intensity
HADS	4- I can laugh and see the funny side of things	Appraisal	As much as I always could, Not quite so much now, Definitely not so much now, Not at all	Intensity
HADS	5-Worrying thoughts go through my mind:	Appraisal	A great deal of the time, A lot of the time, From time to time but not too often, Only occasionally	Intensity
HADS	6-I feel cheerful	Appraisal	Not at all, Not often, Sometimes, Most of the time	Intensity
HADS	7-I can sit at ease and feel relaxed	Appraisal	Definitely, Usually, Not often, Not at all	Intensity
HADS	8-I feel as if I am slowed down	Appraisal	Nearly all the time, Very often, Sometimes, Not at all	Intensity

	Main concepts: What is this information about?	Additional concepts contained in the information	ICF category of main concept	ICF category of other concepts	Annotation
	Stress in relationships	Dizziness	**d750**- Informal social relationship **d760**- Family relationship	**b2401**- Dizziness	
	Feeling depressed	Dizziness	**b152**- Emotional functions	**b2401**- Dizziness	
	Interference with responsibilities	Dizziness	**d640**- Doing houseworks **d850**- Remunerative employment	**b2401**- Dizziness	
	Bending over	Dizziness	**d4105**- Bending	**b2401**- Dizziness	
	Feel tense		**b152** - Emotional functions		
	Enjoy		**b152** - Emotional functions		
	Feeling frightened		**b152** - Emotional functions		
	Laughing		**b152** - Emotional functions		
	Worrying thoughts		**b152** - Emotional functions	**b140**-Attention functions	
	Feeling cheerful		**b152** - Emotional functions		
	Feeling relaxed		**b152** - Emotional functions		
	Feeling slowed down		**b152** - Emotional functions	**b130**-Energy and drive functions	

Table S4. *Continued*

Name of symptoms	Verbatim health information	Perspective adopted in information	Response options	Classification of response options
HADS	9- I get a sort of frightened feeling like 'butterflies' in the stomach	Appraisal	Not at all, Occasionally, Quite often, Very often	Intensity
HADS	10-I have lost interest in my appearance	Appraisal	Definitely, I don't take as much care as I should, I may not take quite as much care, I take just as much care as ever	Intensity
HADS	11-I feel restless as I have to be on the move	Appraisal	Very much indeed, Quite a lot, Not very much, Not at all	Intensity
HADS	12-I look forward with enjoyment to things	Appraisal	As much as I ever did, Rather less than I used to, Definitely less than I used to, Hardly at all	Intensity
HADS	13-I get sudden feelings of panic	Appraisal	Very often indeed, Quite often, Not very often, Not at all	Intensity
HADS	14-I can enjoy a good book or radio or TV program	Appraisal	Often, Sometimes, Not often, Very seldom	Intensity
EuroQoL- 5 Dimension- 5 Level (EQ-5D-5L)				
EQ-5D-5L	1-Mobility	Descriptive-Capacity	1,2,3,4,5	Intensity
EQ-5D-5L	2-Self-care	Descriptive-Capacity	1,2,3,4,5	Intensity
EQ-5D-5L	3-Usual activities	Descriptive-Performance	1,2,3,4,5	Intensity
EQ-5D-5L	4-Pain/Discomfort	Appraisal	1,2,3,4,5	Intensity
EQ-5D-5L	5-Anxiety/Depression	Appraisal	1,2,3,4,5	Intensity

Main concepts: What is this information about?	Additional concepts contained in the information	ICF category of main concept	ICF category of other concepts	Annotation
Feeling frightened		**b152** - Emotional functions		
Loss of interest in appearance		**b152** - Emotional functions		
Feeling restless		**b152** - Emotional functions		
Anticipation of enjoyment		**b152** - Emotional functions	**d920** - Recreation and leisure	
Feeling panic		**b152** - Emotional functions		
Enjoyment of leisure activities		**b152** - Emotional functions	**d920** - Recreation and leisure	
Walking		**d450** - Walking		
Washing Dressing		**d510**- Washing oneself **d540**- Dressing		
Usual activities	Working Studying Housework Family Leisure activities	**d230**- Carrying out daily routine	**d720**- Complex interpersonal interactions **d760**- Family relationships **d640**-Doing housework **d920**- Recreation and leisure	Working and studying are considered under the complex interpersonal interactions
Pain or discomfort		**b280**- Sensation of pain	**d760** - Family relationships **e310**-Immediate family	
Anxiety or depression		**b1529**- Emotional functions, unspecified		

Table S5. Chronic unilateral vestibular hypofunction symptoms: Physical, cognitive and emotions

Semptoms	Percentage (%)	N
Physical		
- Chronic dizziness	80%	12/15
- Imbalance (Unsteadiness)	80%	12/15
- Supermarket effect	73%	11/15
- Head movements worsen symptoms	73%	11/15
- Recurrent vertigo	53%	8/15
- Tinnitus	47%	7/15
- Darkness worsens symptoms	40%	6/15
- Autonomic complaints	40%	6/15
- Tiredness	33%	5/15
- Headache	33%	5/15
- Hearing loss	33%	5/15
- Brain fog	27%	4/15
- Neck pain	20%	3/15
- Sweating	20%	3/15
- Aural fulness	13%	2/15
- Oscillopsia	13%	2/15
Cognitive		
- Concentration problems	67%	10/15
- Forgetfulness	40%	6/15
- Difficulties with dual tasking	27%	4/15
- Problems with spatial orientation		
• Disorientation	13%	2/15
• Misjudging distances	13%	2/15
Emotions		
- **Sadness**		
o Suffering	**73%**	**11/15**
• Suffering	7%	1/15
o Sadness		
• Sadness	47%	7/15
• Depression		
• Despair		
• Woe		
o Neglect		
• Embarrasment	20%	2/15
• Isolation		
• Insecurity		

Semptoms	Percentage (%)	N
o Disappointment	60%	9/15
• Disappointment		
• Displeasure		
- **Fear**		
o Horror	**60%**	**9/15**
• Fear	13%	2/15
• Horror		
• Panic		
o Nervousness		
• Anxiety	60%	9/15
• Distress		
• Worry		
- **Anger**	**53%**	**8/15**
o Exasperation	47%	7/15
• Exasperation		
• Frustration		
o Irritation	20%	3/15
• Irritation		
• Annoyance		
- **Joy**	**27%**	**4/15**
o Cheerfulness	7%	1/15
• Happiness		
o Contentment	13%	2/15
• Contentment		
o Optimism	13%	2/15
• Optimism		
• Hope		
• Eagerness		
- **Love**	**20%**	**3/15**
o Affection	20%	3/15
• Fondness		
• Sentimentality		
• Affection		

4

CHAPTER 4

Chronic unilateral vestibular hypofunction: Insights into etiologies, clinical subtypes, diagnostics and quality of life

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ABSTRACT

Objective

Chronic unilateral vestibular hypofunction (UVH) can lead to disabling vestibular symptoms and a decrease in quality of life. The aim of this study was to investigate etiologies, clinical subtypes, symptoms, and quality of life (QoL) in patients with chronic UVH.

Methods

A retrospective study was performed on 251 UVH patients in a tertiary referral center. Inclusion criteria comprised reduced or absent caloric responses, with a caloric asymmetry ratio ≥25%. Patients with central vestibular pathology, symptom duration <3 months, and incomplete responses to questionnaires were excluded. Patient records were assessed for etiologies, secondary vestibular diagnoses, clinical subtypes, and questionnaires related to QoL. Additionally, multiple linear regression analysis was performed to evaluate factors influencing QoL.

Results

Thirteen different etiologies were identified, with Menière's Disease as most prev-alent (31%, n=79). The most frequently reported secondary vestibular diagnoses were benign paroxysmal positional vertigo (BPPV) (21%, n=54) and persistent postural perceptual dizziness (PPPD) (19%, n=47). Five distinct clinical subtypes were identified: recurrent vertigo with UVH (47%), rapidly progressive UVH (25%), idiopathic/unknown UVH (18%), slowly progressive UVH (8%), and congenital UVH (2%). Over 80% of UVH patients experienced moder-ate-to-severe handicap, as indicated by the Dizziness Handicap Inventory. Approximately 20-25% of UVH patients exhibited moderate-to-severe depression and anxiety, based on the Hospital Anxiety and Depression Scale. Multiple linear regression analyses demonstrated that the presence of PPPD significantly reduced QoL in chronic UVH patients.

Conclusions

Chronic UVH is a heterogeneous disorder. Secondary vestibular diagnoses like BPPV and PPPD often co-exist and can significantly impact QoL. A structured diagnostic approach and tailored inter-ventions are crucial to address the diverse needs of UVH patients.

1 INTRODUCTION

Unilateral vestibular hypofunction (UVH) is a complex disorder characterized by a unilaterally decreased or absent vestibular function, affecting the vestibular end-organ, vestibular nerve, or both. Patients may experience a range of symptoms [1-4]. When UVH occurs, the central nervous system attempts to decrease symptoms via a process called vestibular compensation [5, 6]. However, its effectiveness can be influenced by various factors such as age, the etiology of vestibular hypofunction, the presence of co-morbidities, psychological factors such as depression or anxiety, environmental factors, level of physical activity, and individual variability to adapt and compensate [7-10]. UVH can therefore result in chronic symptoms like chronic dizziness and imbalance [3, 11]. Despite being widespread, the exact prevalence of UVH remains uncertain due to its diverse presentation. Thus, the impact of UVH remains controversial and is often underestimated. Nevertheless, chronic UVH (present for > 3 months) reduces quality of life (QoL) and imposes a significant socioeconomic impact [3, 12].

UVH can have different etiologies such as Menière's Disease (MD), infec-tion/inflammation, Vestibular Migraine (VM), vascular, iatrogenic, neoplasm, and trauma [3, 13]. Identifying the etiology can be challenging due to its heterogeneous nature, especially since the symptoms might overlap with other vestibular disorders. This com-plexity requires thorough evaluation. Moreover, UVH can present with different clinical subtypes, including recurrent vertigo with UVH, rapidly progressive UVH, slowly progressive UVH, and idiopathic/unknown UVH [14, 15]. These variations complicate the identification of its exact cause, thereby hindering accurate diagnosis.

Diagnosing UVH can be challenging, especially since no standardized diagnostic criteria are currently available. Therefore, UVH is frequently under- or misdiagnosed [16, 17]. Various clinical diagnostic tests can be used for vestibular assessment: the caloric test, rotatory chair test, (video) head impulse test (vHIT), vestibular evoked myogenic po-tentials, dynamic visual acuity, etc. [18, 19]. Additional tests, such as audiological as-sessment and imaging, may be used to help with the diagnosis and identify potential underlying causes [20]. Although many of these tests provide objective information about the vestibular and audiological function, they may not fully capture the complete picture of patients' overall functional health status [21-24].

Chronic UVH can decrease quality of life (QoL). One in three UVH patients (with chronic symptoms) still continues to experience significant handicap [3]. This may not only result from inadequate vestibular compensation but also from environmental factors, psycho-logical conditions, and functional problems such as Persistent Postural-Perceptual Diz-

ziness (PPPD) [25-29]. Therefore, evaluating QoL is valuable, since it enables a more comprehensive evaluation of the impact of chronic UVH [30-32]. However, it is important to mention that questionnaires currently used to evaluate the impact of vestibular deficits on QoL, like the Dizziness Handicap Inventory (DHI), were not specifically developed for UVH. This might impede the thorough evaluation of UVH patients before and after therapeutic interventions. In this context, a patient-reported outcome measure (PROM) is needed for patients with chronic UVH.

As such, further research is required to explore potential etiologies of chronic UVH, and to fully understand the clinical manifestations and quality of life in UVH patients. This retrospective study therefore aimed to investigate the etiologies, clinical subtypes, symptoms and QoL in patients with chronic UVH. The findings from this study could potentially contribute to the development of diagnostic criteria for chronic UVH.

2 MATERIALS AND METHODS

2.1 Ethical Approval

The study protocol was approved as non-WMO (Wet Medisch-Wetenschappelijk Onderzoek) research by the medical ethical testing committee of the University Maastricht/ academic hospital Maastricht (UM/MUMC+) as well as consent from the advisory board of the MUMC+ (METC 2021-2936 and date of approval 28/12/2022). This study followed the guidelines outlined by Dutch legislation.

2.2 Participants

This retrospective study involved patients diagnosed with UVH by two of the authors (MCG, RvdB) at a tertiary referral center, between 2017 and 2021. UVH patients were included based on reduced or absent responses during bithermal caloric irrigation, characterized by a caloric asymmetry ratio ≥25% between ears [33], where the absolute value of the healthy side was within the range of 25°/s to 83°/s (sum of the mean slow-phase eye velocity in both cold and warm irrigations). Patients with central ves-tibular pathology, incomplete responses to questionnaires related to quality of life, and symptom duration < 3 months were excluded from the study (Figure 1).

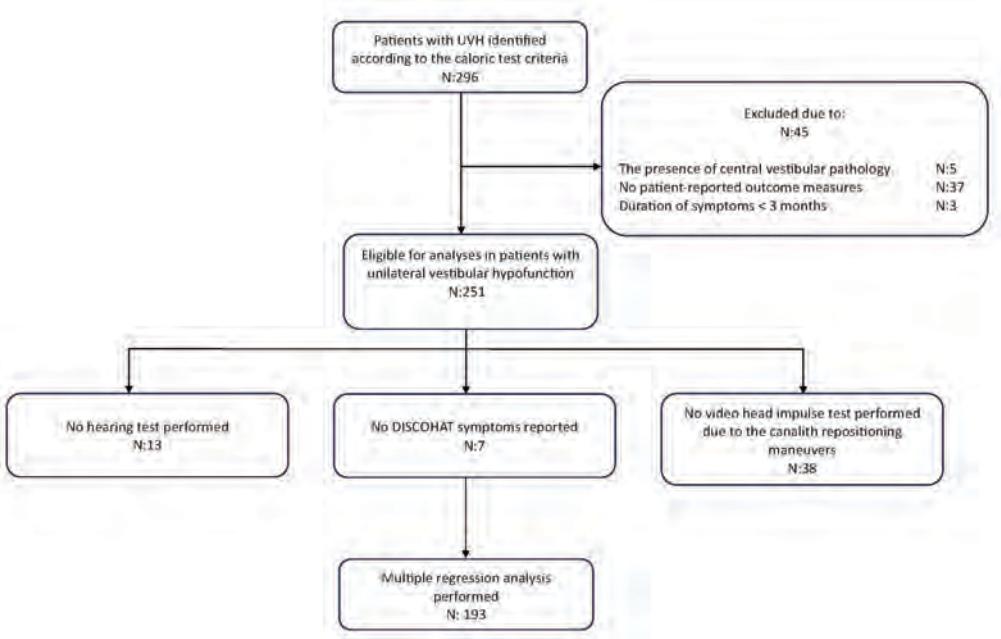


Figure 1. A flowchart of our retrospective study selection

2.3 Etiology and clinical subtypes

The medical history of the patients was analyzed from their files to identify the etiology of UVH and possible secondary vestibular diagnoses (conducted by MCG). The diagnosis of MD [34], VM [35], benign paroxysmal positional vertigo (BPPV) [36], and PPPD [37] was established according to the Bárány Society's Classification Committee criteria. Each etiology was assigned one of three levels of certainty: definite, probable, or idiopathic/unknown.

Etiologies of UVH were classified into different clinical subtypes:

- Recurrent vertigo with UVH: This subtype involved recurrent, brief vertigo attacks. Patients may have experienced vertigo, imbalance and/or oscillopsia (an illusion of an unstable vision). Conditions linked to this subtype included MD, VM, BPPV, benign recurrent vertigo, auto-immune inner ear disease, and overlap MD/VM.
- Rapidly progressive UVH: Patients in this subtype experienced a sudden onset of UVH symptoms, which rapidly progressed. Conditions could in-clude infection/inflammation (like acute unilateral vestibulopa-thy/vestibular neuritis, labyrinthitis), trauma (labyrinthine concussion), vascular (inner ear ischemia), and iatrogenic factors such as stapedotomy or intratympanic/systemic gentamicin administration.

- Slowly progressive UVH: Clinical symptoms of UVH developed gradually in this subtype, typically without episodes of vertigo. Conditions associated with this subtype included vestibular schwannoma, cholesteatoma, retro-fenestral otosclerosis, labyrinthitis ossificans, and iatrogenic factors such as radiation therapy.
- Idiopathic/Unknown UVH: In this subtype, the dizziness complaints or vertigo attacks could not be attributed to any specific vestibular disorder or trauma. However, patients exhibited symptoms of vestibular hypofunction (e.g. imbalance, dizziness with fast head movements) despite never expe-riencing any specific episodes.
- Congenital UVH: This subtype referred to UVH caused by genetic factors, such as inner ear malformations.

Patients were further categorized based on the presence of attacks. Four different categories were established: no attack, one attack, previous attacks, and current attacks. Clinical subtypes without attacks, namely the slowly progressive UVH and idio-pathic/unknown UVH subtypes, were combined and categorized as “no attack”. Patients categorized with rapidly progressive UVH experienced “one attack”. Patients experi-encing recurrent vertigo with UVH were divided into “current attacks” and “previous attacks” based on a two-month duration cut-off value.

2.4 Symptoms and Co-morbidities

At the tertiary referral center of this study, templates for medical history taking are based on the 4-step approach [38]. This systematic method facilitates the structured evaluation of various symptoms and co-morbidities. DISCOHAT symptoms, previously described [11], were identified through history-taking. Briefly, "DISCOHAT" is an ac-ronym used to categorize chronic vestibular symptoms. This includes Darkness worsens symptoms, Imbalance, Supermarket effect, Cognitive complaints, Oscillopsia, Head movements worsen symptoms, Autonomic complaints and Tiredness. Patients were further categorized into three groups based on symptom duration: 3-12 months, 12-24 months, and ≥24 months. This categorization made it possible to investigate how different durations of symptoms were related to QoL scores. Co-morbidities such as migraine headaches, non-migraine headaches, hypertension, diabetes, depression, anxiety, au-toimmune disorders, substance use, and cognitive decline were investigated within the UVH patient cohort. The presence of symptoms and co-morbidities was classified as “present” and “missing data” based on available patient information.

2.5 Objective vestibular testing

All patients underwent vestibular testing including bithermal caloric irrigation and vHIT. These tests were conducted by trained laboratory technicians following stand-ardized protocols [20, 39]. The caloric test was performed with warm (44°C) and cold (30°C) water

irrigations, 300 ml each, in a dark room. The caloric asymmetry was determined using the Jongkees' formula. The vHIT was conducted using the ICS Impulse (GN Otometrics; Taastrup, Denmark) and EyeSeeCam (Interacoustics VOG; Munich, Ger-many). This test involved unpredictable, rapid (>150°), and low-amplitude (±20°) head movements in the horizontal plane, while the patient visually fixated on an earth-fixed target. At least seven head impulses needed to be correctly performed in both directions. The horizontal vestibulo-ocular reflex gain for each direction was calculated by the software.

2.6 Ancillary testing

Non-vestibular diagnostic procedures included: pure tone audiometry, computed tomography (CT), and magnetic resonance imaging (MRI). Pure tone audiometry in-cluded the collection of modified Fletcher indexes (FI) and the type of hearing loss. The degree of hearing loss based on modified FI was determined using the criteria established by the American Speech-Language-Hearing Association (ASHA) [40]. Findings from both MRI and CT scans were documented.

2.7 Quality of life and symptoms (QoL)

The QoL was assessed using digital questionnaires: Dizziness Handicap Inventory (DHI), Hospital Anxiety and Depression Scale (HADS), and the European Quality of Life 5 Dimension 5 Level (EQ-5D-5L). The DHI is a validated self-report questionnaire con-sisting of 25 questions that quantifies the impact of dizziness on daily life. Patients respond to each question with "yes", "sometimes", or "no" and each response is assigned a score of four, two, or zero points, respectively. The total DHI score reflects the self-perceived level of dizziness handicap, categorized as mild (0-30), moderate (31-60), or severe (61-100) [41, 42]. The HADS assesses the presence of anxiety and depression levels in patients. Scores ranging from 0 to 7 indicate "normal", 8 to 10 "mild", 11 to 14 "moderate", and 15 to 21 "severe" levels of anxiety or depression [43]. The EQ-5D-5L consists of two sections: the EQ-5D descriptive system and the EQ Visual Analog Scale (VAS). While the former evaluates the patient's health state across five dimensions—mobility, self-care, usual activities, pain/discomfort, and anxiety/depression—the latter, the EQ VAS, is used to assess the patient's self-rated overall health condition [44, 45]. Both the EQ-5D-5L VAS and index scores were used in the analyses.

2.8 Statistical analysis

Data were analyzed using both visual (histogram and Q-Q plots) and statistical (Shapiro-Wilk test) methods. Results were expressed as mean ± standard deviation for normally distributed data and as median (Interquartile range=IQR) for non-normally distributed data. Bar plots and scatter plots were used to depict frequency distributions and the relationship between variables, respectively. To quantify the association between

variables, Pearson correlations and corresponding tests were used. Multiple linear regression analyses were conducted to investigate the predictors influencing distinct dimensions of QoL in patients with UVH. Predictors included presence of PPPD, migraines, hearing status, duration of symptoms, the presence of attacks, and vestibular test results. Presence of PPPD and migraines were coded as binary variables (yes/no). Hearing status was treated as a continuous variable and coded such that an increase in the hearing score corresponded to an increase in the degree of hearing loss. Duration of symptoms and attacks were categorical variables as previously described. A subgroup analysis categorized caloric test results into three groups: ≥25°/s, ≥6°/s and <25°/s, and <6°/s. vHIT was not included in the subgroup analysis due to its potential to introduce selection bias (e.g., vHIT was not performed in BPPV patients). Any patients with missing data related to these factors were excluded from the analysis, which resulted in a final cohort of 193 patients (Figure 1). For factors with three or more levels, omnibus F-tests were used to first assess the presence of any differences between groups, before interpreting individual group contrasts. A significance level of 0.05 was used for the statistical analyses. All analyses were conducted using R (version 4.2.2).

3 RESULTS

A total of 251 patients were included in the study. The mean age of patients at the time of diagnosis was 59 ± 13 years, with age ranging from 18 to 84 years. Among the study population, 58% were female and 42% were male. The patient characteristics are presented in Table 1.

Table 1. Characteristics of UVH patients

Variables (N=251)	**Mean±SD ; (Range)**
Age	58.96±13.42 ; (18-84)
Gender	**N (%)**
Female	145 (58)
Male	106 (42)
Profession	
Employed	137 (55)
Unemployed	33 (13)
Retired	38 (15)
Missing	43 (17)
Duration of symptoms	
≥3-11 months	62 (25)

Table 1. *Continued*

Variables (N=251)	Mean±SD ; (Range)
>12-23 months	50 (20)
≥24 months	139 (55)
The presence of attacks	
No attack	71 (28)
One attack	63 (25)
Previous attacks	44 (18)
Current attacks	73 (29)
Side of lesion	
Right	138 (55)
Left	113 (45)

Abbreviations: SD**,** Standard deviation

3.1 Etiology

Figure 2. presents the etiologies of UVH patients, classified by diagnostic certainty. Thirteen different etiologies were identified, with Menière's Disease as the most prevalent (31%, n = 79). A definite etiology of UVH was established in 48% of cases (n = 121), while a probable etiology was identified in 34% (n = 84). The etiology of UVH remained unknown/idiopathic in 18% of cases (n = 46). More details about etiologies of UVH can be found in Table S1.

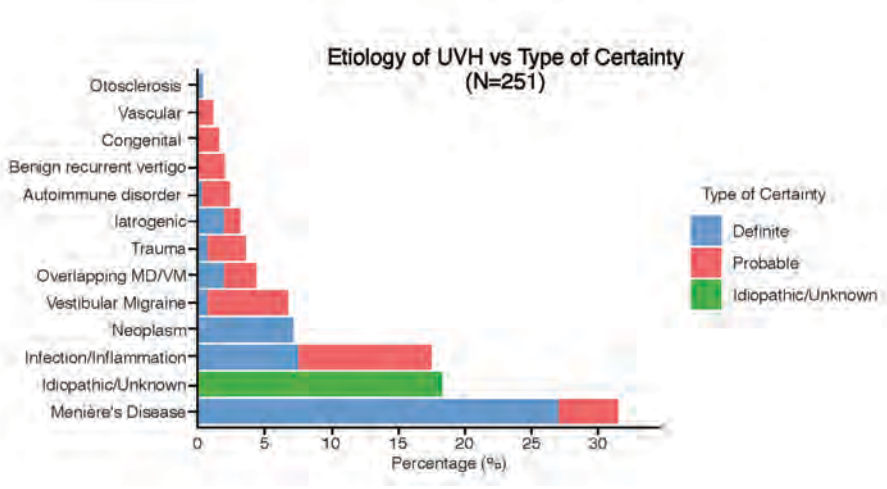


Figure 2. Distribution of etiologies in the UVH population divided into type of certainty.

Figure 3. presents the secondary diagnoses in UVH patients. Secondary diagnoses were identified in 119 UVH patients. The most frequently reported secondary diagnoses were BPPV (21%, n = 54) and PPPD (19%, n = 47). Other secondary diagnoses included neurologic

disorders (3%, n = 7), iatrogenic causes (2%, n = 6), endolymphatic hydrops (0.8%, n = 2), benign recurrent vertigo (0.4%, n = 1), overlapping MD/VM (0.4%, n = 1), and SSCD (0.4%, n = 1). BPPV was identified as a secondary diagnosis in patients with the following etiologies: idiopathic/unknown UVH (n = 23), infection/inflammation (n = 10), MD (n = 6), trauma (n = 5), and iatrogenic (n = 4). PPPD was given as a secondary diagnosis in patients with the following etiologies: infection/ inflammation (n = 20), MD (n = 11), VM (n = 5), overlap MD/ VM (n = 5), and idiopathic/unknown (n = 4).

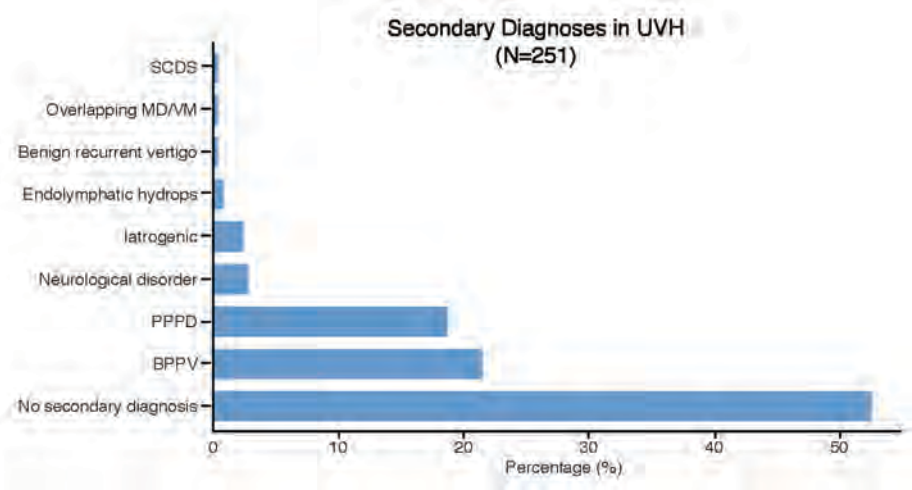


Figure 3. Distribution of secondary diagnoses in the UVH population

3.2 Clinical subtypes of UVH

Figure 4. illustrates the previously discussed etiologies subdivided into clinical subtypes. Five distinct clinical subtypes were identified: Recurrent vertigo with UVH (47%, n = 117), rapidly progressive UVH (25%, n=63), idiopathic/unknown UVH (18%, n=46), slowly progressive UVH (8%, n=21), and congenital UVH (2%, n=4). Most etiologies only had one clinical subtype (e.g., Menière's Disease was always paired with recurrent vertigo with UVH), while only iatrogenic and autoimmune disorders presented with different clinical subtypes.

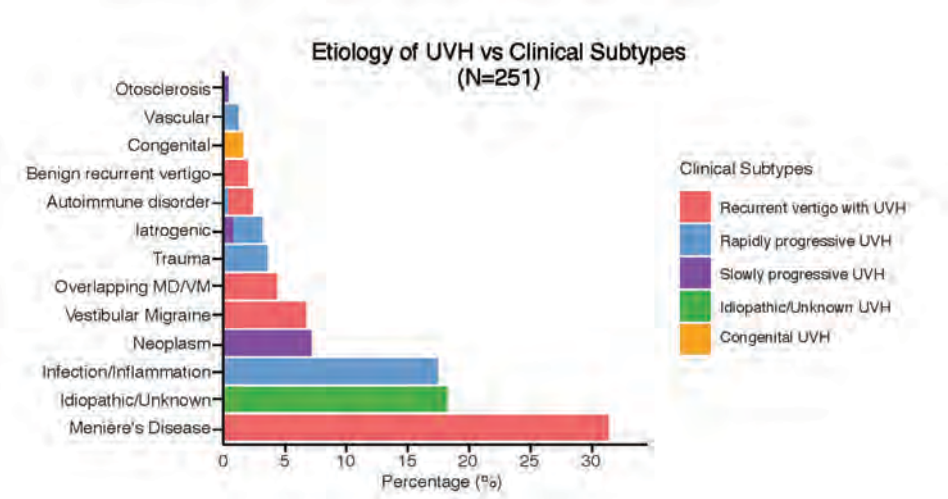


Figure 4. Clinical subtypes of UVH with respect to the etiologies

3.3 Co-morbidities and vestibular symptoms

Eight different co-morbidities were investigated. The most prevalent were non-migraine headaches (36%, n=91) and hypertension (34%, n=86) (Figure S1). Regarding DISCOHAT symptoms, imbalance was most common (70%, n=175), whereas oscillopsia was least reported (22%, n=57) (Figure S2).

3.4 Imaging

Cerebral imaging was documented in 82% of patients (n=168 MRI; n=37 CT). Abnor-malities were detected in 17% (n=41) through MRI scans and in 4% (n=11) through CT scans. Vestibular schwannoma was the most frequently reported MRI abnormality, whereas superior semicircular canal dehiscence (SCD) and trauma/skull base fracture were most frequently demonstrated on CT scans. Sixty-one percent of patients (n=153) exhibited no abnormalities, while 18% (n=46) did not require imaging (Table 2).

Table 2. MRI and CT findings in UVH patients

Type			N (%)
MRI	Normal		127 (50.6)
N= 168	Abnormal	Vestibular schwannoma	17 (6.8)
		Vascular lesion	13 (5.2)
		Inner ear ossification/fibrosis	3 (1.2)
		Inner ear dysplasia	2 (0.8)
		Cerebral atrophy	2 (0.8)
		Other	4 (1.6)
CT	Normal		26 (10.4)
N= 37	Abnormal	SCDS	3 (1.2)
		Trauma/Skull base fracture	3 (1.2)
		Post-operative changes	2 (0.8)
		Other	3 (1.2)
Not tested			46 (18.3)
Total			251 (100)

Abbreviations: MRI, Magnetic Resonance Imaging; CT, Computerized tomography; SCDS, Superior canal dehissance syndrome

3.5 Hearing

Pure tone audiometry was conducted on 238 patients. Among them, 64% (n=152) showed either normal hearing or slight t moderate hearing loss in both ears, with a modified Fletcher Index ranging from -10 to 55 decibels. No hearing loss was detected in 17% of the patients (n=40). Additionally, 52% of the patients demonstrated asymmetric hearing loss. The detailed results of the pure tone audiometry are summarized in Table S2.

3.6 Vestibular testing

Based on the caloric test, 138 patients had UVH on the right side, while 113 patients had UVH on the left side. The caloric asymmetry analysis revealed a mean score of 47.71±19.99 for the right side and 53.39±21.45 for the left side. When examining the vHIT gain, the side affected by the caloric test had a median gain of 0.88 (0.20), slightly lower than the non-affected side, which had a median gain of 0.89 (0.14) ($p>0.05$). The correlation between the caloric asymmetry and the vHIT asymmetry was moderately significant ($r=0.44$; $p<0.001$) (Figure S3).

3.7 Quality of life (QoL) and psychological symptoms

More than 80% of UVH patients experienced moderate-to-severe handicap, as indicated by the DHI. The DHI showed a mean score of 51.63±21.61, indicating a moderate handicap. The functional subscale had the highest score (20.39 out of max. 36 points). Approximately

20-25% of UVH patients reported moderate-to-severe depression and anxiety, based on the HADS. The HADS showed median scores regarding anxiety and depression (depression = 6 (IQR 7.5), anxiety = 6 (IQR 6.5)). The EQ-5D-5L index demonstrated a median score of 0.734 (0.34), with a range from –0.409 to 1.00, which is lower than the Dutch age-adjusted reference value of 0.839 for individuals aged 60–70 years. In addition, the EQ-5D-5L VAS showed a median score of 65 (IQR = 30).

Table 3. Questionnaire findings related to handicap level and quality of life in UVH patients

Handicap Level / Quality of Life (N=251)	Mild N(%)	Moderate N(%)	Severe N(%)	Mean±SD
DHI Total	43 (17%)	118 (47%)	90 (36%)	51.63±21.61
				Median (IQR)
HADS Depression	44 (18%)	40 (16%)	10 (4%)	6 (7.5)
HADS Anxiety	41 (16%)	42 (17%)	21 (8%)	6 (6.5)
EQ-5D-5L Index				0.734 (0.34)
EQ-5D-5L VAS				65(30)

Abbreviations: DHI, Dizziness handicap inventory; HADS, Hospital Anxiety and Depression Scale; EQ-5D-5L: EuroQoL- five dimensions-five levels; SD, Standart deviation; IQR, Interquartile range

3.8 Vestibular testing and QoL

Weak positive correlations were found between caloric asymmetry and DHI total scores (r = 0.14, p = 0.02), as well as between caloric asymmetry and HADS Depression scores (r = 0.12, p = 0.04). No significant correlation was found between caloric asymmetry and HADS Anxiety scores, or between caloric asymmetry and EQ-5D-5L scores (both p > 0. 05) (Figure S4). Similarly, no significant correlation was observed between vHIT asymmetry and questionnaires related to QoL (all p>0.05) (Figure S5). Additional correlation analyses were conducted within questionnaires. Strong positive correlations were observed between Physical and Functional subscales of the DHI (r=0.74; p < .001), as well as between the Functional and Emotional subscales (r=0.72; p < .001). Moderate positive correlations were found between DHI Functional subscales and both HADS Depression and Anxiety scores (r = 0.55 and 0.49; p<.001, respectively). Weak positive correlations were found between the DHI Physical score and both HADS Depression and Anxiety scores (r = 0.39 and 0.38; p<.001, respectively) (Figure S6).

3.9 Factors influencing quality of life and symptoms

Seven different models were fitted using multiple linear regression analyses to investigate factors related to the various QoL outcomes (questionnaires related to QoL). Across

the models (Table 4), the PPPD variable exhibited a significant relationship with the QoL outcomes, indicating that the presence of PPPD had an adverse impact on QoL. Patients with previous vertigo attacks reported significantly lower DHI Functional and HADS Anxiety scores, compared to those with no attacks. Caloric test results <6°/s exhibited significant negative associations with DHI physical, functional subscores, and total DHI scores ($p<0.05$), when compared to caloric test results ≥25°/s. Migraine and duration of symptoms were not significantly related to QoL. Hearing loss was positively associated with DHI functional subscores ($p=0.04$), indicating that higher levels of hearing loss resulted in poorer functional quality of life. Overall, the models showed varying levels of predictive power (adjusted R-squared values ranging from 0.04 to 0.21).

Table 4. Results from multiple linear regression analysis examining factors related to quality of life and psychological symptoms in UVH patients (n=193)

Predictors	Baseline/Reference	Outcome Variable						
N=193		DHI Total Score	DHI Physical Score	DHI Functional Score	DHI Emotional Score	HADS Depression Score	HADS Anxiety Score	EQ-5D-5L VAS Score
(Intercept)		47.04*** (5.08)	16.08*** (1.69)	16.53*** (2.19)	14.44*** (2.07)	6.68*** (1.16)	7.76*** (1.12)	66.29*** (5.21)
PPPD	**Yes**	**16.79*** (3.51)**	**5.40*** (1.17)**	**6.69*** (1.51)**	**4.70** (1.43)**	**2.07* (0.80)**	**2.41** (0.78)**	**-12.59*** (3.59)**
	No							
Migraine	**Yes**	4.68 (3.48)	0.56 (1.16)	2.24 (1.50)	1.88 (1.41)	1.02 (0.80)	0.30 (0.77)	-4.70 (3.59)
	No							
Hearing	**Continuous variable**	-1.03 (0.84)	**0.56* (0.28)**	-0.27 (0.36)	-0.21 (0.34)	-0.11 (0.19)	-0.19 (0.19)	0.85 (0.86)
The presence of attacks	†	F(3,177) = 2.890, p = 0.136	**F(3,177) = 3.136, p = 0.026**	F(3,177) = 2.060, p = 0.107	F(3,177) = 2.920, p = 0.135	F(3,177) = 0.727, p = 0.536	**F(3,177) = 2.185, p = 0.041**	F(3,177) = 1.148, p = 0.331
	One attack	2.76 (4.22)	0.94 (1.41)	2.04 (1.81)	-0.22 (1.72)	-0.98 (0.97)	-1.66 (0.93)	-4.31 (4.31)
	No attack							
	Previous attacks	-7.05 (4.30)	**-3.40* (1.44)**	-1.29 (1.85)	-2.36 (1.75)	-1.38 (0.99)	**-1.93* (0.95)**	3.62 (4.42)
	No attack							
	Current attacks	4.23 (3.85)	-0.62 (1.28)	2.51 (1.66)	2.34 (1.57)	-0.90 (0.88)	-0.34 (0.85)	-2.08 (3.97)
	No attack							
Duration of Symptoms	†	F(2,177) = 1.741, p = 0.178	F(2,177) = 1.334, p = 0.024	F(2,177) = 1.580, p = 0.208	F(2,177) = 2.325, p = 0.100	F(2,177) = 0.256, p = 0.774	F(2,177) = 1.181, p = 0.329	F(2,177) = 0.095, p = 0.908
	12-24 months	-2.25 (4.25)	0.79 (1.42)	-0.01 (1.83)	-3.03 (1.73)	-0.62 (0.98)	-0.45 (0.94)	0.17 (4.34)
	3-12 months							
	≥24 months	4.34 (3.36)	1.80 (1.12)	2.23 (1.44)	0.31 (1.37)	-0.46 (0.77)	0.76 (0.74)	-1.23 (3.43)
	3-12 months							

Predictors	Baseline/Reference	Outcome Variable						
	†	**F(2,177) = 3.780, p = 0.024**	**F(2,177) = 5.853, p = 0.003**	**F(2,177) = 4.045, p = 0.019**	F(2,177) = 0.490, p = 0.612	F(2,177) = 2.224, p = 0.111	F(2,177) = 1.059, p = 0.348	F(2,177) = 1.449, p = 0.237
Vestibular Test Result	**Caloric ≥6°/s and <25°/s** Caloric ≥25°/s	-1.23 (3.60)	-1.07 (1.20)	-0.17 (1.55)	0.01 (1.46)	0.27 (0.83)	-0.28 (0.80)	0.78 (3.72)
	Caloric <6°/s Caloric ≥25°/s	**10.85*** (5.29)	**3.90*** (1.77)	**5.18*** (2.28)	1.76 (2.15)	2.30 (1.21)	1.12 (1.17)	-6.84 (5.44)
R^2		0.23	0.25	0.22	0.14	0.09	0.10	0.15
Adj. R^2		0.19	0.21	0.17	0.09	0.04	0.04	0.10

Legend: Multiple linear regression analyses were conducted, incorporating data from 193 participants. The analyses examined the effects of six different predictors on distinct models of quality of life and symptoms. Each predictor's baseline/reference value is indicated in regular font, while the values of interest for comparison are highlighted in bold. For "Hearing", an increase in hearing scores corresponds to an increase in the degree of hearing loss. The † symbol denotes an omnibus test. Omnibus tests were conducted for factors with three or more categorical variables to assess differences between the groups. **†:** Omnibus test; $^{***}p < 0.001$; $^{**}p < 0.01$; $^{*}p < 0.05$.

4 DISCUSSION

In this study, 251 patients with chronic UVH were evaluated regarding etiologies, secondary diagnoses, clinical subtypes, vestibular and psychological symptoms, and quality of life. Thirteen different etiologies were identified, with MD being the most prevalent. The most frequently reported secondary vestibular diagnoses were BPPV and PPPD. Five different clinical subtypes were identified, varying from recurrent vertigo attacks to idiopathic without attacks. Imbalance was the most predominant symptom, while oscillopsia was the least frequently reported symptom in UVH patients. The impact on quality of life was profound, and over 80% experienced moderate-to-severe handicap, as measured by the DHI. Moreover, approximately 20-25% of UVH patients demonstrated moderate-to-severe levels of depression and anxiety, based on the HADS. The presence of PPPD was associated with a significant reduction in QoL among chronic UVH patients.

4.1 Etiologies

MD was identified as the most common etiology of UVH (31%), consistent with a previous systematic review [3]. However, prevalence of UVH etiologies vary in literature. This might be related to several factors. One such factor is the variability in diagnostic criteria for UVH. For example, in a study of 302 patients, acute unilateral peripheral vestibulopathy and vestibular schwannoma were identified as the primary etiologies, when UVH was diagnosed using vHIT criteria [46]. On the other hand, when UVH was diagnosed based on caloric testing criteria, MD cases were more frequently identified [47, 48]. This dissociation between the vHIT and caloric test, could (partially) be explained by the presence of hydrops [49]. Selection bias is another important consideration. For in-stance, ENT surgeons often see patients with hearing loss. This could increase the frequency of vestibular disorders in which hearing loss and vestibular symptoms are combined (e.g. Menière's Disease, genetic inner ear disorders, etc.). Furthermore, tertiary referral centers encounter a different patient population than primary care providers. To summarize, the prevalences of etiologies in UVH patients depends on the diagnostic criteria and the clinical setting.

4.2 Secondary diagnoses

The most frequent secondary diagnoses in this UVH population were BPPV (21%) and PPPD (19%). BPPV, in particular, is known to co-exist with various pathological conditions [50]. While the lifetime prevalence of BPPV is reported as 2.4% [51], its prevalence as a secondary condition to UVH, such as vestibular neuritis [52-55] and Menière's Disease [56-58], varies from 1.8% to 22.2% [55]. This wide range shows the need to consider underlying vestibular conditions when diagnosing UVH. While most patients with vestibular symptoms are diagnosed with a single vestibular disorder, the occurrence of multiple diagnoses ranges from 3.7% [59] to 30.1% [60, 61]. Thus, if symptoms persist following BPPV treatment,

assessment for other vestibular diagnoses like UVH becomes necessary. After all, BPPV may serve as a potential indicator of vestibular hypofunction [55]. Therefore, the presence of persistent symptoms highlights the need for positional testing, as UVH and BPPV can present with similar symptoms [62], such as dizziness with quick head movements [16].

The prevalence of PPPD was found to range from 19% to 21.8% among three studies conducted within a tertiary vertigo clinic population [63-65]. This is consistent with the findings of this study (19%). PPPD can be triggered by both acute and episodic vestibular disorders [37, 66, 67]. A previous study indicated that patients with a history of multiple vestibular disorders (Menière's Disease, Vestibular Migraine, BPPV) are at an increased risk of developing PPPD [67]. Therefore, when encountering patients with vestibular hypofunction and a decreased QoL, clinicians should explicitly screen for PPPD.

Preferably, a structured approach is used, such as the 4-step approach history taking [38]. Screening for PPPD enables healthcare professionals to identify PPPD early on, and to tailor interventions. These interventions may include physical therapy, treatment of co-existing vestibular and functional disorders, and/or addressing psychological aspects [68]. To summarize, a comprehensive approach that addresses both UVH and PPPD is essential for optimizing patient care and enhancing their QoL.

4.3 Clinical Subtypes

The majority of UVH patients exhibited clinical subtypes consistent with their eti-ology (e.g., Menière's Disease - recurrent vertigo with UVH), while only iatrogenic and autoimmune disorders presented with different clinical subtypes. Among the idiopathic/unknown UVH patients, no attacks were reported, indicating an overlap in clinical presentations between slowly progressive UVH and idiopathic/unknown UVH. This overlap contributes to the complexity of the diagnostic process. Additionally, these findings show that vertigo does not need to be present as a symptom in patients with UVH.

4.4 Co-morbidities

Non-migraine headache (36%) and hypertension (34%) were the most commonly reported co-morbidities in this UVH population. This is congruent with previous literature, which showed significant associations of non-migraine headache and hypertension with vestibular disorders [60, 69-71]. However, the relationship between co-morbidities and UVH is complex. While some can directly contribute to vestibular hypofunction, others arise from underlying pathologies. For example, conditions like hypertension and diabetes can affect vascular health, which in turn may impact the blood supply of vestibular system. Similarly, depression and anxiety can exacerbate vestibular symptoms through psychological mechanisms. However, these co-morbidities may also co-occur with UVH due

to shared risk factors and common underlying pathologies (e.g., de-pression and anxiety can occur after UVH). Furthermore, autoimmune disorders are commonly associated with UVH. Among six patients with autoimmune disorders in this study, a causal relationship between UVH and autoimmunity was very likely. Additionally, nine patients with known autoimmune disorders experienced Menière's Disease and Vestibular Migraine, suggesting a potential association between UVH and auto-immunity. Two patients had idiopathic UVH, potentially linked to autoimmunity. The prevalence of autoimmune disorders in western countries is typically around 8% [72], consistent with the 7% observed in our population. Thus, while autoimmune disorders may not directly cause UVH, they might play a modulating role in its development [73].

4.5 Symptoms

Imbalance was most frequently reported symptom. Therefore, it might be considered the main symptom of UVH. Additionally, the spectrum of other symptoms related to UVH varied from supermarket effect and oscillopsia to cognitive complaints and tiredness. Oscillopsia was reported in 22% of the patients, which is consistent with previous findings [3, 11]. This suggests that input from the remaining vestibular organ and central compensation mechanisms (e.g. compensatory saccades), may be sufficient to enable gaze stabilization and maintain dynamic visual acuity. However, it can still fail in a subset of UVH patients.

4.6 Imaging

In 61% percent of UVH patients who underwent imaging, no abnormalities were found. Imaging is considered necessary in some diagnostic work-ups (e.g. MRI in Menière's Disease to rule out a vestibular schwannoma) [34]. Unfortunately, in routine clinical practice, there is still an overuse of imaging in vestibular patients (e.g. BPPV). This increases costs and radiation exposure [74-76]. Relying more on history taking and clinical examination to assess vestibular patients, can reduce this overuse and improve healthcare efficiency [38]. Therefore, incorporating clinical guidelines to determine when imaging is necessary for UVH patients, could help reduce unnecessary scans.

4.7 Vestibular testing

4.7.1 *Caloric test*

Inclusion criteria involved a unilateral caloric asymmetry ratio of ≥25%, along with normal caloric test results on the 'healthy' side. This implies that the 'healthy' side needed to demonstrate absolute values within the range of 25°/s to 83°/s (sum of bithermal caloric irrigations). While vestibular asymmetry is often regarded as a criterion [11, 77, 78], the significance of the absolute values tends to be overlooked. For example, patients with a

bilateral vestibulopathy might be misdiagnosed as UVH, in case the absolute values are not evaluated [79]. Currently, no world-wide consensus is (yet) reached on caloric test criteria for UVH. For caloric test criteria, it would be preferred to take both vestibular asymmetry and absolute values into account.

4.7.2 *(Video) head impulse test*

vHIT is less sensitive than the caloric test for detecting UVH [80]. This might (partially) be explained by vHIT primarily assessing high-frequency vestibular function, while the caloric test reflects function of the lower frequencies [80]. Additionally, the presence of endolymphatic hydrops might contribute to the discrepancy between vHIT and caloric test results (see above [49]). Only a moderate positive correlation between both tests was found in this study, congruent with literature [80, 81]. It was previously demonstrated that in most cases the caloric asymmetry needs to exceed 40-60%, in order to become noticeable in vHIT [82-84]. Nevertheless, vHIT is a much quicker test with a lower burden than the caloric test. It was therefore proposed to first perform a vHIT, and the caloric test only on indication. In case vHIT is abnormal, no caloric test needs to be performed. However, many vestibular patients have a normal vestibular function. Therefore, 13 vHITs need to be performed, in order to save 1 caloric test [85].

Finally, vestibular function tests often focus on only one part of the vestibular system (e.g. horizontal canal). The otolith function is frequently not included. Nevertheless, otolith function might be important as otolith dysfunction seems quite prevalent in PPPD [86, 87].

4.8 QoL and psychological symptoms

In a previous review, around 30% of UVH patients were found to have at least a moderate handicap [3]. In this study, more than 80% reported moderate to severe handicap according to DHI scores. Multiple factors could contribute to this difference such as selection bias (e.g. this study involved a tertiary referral center) and different study designs (systematic review versus retrospective study). Despite this difference, both studies show that a significant amount of UVH patients experience at least a moderate handicap. Furthermore, a subset of UVH patients reported moderate anxiety, consistent with literature [88, 89]. It is therefore imperative to take QoL and psychological/psychiatric factors into account, when evaluating UVH patients in clinic [32].

4.9 Vestibular testing and QoL

A weak correlation was found between caloric asymmetry and DHI total scores, which is inconsistent with previous literature [24, 84, 90, 91]. Additionally, as stated above, caloric test results <6°/s exhibited significant negative associations with DHI physical, functional subscores, and total DHI scores. This could imply that severe ves-tibular hypofunction

can decrease patient's perceived dizziness-related disability. Cur-rently, several vestibular specific PROM exist like the DHI, and the vestibular disorders activities of daily living scale (VADL) to evaluate QoL. The DHI evaluates different aspects of vestibular complaints (function, physical, and emotional) and the VADL assesses the independency in activities of daily living. However, both questionnaires are not specifically tailored to UVH. Therefore, there is a need for a UVH-specific PROM. To establish such a validated PROM, qualitative research using semi-structured and un-structured interviews is required to explore the full spectrum of chronic UVH symptoms.

Additionally, strong correlations were observed between the DHI Physical and Functional subscales (r=0.74), as well as between the Functional and Emotional subscales (r=0.72). Physical symptoms in UVH can adversely affect the ability to perform daily activities of patients. For instance, patients with chronic dizziness due to UVH may en-counter difficulties in activities such as walking, climbing stairs, or driving. This can lead to significant limitations in daily functional domains such as work, school, or social ac-tivities. Additionally, these limitations may increase emotional stress and anxiety. It indicates that UVH is complex and multifaceted, which affect not only physical symptoms but also functional and emotional aspects of life.

4.10 Factors related to QoL

Several factors were found to be related to QoL. Patients with PPPD reported de-creased QoL among all outcome measures, which is consistent with literature [92, 93]. The decreased QoL in PPPD patients is likely due to persistent and pervasive nature of dizziness symptoms triggered by common daily activities such as standing, moving, or exposure to visual stimuli. These symptoms occur frequently, last for extended periods, and are challenging to avoid. Additionally, PPPD is characterized by its uncertain pathophysiology and limited treatment options, which further contribute to its negative impact on QoL. Furthermore, no association was found between the presence of migraine and QoL. This could be attributed to assessing patients during migraine-free periods [94, 95].

4.11. Management of chronic UVH

Although this study did not include data on previous treatments, addressing the management of chronic UVH is crucial. Management can involve different strategies, depending on the case: treatment of the underlying disorder (e.g., Menière's Disease), treatment of secondary disorders (e.g., PPPD), treatment of vestibular hypofunction. Regarding treatment of the underlying and secondary disorders, several new treatment options are currently investigated for e.g. Menière's Disease [96], Vestibular Migraine [97] and PPPD [98]. Regarding treatment of chronic UVH, vestibular rehabilitation is the

first choice [99]. However, not all patients show a significant response. For these patients, emerging strategies like a vestibular implant, might be considered in the future [100,101].

4.12 Limitations

Inclusion criteria included vestibular symptoms and reduced responses on bithermal caloric tests. However, this selected patient group may not fully represent the entire UVH population, as the caloric test may overlook specific canal or otolith dysfunctions, resulting in a lower sensitivity [102]. Furthermore, reduced caloric responses may not always indicate a vestibular hypofunction, which can compromise specificity. Uncontrollable factors like temporal bone anatomy can impede temperature conduction, which can possibly result in false-positive outcomes [102, 103]. To overcome this factor as much as possible, laboratory-specific normative values were used. Finally, no specific analyses were performed on the presence of vestibular compensation status. After all, no world-wide consensus is yet present on the definition of a 'compensated patient' (e.g. absence of spontaneous nystagmus, absence of asymmetry in rotatory chair testing, etc.). The sample size was also too small to add compensation status to the multiple linear regression analyses.

5 CONCLUSIONS

Chronic UVH is a heterogeneous disorder. It can result from many etiologies with different clinical presentations. UVH patients should explicitly be screened for secondary vestibular diagnoses such as BPPV and PPPD (and vice versa) because of their high prevalence. Furthermore, chronic UVH can significantly decrease QoL, especially in case of co-existing PPPD. These findings highlight the need for a structured diagnostic ap-proach and tailored interventions for chronic UVH patients. Interventions might vary from physical therapy, treatment of co-existing vestibular and functional disorders, to novel strategies like the vestibular implant.

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SUPPLEMENTARY MATERIAL

Table S1. Etiologies and primary diagnoses of UVH

Etiologies	Diagnoses	N	%
Menière's Disease	Menière's Disease	79	31
Infection/Inflammation	Acute unilateral vestibulopathy/ Vestibular neuritis	35	14
	Labyrinthitis	9	4
Neoplasm	Vestibular schwannoma	17	7
	Intrameatal lipoma	1	0.5
Vestibular Migraine	Vestibular Migraine	17	7
Overlapping MD/VM	Overlapping MD/VM	11	4
Trauma	Labyrinthine concussion	1	0.5
	Skull base fracture	8	3
Iatrogenic	Stapedotomy	5	2
	Cholesteatoma	1	0.5
	Myringo/tympanoplasty	1	0.5
Autoimmune disorder	Autoimmune inner ear disease	6	2
Benign recurrent vertigo	Benign recurrent vertigo	5	2
Congenital	Congenital inner ear malformations	4	2
Vascular	Inner ear ischemia	3	1
Otosclerosis	Otosclerosis	2	1
Idiopathic/Unknown	Idiopathic/Unknown	46	18
Total		251	100

Table S2. Results of pure tone audiometry

Hearing status (N = 238)	FI (dB)	Asymmetric hearing		Symmetric hearing	
		Best ear	Worst ear	Best ear	Worst ear
Normal hearing	-10 to 15	47	0	47	40
Slight hearing loss	16 to 25	33	5	24	23
Mild hearing loss	26 to 40	27	19	21	24
Moderate hearing loss	41 to 55	12	29	7	12
Moderately severe hearing loss	56 to 70	4	36	8	7
Severe hearing loss	71 to 90	1	24	2	1
Profound hearing loss	91+	0	11	5	7
Not tested	13				
Total	251	124	124	114	114

Abbreviations: FI, Fletcher Index

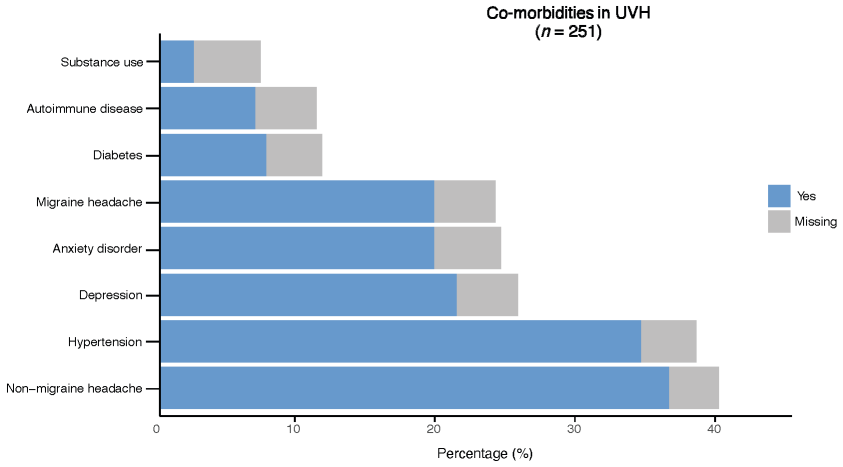


Figure S1. Distribution of co-morbidities in the UVH population

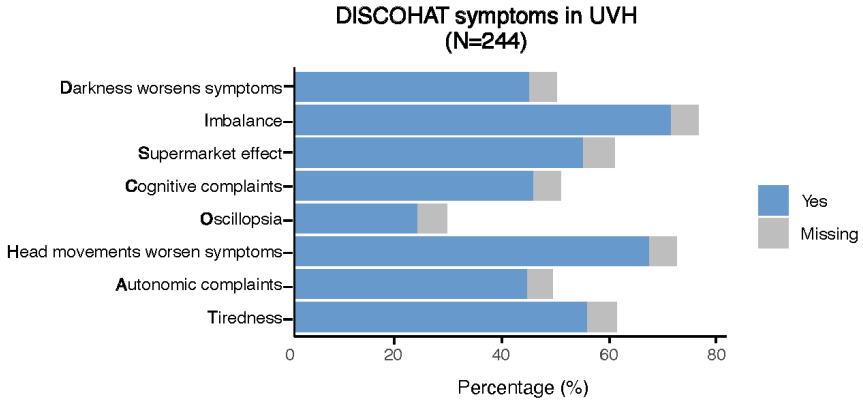


Figure S2. Distribution of DISCOHAT symptoms in the UVH population

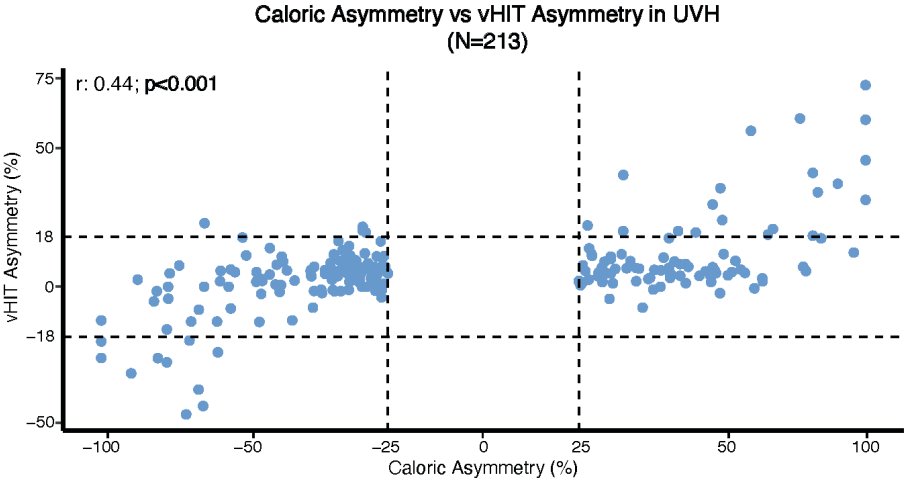


Figure S3. Scatterplot illustrating the correlation between caloric asymmetry and vHIT asymmetry in the UVH population

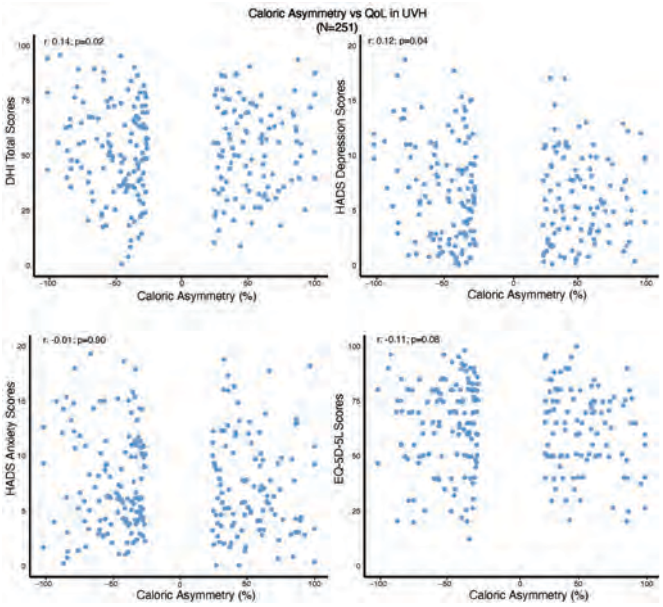


Figure S4. Scatterplot illustrating the correlation between caloric asymmetry and questionnaires related to QoL in the UVH population

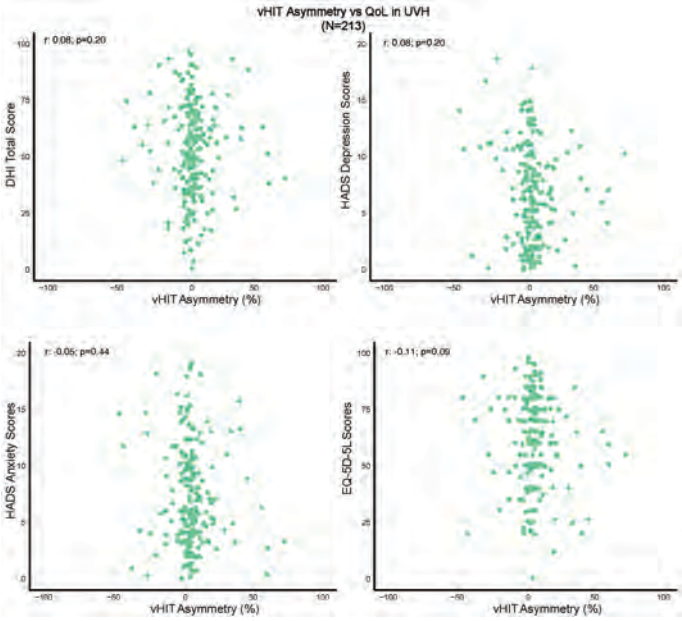


Figure S5. Scatterplot illustrating the correlation between vHIT asymmetry and questionnaires related to QoL in the UVH population

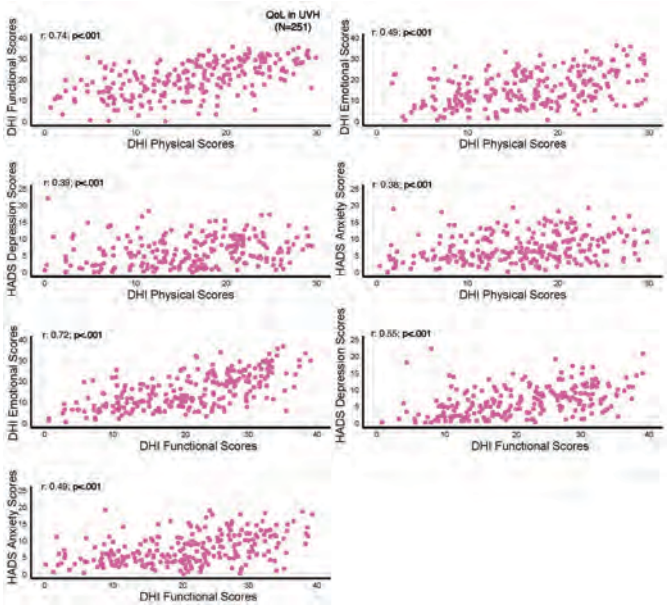


Figure S6. Scatterplot illustrating the correlation between questionnaires related to QoL in the UVH population

5

CHAPTER 5

Comparison of quality of life between patients with chronic unilateral vestibular hypofunction and bilateral vestibulopathy

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ABSTRACT

Objective

To compare symptom burden, functional impact, emotional well-being and health-related quality of life (HRQoL), between patients with chronic unilateral vestibular hypofunction (UVH) and bilateral vestibulopathy (BVP), using a set of patient-reported outcome measures (PROMs).

Method

This cross-sectional study included 100 chronic UVH patients and 148 BVP patients from a tertiary referral center. Normative data of healthy subjects were obtained from literature. Chronic UVH was diagnosed based on video head impulse test criteria and the presence of persistent symptoms (≥3 months), including at least one of the following: chronic dizziness, unsteadiness, oscillopsia, or symptoms worsened by head movements. BVP patients had to meet the Bárány Society diagnostic criteria. PROMs included condition-specific PROMs such as Bilateral Vestibulopathy Questionnaire (BVQ), Dizziness Handicap Inventory (DHI), and Oscillopsia Severity Questionnaire (OSQ) to assess symptom burden and functional impact; the Hospital Anxiety and Depression Scale (HADS) to assess emotional well-being; and generic PROMs such as the 5-level EQ-5D of the EuroQol Group (EQ-5D-5L) and the Health Utility Index Mark 3 (HUI-3) to evaluate HRQoL. Total scores were compared across groups. Standardized mean differences (SMD) were calculated to quantify the differences across all PROMs.

Results

BVP patients reported higher symptom burden and functional limitations than chronic UVH patients in condition-specific PROMs (BVQ, DHI, OSQ) ($p<0.05$). No significant differences were found between the groups in HADS and generic PROMs. In addition, chronic UVH and BVP patients exhibited significantly worse outcomes across multiple domains compared to healthy normative data, including greater symptom burden, higher emotional distress, and lower HRQoL ($p<0.05$; BVQ not measured due to absence of healthy norms). SMD analysis showed that when effect sizes between groups were large or moderate, the differences were statistically significant. Conversely, when effect sizes were very low or small, there were no statistically significant differences (except for the OSQ, which remained significant despite a small effect size).

Conclusion

Chronic UVH and BVP are associated with significantly reduced QoL. BVP patients report a greater symptom burden and functional limitations compared to patients with chronic UVH. These findings demonstrate the need for tailored assessments and targeted rehabilitation strategies for vestibular patients.

1 INTRODUCTION

Chronic unilateral vestibular hypofunction (UVH) and bilateral vestibulopathy (BVP) are heterogeneous disorders, resulting from reduced or absent vestibular function in respectively one or two vestibular end-organs, vestibular nerves, or a combination of both (1-4). Patients with chronic UVH or BVP commonly experience a range of symptoms including unsteadiness, oscillopsia, visually-induced dizziness, cognitive complaints, autonomic dysfunction, tiredness, and spatial disorientation (5-9). The severity and nature of these symptoms can vary widely. Symptoms are influenced by factors such as the underlying etiology, co-morbid conditions, psychological factors, level of physical activity, and the stage of vestibular compensation (10-14). These disorders have a wide range of etiologies, which make it challenging to identify the exact cause in many cases (3, 5, 6, 15, 16). The diagnosis of BVP is currently guided by the Bárány Society criteria, which rely on a combination of vestibular symptoms and objective test findings (4). In contrast, no standardized diagnostic criteria exist (yet) for chronic UVH. This adds to the complexity of diagnosing this condition. The reported prevalences of UVH and BVP vary. Chronic UVH is considered widespread, although its exact prevalence remains uncertain (6). Furthermore, BVP has an estimated prevalence of 28 to 81 per 100,000 adults (17). However, this is likely an underestimation (18, 19). Overall, both chronic UVH and BVP present with various clinical pictures, which often lead to misdiagnosis (19, 20).

Chronic UVH and BVP can both reduce quality of life (QoL) and impose substantial socioeconomic burdens, which are often underestimated (5, 6, 21-23). To fully understand their impact on QoL, semi-structured interviews were previously conducted to explore the full spectrum of symptoms, challenges, and coping behaviors in both patient groups. These findings revealed a variety of symptoms, significant functional limitations in daily life activities, reduced social interactions, and a marked decline in overall QoL across both groups (8) (chronic UVH manuscript under review).

In addition to qualitative insights, patient-reported outcome measures (PROMs) play a crucial role in evaluating QoL, by capturing patient's subjective experience without external interpretation by healthcare providers (24, 25). PROMs are classified into condition-specific and generic measures (26). Condition-specific PROMs are designed to assess several aspects, such as the impact of a particular disease (e.g., the Bilateral Vestibulopathy Questionnaire (BVQ)), a set of related conditions like dizziness (e.g., the Dizziness Handicap Inventory (DHI)), or specific domains (e.g., the Hospital Anxiety and Depression Scale (HADS)). Instruments like the Oscillopsia Severity Questionnaire (OSQ) also fall under this category, as these target disorder-related challenges in specific patient populations. In contrast, generic PROMs are not tailored to any particular disease or

condition. Instead, these are designed to assess overall health and well-being, often with a focus on health-related quality of life (HRQoL). Examples include the 5-level EQ-5D from EuroQol (EQ-5D-5L) and the Health Utility Index Mark 3 (HUI-3) (27). These PROMs, widely used in vestibular research and clinical practice, provide valuable insights into patients' experiences. Furthermore, comparisons across different levels of symptom severity and impact on QoL are facilitated.

Previous studies using the DHI, HADS, and EQ-5D-5L showed that chronic UVH and BVP are associated with moderate to severe handicaps, based on DHI. HADS results indicated that anxiety and depression levels remain within normal ranges in both conditions. Additionally, EQ-5D-5L findings highlighted a significant reduction in QoL for both patient groups (6, 8). Despite the growing body of evidence on the negative impact on QoL (5, 6, 21, 23), previous studies focused on either chronic UVH or BVP. However, a comparison of QoL between chronic UVH and BVP patients using a set of validated PROMs, was not yet performed. In addition, these two conditions can differ significantly in terms of their pathophysiology, symptom profiles, and compensatory mechanisms (28, 29). Understanding the differences between these populations is crucial. It may allow for more individualized, condition-specific management strategies, rather than applying a one-size-fits-all approach. Therefore, the aim of this study was to investigate the differences in symptom burden, functional impact, emotional well-being and HRQoL between chronic UVH patients and BVP patients, using condition-specific and generic PROMs.

2 MATERIALS AND METHODS

Participants

This study was conducted at Maastricht University Medical Center+ during different time periods. Chronic UVH patients were included between August and December 2024. BVP patients were already recruited between April 2021 and January 2022. Patients were selected based on specific clinical and diagnostic criteria. For chronic UVH, inclusion required at least one of the following symptoms: chronic dizziness, unsteadiness, oscillopsia, or symptoms worsened by head movements. Patients with symptoms persisting for ≥3 months were considered eligible. Diagnosis was confirmed by the video head impulse test (vHIT). VHIT results had to show a reduced vestibulo-ocular reflex (VOR) gain on the affected side (<0.7) with normal VOR gain on the healthy side (≥0.8–≤1.2) and a ≥18% asymmetry between ears (manuscript under review). For BVP, patients met the Bárány Society diagnostic criteria, which included unsteadiness and/or oscillopsia during walking or head movements, a reduced caloric response (sum of bithermal maximal peak SPV <6°/s), and/or a bilaterally reduced VOR gain (vHIT <0.6 or torsion swing test VOR

gain <0.1) (4). Detailed descriptions of the test procedures were provided previously (30). All patients were required to be ≥18 years old and proficient in written Dutch. Patients with a medical history of neurological disorders (such as multiple sclerosis, stroke, or Parkinson's disease) were excluded.

Patient-reported outcome measures (PROMs)

Bilateral Vestibulopathy Questionnaire (BVQ)

The BVQ assess the full spectrum of symptoms and the impact on daily life in BVP patients. It includes 24 items across four subscales: imbalance, oscillopsia, cognition and emotion. Responses are rated on a 6-point Likert-scale with the following levels: always, frequently, regularly, sometimes, rarely, and never. The BVQ total score is calculated by summing the mean scores of its four constructs. Each construct score is the mean of its item scores, obtained by dividing the total item score by the number of items in that construct. Higher scores indicate higher symptom severity (31).

Dizziness Handicap Inventory (DHI)

The DHI evaluates the impact of dizziness on QoL. It consists of 25 questions divided into three subscales: physical, functional and emotional. Responses are scored using three options: yes (4 points), sometimes (2 points), and no (0 points). The overall DHI score is calculated by summing the scores of all items, ranging from 0 to 100. Higher scores indicate worse outcomes. Scores are categorized as follows: 0–14 indicates no handicap, 16–34 mild handicap, 36–52 moderate handicap, and 54 or higher severe handicap (32). In this study, a score of 5 was considered representative of healthy subjects, based on literature (33).

Hospital Anxiety and Depression Scale (HADS)

The HADS identifies possible anxiety and/or depression. It consists of 14 questions divided into two subscales: anxiety and depression. Each item is scored on a scale of 0 to 3. Separate subscale scores for anxiety and depression are calculated by summing the respective item scores. The total score for each subscale ranges from 0 to 21, with the following cut-offs: A score between 0 and 7 points indicates no anxiety or depression; a score between 8 and 10 points indicates possible anxiety or depression; and scores exceeding 10 points indicate probable anxiety or depression (34, 35). In short, the higher scores indicate worse outcomes. Based on a previous study, an anxiety score of 4 and a depression score of 2 were used as reference values in this study (33).

Euro-QoL 5 Dimension and 5 Level (EQ-5D-5L)

The EQ-5D-5L measures generic health status and health-related quality of life (HRQoL). It includes five dimensions: mobility, self-care, usual activities, pain/discomfort and

anxiety/depression. Each dimension is rated on a 5-point scale (1 = no problems to 5 = severe problems/unable to). Scores can be converted into an EQ-5D-5L index score ranging from -0.059 to 1.0 (36, 37). Additionally, the instrument includes a visual analog scale (VAS) for assessing perceived health status. Low scores in both EQ-5D-5L VAS and index values, reflect worse outcomes. In healthy populations, EQ-5D-5L index scores of ≥0.839 and VAS scores of ≥80 are found (37, 38). Based on previous studies, an index value of 0.839 ± 0.179 and a VAS score of 80.7 ± 17.2 were used as reference values in this study (37, 38).

Health Utility Index 3 (HUI-3)

The HUI-3 assesses general health status and HRQoL. It includes 15 questions with eight attributes: vision, hearing, speech, ambulation, dexterity, emotion, cognition, and pain. Each attribute is rated across five or six levels of (dis)ability. Scores are transformed into HRQoL values using a population-validated utility function, yielding a range from 1 to 0. Low scores refer to worse outcomes. HUI-3 scores are categorized as follows: No disability (1.00), mild disability (0.89–0.99), moderate disability (0.70–0.88), and severe disability (<0.70) (39). For healthy individuals, an overall health utility score of ≥0.85 is considered representative (40).

Oscillopsia Severity Questionnaire (OSQ)

The OSQ evaluates the severity of oscillopsia in various daily activities. It consists of nine questions. Responses are rated on a 5-point Likert scale with the following levels: 1 (never), 2 (seldom), 3 (sometimes), 4 (often), and 5 (always). The overall score is calculated as the average of all item scores, ranging from 1 (no severity) to 5 (maximum severity). A mean score of 3 or higher indicates moderate to extreme oscillopsia severity (41). A mean score of ≤2 suggests minimal oscillopsia severity, which is considered normal in healthy individuals (41).

All PROMs used in this study are validated instruments, with the exception of the OSQ, which was not validated yet.

Normative data of healthy subjects

Normative data of healthy subjects were obtained from previous studies or other sources, depending on the PROM. Regarding the DHI and HADS, normative data was obtained from 151 Dutch-speaking healthy subjects (59.6% female, mean age 50.9 ± 18.5 years) (33). For the EQ-5D-5L, the reference index scores were derived from the Dutch population (n=1003). The index score of the 60 year-old group was used as a reference (37). The reference EQ-5D-5L VAS score was obtained from another study (n=2367, 51.1% female, mean age 48.4 ± 16.4 years) (38). Regarding the HUI-3, normative data were derived from a group of 2060 subjects (40). For the OSQ, data were collected from 57

healthy subjects (25 female, mean age 41 years, range 20-77 years) (41). For the BVQ, no normative data is yet available (31, 42). Therefore, no comparison with healthy subjects was made in this study.

Data analysis

Data were analysed using both visual methods (histogram and Q-Q plots) and statistical tests (Shapiro–Wilk test) to assess the normality of the distributions. A one-sample t-test was conducted to compare the QoL scores between the chronic UVH group and normative data based on healthy subjects (43). For comparisons between the chronic UVH and BVP groups, the Mann-Whitney U test was applied due to the non-normal distribution of the data. Violin plots were used for visualization, and the significance level was set at 0.05. Additionally, to quantify the difference between groups, standardized mean differences (SMD) were calculated (44). The SMD is a measure of effect size that quantifies the difference between two groups relative to their variability. In this study, the SMD between the chronic UVH group and BVP group was calculated using the formula: (mean_BVP - mean_UVH)/sd_pooled, where the pooled standard deviation was derived from both groups. Additionally, the SMD between the chronic UVH group and the group of healthy subjects was computed using the formula: (mean_UVH – mean_healthy)/sd_UVH. Similarly, the SMD between the BVP group and the healthy control group was calculated using the formula: (mean_BVP – mean_healthy)/sd_BVP. The interpretation of the SMD values was based on Cohen's guidelines: values of 0.2 or less indicated very low effect, 0.2–0.49 indicated a small effect, 0.5–0.79 represented a moderate effect, and values of 0.8 or higher suggested a large effect (45).

For the comparison between chronic UVH and BVP:

- Positive SMD values indicated worse outcomes in BVP for BVQ, DHI, OSQ, and HADS.
- Negative SMD values indicated worse outcomes in BVP for HUI-3 and EQ-5D-5L compared to chronic UVH.
- For the comparison between chronic UVH and normative data based on healthy subjects:
- Positive SMD values indicated worse outcomes in chronic UVH for DHI, OSQ, and HADS.
- Negative SMD values indicated worse outcomes in chronic UVH for HUI-3 and EQ-5D-5L.
- For the comparison between BVP and normative data based on healthy subjects:
- Positive SMD values indicated worse outcomes in BVP for DHI, OSQ, and HADS.
- Negative SMD values indicated worse outcomes in BVP for HUI-3 and EQ-5D-5L.

A barplot was used for visualization, and all analyses were performed using R (version 4.3.1; R Foundation for Statistical Computing, Vienna, Austria) (46).

Ethical considerations

This study was conducted in accordance with the legislation and ethical standards on human experimentation in the Netherlands and in accordance with the Declaration of Helsinki (amended version 2013). The study protocol was classified as non-WMO (Wet medisch-wetenschappelijk onderzoek) research and received approval from the Medical Ethics Review Committee of Maastricht University and the Maastricht University Medical Center+ (UM/MUMC+) (approval number METC 2025-0031). Approval was also obtained from the Advisory Board of MUMC+. Written informed consent was obtained from all patients participating in this study.

3 RESULTS

Patient characteristics

A total of 248 patients were included in this study. This comprised 100 patients with chronic UVH and 148 patients with BVP. All patients completed the disease-specific and generic PROMs. The mean age of patients at the time of diagnosis was 63.8 ± 12.0 years, with ages ranging from 20 to 90 years. Among the study population, 52% were male and 48% were female. The characteristics of chronic UVH and BVP patients are separately presented in Table 1.

For chronic UVH patients, the mean horizontal vHIT VOR gain was 0.47±0.14 on the affected side and 0.93 ± 0.08 on the healthy side. In BVP patients, the mean horizontal vHIT VOR gain was 0.33±0.27 for the right ear and 0.32+0.23 for the left ear (31).

Table 1. Patient characteristics of chronic UVH and BVP

	Chronic UVH patients N=100	**BVP patients N=148**	**Total N=248**
	Mean±SD ; (Range)		
Age	64.1±10.8 (29-90 years)	63.7±12.9; (20-89 years)	63.8±12.0 (20-90 years)
Gender	**N (%)**		
Male	55 (55)	74 (50)	129 (52)
Female	45 (45)	74 (50)	119 (48)
Side of lesion			
Right	33 (33)	-	33 (13)
Left	67 (67)	-	67 (27)
Both	-	148 (100)	148 (60)
Etiologies			
Idiopathic	10 (10)	55 (37.2)	65 (26)
Infection/Inflammation	33 (33)	17 (11.5)	50 (20)
Menière's disease	19 (19)	8 (5.4)	27 (11)
Genetic	-	26 (17.6)	26 (10)
Neoplasm	22 (22)	-	22 (9)
Ototoxicity	-	20 (13.5)	20 (8)
Autoimmune disorders	1 (1)	8 (5.4)	9 (4)
Vestibular migraine	5 (5)	4 (2.7)	9 (4)
Mixed etiologies	5 (5)	3 (2.0)	8 (3)
Iatrogenic	3 (3)	1 (0.7)	4 (1.5)
Neurodegenerative conditions	-	3 (2.0)	3 (1)
Congenital	-	2 (1.4)	2 (1)
Benign recurrent vertigo	1 (1)	-	1 (0.5)
Vascular	-	1 (0.7)	1 (0.5)
Metabolic	1 (1)	-	1 (0.5)

Abbreviations: SD, Standard deviation

Chronic UVH patients versus BVP patients

Significant differences were found in BVQ total scores, DHI total scores, and OSQ total scores between chronic UVH patients and BVP patients ($p<0.05$). No significant differences were observed in EQ-5D-5L Index, EQ-5D-5L VAS, HADS-anxiety, HADS-depression, and HUI-3 overall utility scores ($p>0.05$) (Figure 1.).

The SMD analysis identified moderate effects in BVQ total scores and DHI total scores, indicating significantly poorer outcomes in BVP patients compared to chronic UVH patients, with a greater impact on symptom burden and functional limitations. In contrast, all other PROMs exhibited very low to small effects, suggesting minimal differences between the two groups regarding these aspects (Figure 2).

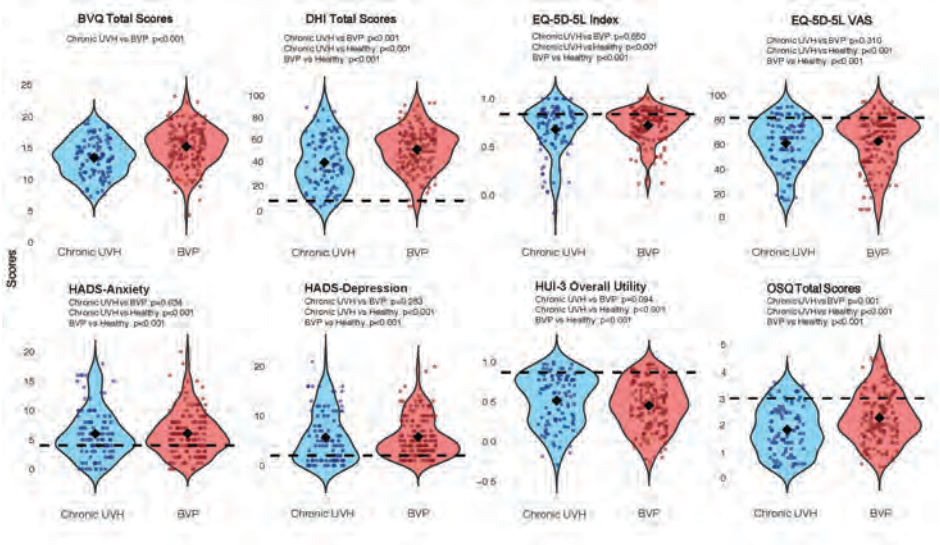


Figure 1. Violin plots illustrating the comparison of QoL across chronic UVH patients, BVP patients and healthy subjects, using a set of PROMs. Dashed lines represent normative data of healthy subjects derived from previous studies or other sources. 'Chronic UVH vs BVH' indicates the p-value for the comparison between chronic UVH patients and BVP patients. 'Chronic UVH vs Healthy' shows the p-value for the comparison between chronic UVH patients and normative data of healthy subjects. 'BVP vs Healthy' shows the p-value for the comparison between BVP patients and normative data of healthy subjects. Squares within each violin plot indicate mean scores. The wider sections of violin plots indicate a higher data density, whereas narrower sections reflect lower data density.

Chronic UVH patients versus healthy subjects

All PROMs demonstrated statistically significant differences between chronic UVH patients and healthy subjects ($p<0.001$), except the BVQ for which normative data were unavailable. No comparison was conducted for this measure (Figure 1.).

The SMD analysis identified large effects in DHI total scores and HUI-3 overall utility, indicating significantly poorer outcomes for chronic UVH patients compared to healthy subjects. Moderate effects were observed in HUI-3 Ambulation, EQ-5D-5L VAS, EQ-5D-5L Index, and HADS-Depression, which indicated noticeable impact on physical functioning, emotional well-being, and HRQoL. In contrast, very low to small effects were found in

OSQ total scores, HADS-Anxiety, HUI-3 Cognition, HUI-3 Emotion, and HUI-3 Vision. This suggested that chronic UVH patients were almost equal to healthy subjects in these domains (Figure 2.).

BVP patients versus healthy subjects

All PROMs demonstrated statistically significant differences between BVP patients and healthy subjects ($p<0.001$), except the BVQ. After all, as normative data for BVQ were unavailable, no comparison was conducted for this measure (Figure 1.).

The SMD analysis identified large effects in DHI total scores, HADS-Depression, and HUI-3 overall utility, indicating significantly poorer outcomes for BVP patients compared to healthy subjects. Moderate effects were observed for HUI-3 Ambulation, EQ-5D-5L VAS, EQ-5D-5L index, HADS-Anxiety, and OSQ total scores. This indicated noticeable impact on physical functioning, emotional well-being, and HRQoL. In contrast, very low to small effects were found in HUI-3 Cognition, HUI-3 Emotion, and HUI-3 Vision. This suggested that BVP patients were almost equal to healthy subjects in these domains (Figure 2.).

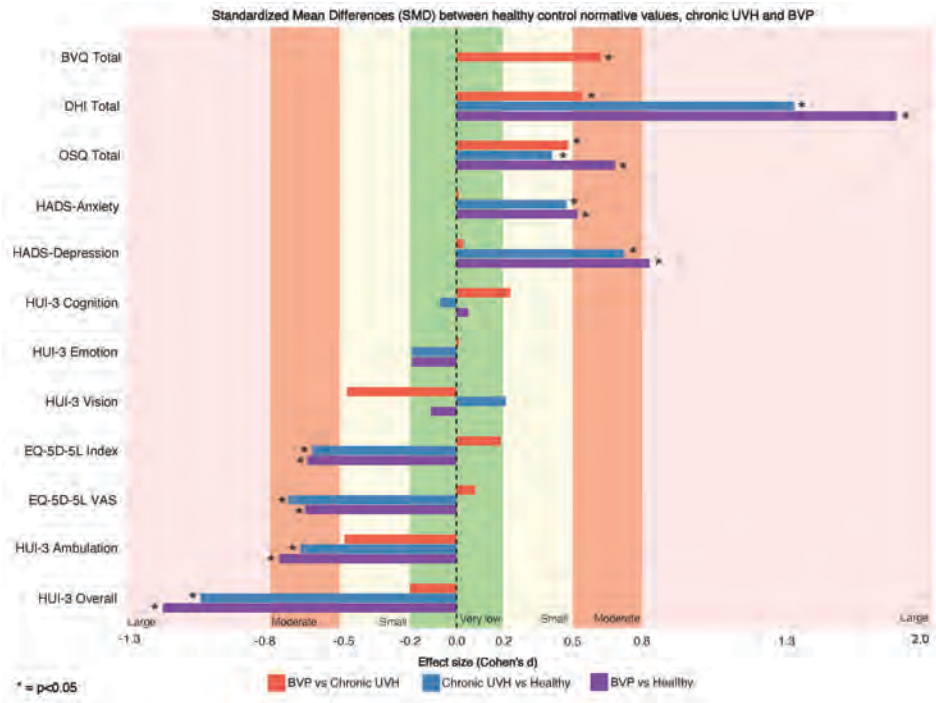


Figure 2. Bar plot of Standardized Mean Differences (SMD) comparing chronic UVH patients, BVP patients and healthy subjects. SMD values are interpreted according to Cohen's guidelines: values ≤ 0.2 indicate a very low effect (green areas), values between 0.2 and 0.49 indicate a small effect (yellow areas), values between 0.5 and 0.79 represent a moderate effect (orange areas), and values ≥ 0.8 suggest a large effect (pink areas). For the comparison between BVP and Chronic UVH, positive SMD values indicate worse outcomes in BVP for BVQ, DHI, OSQ, and HADS, while negative SMD values indicate worse outcomes in BVP for HUI-3 and EQ-5D-5L compared to chronic UVH. For the comparison between chronic UVH and normative data of healthy subjects, positive SMD values indicate worse outcomes in chronic UVH for DHI, OSQ, and HADS, whereas negative SMD values indicate worse outcomes in chronic UVH for HUI-3 and EQ-5D-5L. For the comparison between BVP and normative data of healthy subjects, positive SMD values indicate worse outcomes in BVP for DHI, OSQ, and HADS, whereas negative SMD values indicate worse outcomes in BVP for HUI-3 and EQ-5D-5L. Asterisks (*) indicate statistically significant differences ($p<0.05$).

4 DISCUSSION

This study demonstrated that chronic UVH and BVP patients exhibit worse outcomes across all PROMs compared to healthy subjects (only BVQ not determined). Furthermore, BVP patients experienced a higher symptom burden and functional limitations than chronic UVH patients. This distinction was particularly evident in condition-specific PROMs: BVQ, DHI, and OSQ. However, no significant differences were observed between chronic UVH patients and BVP patients in generic PROMs and HADS.

The differences in symptom burden and functional limitations between chronic UVH patients and BVP patients could be attributed to several factors. First, the extent of vestibular hypofunction might play a role, as it can directly influence functional performance (47). Chronic UVH patients have one intact vestibular organ. This improves compensatory strategies like vestibular compensation, adaptation and sensory substitution (48, 49). These strategies help maintain functional independence despite occasional instability. In contrast, BVP patients lack vestibular input on both sides, which severely limits e.g. vestibular compensation (50, 51). Therefore, BVP patients generally report more unsteadiness (especially in dim light conditions or on uneven surfaces), oscillopsia (blurred vision during head movements), and they have a higher risk of falling (17, 52). This makes daily activities more challenging. The increased functional impairment leads to greater dependence and social isolation, which further reduces QoL (8, 9, 15).

Secondly, vestibular hypofunction does not only have physical, but also psychological and emotional consequences (53). Chronic UVH patients may develop anxiety or depression (6, 23). However, these issues are more pronounced in BVP patients (8, 21, 22). The constant fear of falling, loss of independence, and reduced social participation can severely impact mental well-being. Difficulties in work and daily tasks may lead to a loss of self-confidence (8). This psychological burden might further contribute to the lower QoL reported by BVP patients, compared chronic UVH patients and healthy subjects.

Beyond the severity of vestibular hypofunction, co-morbidities can also influence patient outcomes and QoL. For instance, a previous study found that the presence of Persistent Postural-Perceptual Dizziness (PPPD) significantly reduces QoL in chronic UVH patients (6). PPPD, characterized by persistent dizziness, motion-induced instability, and heightened anxiety, can exacerbate functional limitations and compromise adaptation (54). While PPPD is well documented in UVH, it may also affect a subset of BVP patients, though this has been less frequently studied. This implies that clinicians should explicitly screen for comorbidities, such as PPPD, in patients with vestibular hypofunction and decreased QoL. This could facilitate appropriate management and targeted interventions (55).

Condition-specific PROMs captured significant differences in symptom burden and functional limitations between chronic UVH patients and BVP patients. However, generic PROMs did not show significant differences between the two groups. This difference likely reflects the greater relevance, reliability, and sensitivity of condition-specific PROMs, which are designed to detect subtle changes in vestibular function and its impact on daily life (56). In contrast, generic PROMs assess broad health domains, such as pain, self-care, and speech, which might not always be relevant to patients with chronic UVH or BVP. As a result, these tools may not fully capture the true burden of chronic UVH and BVP,

and therefore possibly underestimate the impact. However, it is recommended that both condition-specific and generic PROMs are used concurrently, to provide a more detailed evaluation of QoL (27, 57).

In case large or moderate effect sizes were observed between groups, a statistically significant difference was found. In case very low to small effect sizes were observed, no statistically significant difference was found, except for the OSQ. This exception might be explained by two possible factors. First, OSQ scores may exhibit lower within-group variability, which can lead to a higher SMD and contribute to statistical significance, even when the absolute difference between groups is modest. Secondly, as a condition-specific PROM focusing on oscillopsia severity, the OSQ may be more sensitive to detect subtle differences between patient groups. At the same time, the lack of psychometric properties might also affect the reliability of the significance. These findings demonstrate the importance of interpreting both statistical significance in conjunction with effect size (58).

Although BVP patients exhibited the highest symptom burden in condition-specific PROMs, our findings reveal that chronic UVH patients also experience substantial functional limitations. This is congruent with a previous study, in which approximately one-third of UVH patients reported moderate to severe disability, despite vestibular rehabilitation (5). These findings indicate that chronic UVH can result in long-term impairment, which highlights the need for individualized therapy in this population. In addition to vestibular rehabilitation, novel therapeutic strategies such as vibrotactile feedback and vestibular implants, originally developed for BVP (59, 60), could also be explored in patients with chronic UVH. However, appropriate patient selection is essential to maximize benefit and minimize risk, as not all chronic UVH patients (e.g., those without oscillopsia or with residual vestibular function) are suitable candidates for vestibular implantation (6, 61).

Several limitations were identified in this study. First, normative data based on healthy subjects were obtained from other studies or sources. This might (partially) compromise perfect comparison with the chronic UVH and BVP patients. Nevertheless, main goal of this study was to compare chronic UVH patients with BVP patients. Secondly, a time interval was present between diagnosis (UVH or BVP) and administration of the PROMs. This interval was different for every patient. Therefore, a (partial) change in vestibular function over time, cannot be ruled out. Thirdly, the BVQ was originally developed to assess symptom burden and functional impact in BVP patients and was not formally validated for use in chronic UVH, which might have not fully captured the symptom profile of patients with chronic UVH. Lastly, while age-specific EQ-5D index values were available and the 60+ category was used, EQ-5D VAS scores were not stratified by age. As a result, the overall

mean VAS score was used from a normative sample with a younger mean age (48.4 ± 16.4 years) than our study population (63.8 ± 12.0 years), which may have influenced the results.

5 CONCLUSION

Chronic UVH and BVP are associated with significantly reduced QoL. BVP patients report a greater symptom burden and functional limitations compared to patients with chronic UVH. These findings demonstrate the need for tailored assessments and targeted rehabilitation strategies for vestibular patients.

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6

CHAPTER 6

Construct validity and reliability of the preliminary version of the Bilateral Vestibulopathy Questionnaire (BVQ) in patients with chronic unilateral vestibular hypofunction

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ABSTRACT

Objective

To evaluate the construct validity and reliability of the preliminary version of the Bilateral Vestibulopathy Questionnaire (BVQ) in patients with chronic unilateral vestibular hypofunction (UVH).

Methods

Patients with chronic UVH completed a set of patient-reported outcome measures (PROMs), including the preliminary version BVQ, the Dizziness Handicap Inventory, the Hospital Anxiety and Depression Scale, the 5-level EQ-5D of the EuroQol Group, the Health Utilities Index, and the Oscillopsia Severity Questionnaire. To assess the construct validity of the preliminary version of the BVQ in chronic UVH patients, both confirmatory and exploratory factor analyses (CFA and EFA) were conducted, followed by convergent validity and known groups validity. The structural properties of BVQ items were also analyzed. Reliability was examined through internal consistency (Cronbach's alpha) and test–retest reliability, using intraclass correlation coefficients (ICCs).

Results

A total of 100 patients with chronic UVH (55% male, mean age 64.1 ± 10.8 years) completed a set of PROMs. The initial CFA did not support a good model fit for the original structure of the preliminary BVQ. However, the EFA identified a revised structure consisting of four factors: imbalance, visuo-spatial processing, emotion, and behaviors and limitations. A subsequent CFA validated this revised structure, which demonstrated acceptable construct validity and model fit. Convergent validity confirmed that the adapted version effectively measured the targeted constructs. Significant score differences between known groups further supported construct validity. Internal consistency was high across all four factors (Cronbach's alpha = 0.80–0.89), and test–retest reliability was acceptable, with intraclass correlation coefficients (ICCs) ranging from 0.70 to 0.89 for most items. Only the final VAS item showed lower stability (ICC = 0.61).

Conclusion

This study provides preliminary evidence for the construct validity and reliability of the adapted BVQ in assessing the impact of chronic UVH. The adapted version of the BVQ consists of four constructs with a total of 16 Likert-scale items and 4 VAS items (in total 20 items), which demonstrated solid psychometric properties. Further research should include cognitive interviews and expert panels to establish content validity in order to confirm the adapted BVQ as a PROM for chronic UVH. Afterwards, it can be renamed as the unilateral vestibulopathy questionnaire (UVQ).

1 INTRODUCTION

Unilateral vestibular hypofunction (UVH) is a complex condition impacting one vestibular organ, vestibular nerve, or a combination of both (1, 2). UVH results in a diverse spectrum of physical, cognitive, and emotional symptoms (3, 4). When UVH occurs, vestibular compensation is triggered to restore balance and spatial orientation. This process helps mitigate symptoms of vestibular hypofunction (5, 6), but its effectiveness varies. This depends on factors like age, etiology, co-morbidities, psychological state, environmental factors, physical activity, and individual adaptability (7-11). Consequently, disabling chronic symptoms remain in about 30% of UVH patients (12). Chronic dizziness and unsteadiness are the most reported physical symptoms of chronic UVH. Other symptoms include e.g. visually-induced dizziness, worsening of symptoms in darkness, autonomic complaints, and, to some extent, oscillopsia (3, 12). Cognitive symptoms associated with chronic UVH include difficulties with concentration, dual-tasking, forgetfulness, and spatial disorientation (4). Emotionally symptoms related to chronic UVH are feelings of sadness, fear, and anger (4). This wide range of chronic symptoms can cause behavioral adaptations which affect daily functioning. This can result in decreased physical activity, reduced social interactions, diminished vitality, and even social isolation (4). Consequently, these challenges can significantly reduce the overall quality of life (QoL) for patients with chronic UVH, as demonstrated by previous studies (3, 12).

Bilateral vestibulopathy (BVP) shares certain similarities with chronic UVH, particularly in the impairment of vestibular function. However, unlike chronic UVH, which affects one vestibular organ, BVP involves reduced or absent function of both vestibular organs (13, 14). Patients with BVP commonly report a wide range of physical, cognitive, and emotional symptoms, all of which significantly impair QoL (15-17). To effectively evaluate these symptoms and their impact on QoL in BVP patients, the Bilateral Vestibulopathy Questionnaire (BVQ) was developed internationally accepted standards as outlined by the COSMIN guidelines (18, 19). The developmental process included expert panel reviews, cognitive interviews with patients, and thorough testing of content validity, construct validity, and reliability. The first preliminary version of the BVQ was created during the content validity phase and included 50 items organized into seven constructs (20). After that, a validated version of the BVQ was created after construct validity and reliability, which included 20 items along with four visual analog scale (VAS) items (21). The 20 items cover four key constructs: imbalance, oscillopsia, emotion, and cognition.

The validated BVQ meets high methodological standards for use in both clinical and research settings in patients with BVP. Similar to BVP, chronic UVH patients also report a wide spectrum of physical, cognitive, and emotional symptoms, which substantially

affect their QoL (3, 4, 12). A previous study showed that while both groups report similar symptoms, the severity is generally lower in chronic UVH patients (manuscript submitted). Due to this similarity and to develop a PROM specific to chronic UVH, the 50 item preliminary version of the BVQ was used as a starting point, as it encompasses a broad range of symptoms also relevant for chronic UVH.

Therefore, this study aimed to investigate the construct validity and reliability of the preliminary version of the BVQ in chronic UVH patients, in order to establish a first step towards a condition-specific questionnaire for chronic UVH patients. While future studies should include cognitive interviews and expert input to establish content validity, the present study offers a valuable step in evaluating the relevance and applicability of the BVQ items in a chronic UVH population.

2 MATERIALS AND METHODS

2.1 Patients

The study was carried out at Maastricht University Medical Center+, The Netherlands, between August and December 2024. Eligible patients documented at least one of the following symptoms during history taking at the time of evaluation: chronic dizziness, oscillopsia, or symptoms worsened by head movements. The diagnosis of UVH was confirmed through the video head impulse test (vHIT), which showed a reduced vestibulo-ocular reflex (VOR) gain on the affected side (<0.7), while the healthy side displayed normal VOR gain values (≥0.8 -VOR gain- ≤1.2). Additionally, an asymmetry of at least 18% between the two ears was required for inclusion (4). Detailed testing protocols were previously described (22). Patients were required to be 18 years or older and able to understand the written Dutch.

2.2 Data Collection

All patients were instructed to complete the a set of questionnaires, including the BVQ (54 items), the 5-level EQ-5D of the EuroQol Group (EQ-5D-5L), the Health Utility Index 3 (HUI-3), the Dizziness Handicap Inventory (DHI), the Hospital Anxiety and Depression Scale (HADS), and the Oscillopsia Severity Questionnaire (OSQ). To assess test-retest reliability, patients were also asked to complete a follow-up BVQ assessment seven days after the initial survey.

Patients were approached by phone to be invited to participate the study. In cases where phone contact could not be established, alternative invitation was conducted through e-mail or postal mail. Upon confirming their participation, patients received a link to the

online survey, created using Qualtrics (Qualtrics software, Version 20204, Qualtrics, Provo, UT, United States), which was delivered via e-mail. For those unable to access the online survey (e.g., due to lack of internet access), a paper version was sent through postal mail. Seven days later, patients received a follow-up invitation to complete the retest questionnaire (BVQ only) either via Qualtrics (automated e-mail) or via postal mail (paper version).

Demographic information, including date of birth, sex, and clinical data such as etiology, secondary diagnosis, duration since onset, and vHIT test results were retrieved from the electronic medical records maintained by the Department of Otorhinolaryngology and Head and Neck Surgery at Maastricht University Medical Center+. Video Head Impulse Test results and clinical data were collected retrospectively, whereas questionnaires were collected prospectively.

2.3 Patient-reported outcome measures (PROMs)

2.3.1 *Bilateral Vestibulopathy Questionnaire (BVQ)*

The validated version of the BVQ evaluates the full range of symptoms and their impact on daily life activities in BVP patients. This validated version consists of 24 items. The 20 items cover four key constructs: imbalance, oscillopsia, emotion, and cognition, using a 6-point Likert scale ranging from “never” to “always.” (21). In addition, four items are rated on a Visual Analog Scale (VAS) from 0 to 100. Construct scores are calculated by averaging item scores within each domain, and the overall BVQ score ranges from 7 to 28. VAS item scores are reported separately and can also be averaged across the study sample (20, 21).

However, for the purposes of the current study on chronic UVH, the validated version was not used. Instead, the original 50 item preliminary version of the BVQ was used, which was created during the initial construction and content validity phase of the instrument. This version encompasses 50 items arranged into seven constructs: imbalance, oscillopsia, other physical symptoms, cognition, emotion, behavior and limitations, and social life. This version also included four VAS items rated from 0 to 100. This broader item pool allowed us to explore whether the items originally developed for BVP also captures the symptomatology of chronic UVH. The preliminary version of the BVQ used in this study is presented in the Supplementary Table S1 (21). The English version included here is a translation from Dutch and has not yet been validated in English.

2.3.2 *Dizziness Handicap Inventory (DHI)*

The DHI is a validated self-report questionnaire designed to measure how dizziness affects an individual’s everyday activities. It contains 25 items distributed across three domains:

physical, emotional, and functional. For each item, respondents can choose from three possible answers—'yes' (scored as 4 points), 'sometimes' (2 points), or 'no' (0 points). The cumulative score can range between 0, indicating no perceived difficulty, and 100, indicating the highest level of self-reported disability due to dizziness. The total DHI scores can be classified into three levels: mild (16–34), moderate (36–52), or severe (54–100) (23).

2.3.3 *Hospital Anxiety and Depression Scale (HADS)*

The HADS is a validated questionnaire designed to assess the extent of anxiety and depression in individuals It comprises 14 items, equally divided into two distinct subscales: (anxiety and depression) with seven items each. Each item is rated on a 4-point Likert scale ranging from 0 to 3. A score between 0 and 7 is considered within the normal range, 8 to 10 suggests a mild level of distress, 11 to 14 indicates moderate distress, and scores between 15 and 21 reflect a severe degree of anxiety or depression (24, 25).

2.3.4 *5-level EQ-5D of the EuroQol Group (EQ-5D-5L)*

The EQ-5D-5L is a validated instrument designed to assess overall health status and health-related quality of life (HRQoL) across multiple domains. It consists of two main components: the EQ-5D descriptive system and the EQ visual analogue scale (EQ-VAS).

The EQ-5D descriptive system evaluates five key dimensions of health: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each rated on a five-point scale, where level 1 indicates no problems and level 5 indicates extreme difficulty or inability. Responses across these dimensions can be combined and translated into a single EQ-5D-5L index value, which ranges from −0.059 (representing a state worse than death) to 1 (indicating perfect health). The EQ-VAS allows individuals to rate their overall health on a vertical visual analog scale, reflecting their perceived health status on the day of assessment (26, 27).

2.3.5 *Health Utility Index 3 (HUI-3)*

The HUI-3 is a standardized self-report tool used to evaluate overall health status and HRQoL. It includes 15 items that assess eight key health attributes: vision, hearing, speech, ambulation, dexterity, emotion, cognition, and pain. Each attribute includes up to six levels for (dis)ability, capturing a wide range of health states. Responses are converted into a utility-based HRQoL score using a validated algorithm derived from general population preferences. These scores range from 1.00, indicating optimal health, to 0, representing death. Based on the global utility score, disability can be categorized into four levels: no disability (1.00), mild (0.89–0.99), moderate (0.70–0.88), and severe (below 0.70) (28).

2.3.6 *Oscillopsia Severity Questionnaire (OSQ)*

The OSQ, which is not fully validated yet, is a 9-item tool designed to examine the severity of oscillopsia in various daily life situations. Each item is rated on a 5-point Likert scale, with response options ranging from 1 ('never') to 5 ('always'). The overall score is determined by calculating the mean of all item responses, resulting in a range from 1 to 5. A mean score of 3 or above is indicative of moderate to severe oscillopsia. Previous evaluations demonstrated that the OSQ exhibits good internal consistency (29).

2.4 Data analysis

Initially, confirmatory factor analysis (CFA) was performed to assess how well the data aligned with the preliminary version BVQ's predefined factor structure. In cases where the CFA results indicated a poor model fit, an exploratory factor analysis (EFA) was subsequently conducted to further investigate the underlying factor structure and to identify any deviations from the preliminaryversion of the BVQ dimensions (30). Following this, the refined model underwent another round of CFA to validate its construct validity (30). Additional psychometric assessments included convergent validity, known-groups validity, examination of structural characteristics, internal consistency, and test–retest reliability. These steps are visually summarized in the flowchart presented in Figure 1. (created by Napkin.ai). All statistical procedures were conducted using R (version 4.3.1; R Foundation for Statistical Computing, Vienna, Austria) (31).

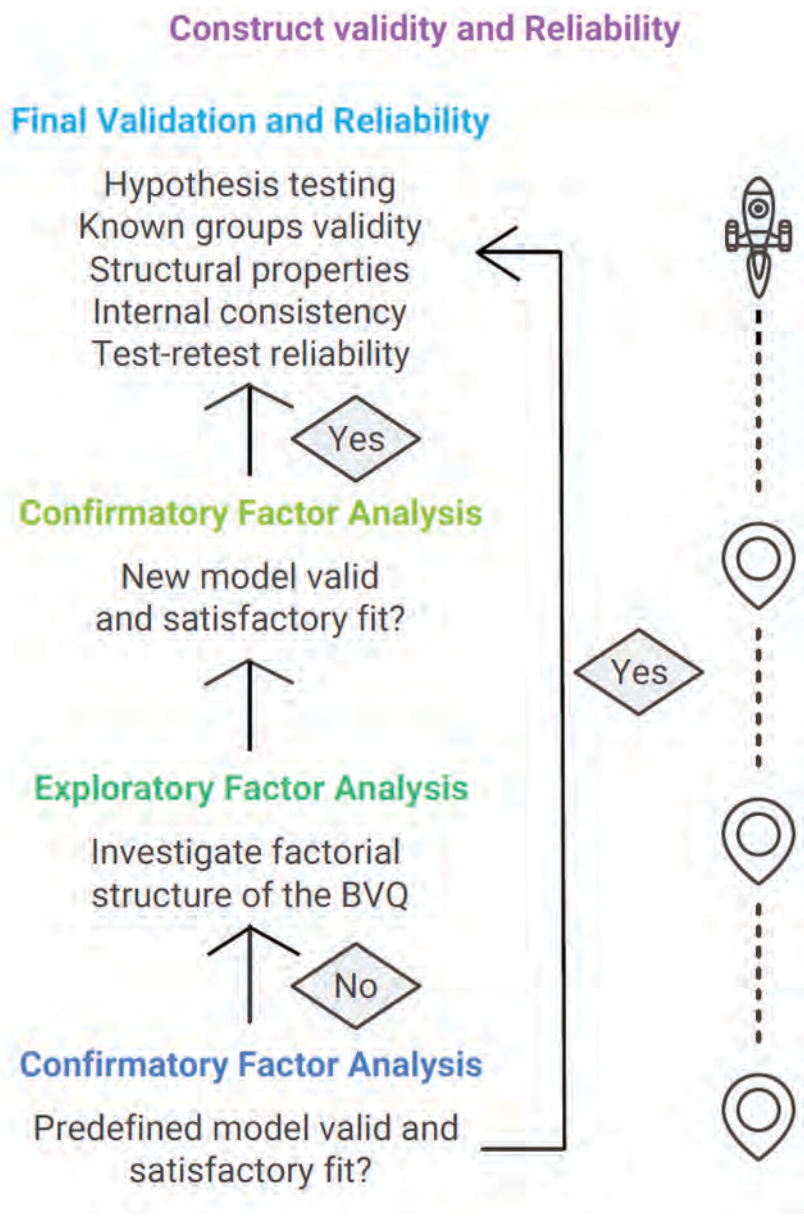


Figure 1. The flowchart of the adapted BVQ validation process

2.4.1 *Construct validity*

2.4.1.1 *Confirmatory and exploratory factor analyse*

To determine whether the original factor structure could be replicated in the new dataset from chronic UVH patients, a CFA was performed using robust maximum likelihood estimation. Goodness-of-fit indices were analyzed to evaluate how well the model aligned with the data. The adequacy of model fit was assessed through several fit indices, including the goodness-of-fit index (GFI), adjusted goodness-of-fit index (AGFI), chi-square index, comparative fit index (CFI), Tucker-Lewis Index (TLI), the root mean square error of approximation (RMSEA), and standardized root mean square residual (SRMR). A model was considered to have a "good fit" if the chi-square index was insignificant, CFI and TLI values were greater than 0.90, and both SRMR and RMSEA values were below 0.08 (32, 33).

Convergent validity was evaluated to investigate whether measures of the target construct were correlated with similar constructs from other tests, described below. Discriminant validity ensures that constructs are distinct, by checking that unrelated constructs have low correlations. Discriminant validity was deemed satisfactory when the correlation coefficients between constructs remained below 0.80 (34).

If the model fit was found to be unsatisfactory, an EFA was conducted to further examine the underlying structure of the preliminary BVQ, excluding the four VAS items. To assess the suitability of the data for factor analysis, the Kaiser-Meyer-Olkin (KMO) measure of sampling adequacy was calculated, with values exceeding 0.80 interpreted as indicative of good sampling adequacy (35). In addition, Bartlett's test of sphericity was applied to assess whether the correlation structure was appropriate for factor analysis; a significance level of $p < 0.05$ was used as the criterion for suitability (35). The scree plot was analyzed to determine the number of constructs with eigenvalues >1 (35). Exploratory factor analysis was conducted using principal component analysis with oblique rotation (direct oblimin), applying a cutoff of 0.60 for item loadings. Based on the results of the EFA, if the adapted version of the BVQ was deemed most suitable, then this adapted version was used in all subsequent psychometric analyses.

2.4.1.2 *Convergent validity*

Convergent validity was assessed by testing predefined hypotheses regarding the relationships between (adapted) BVQ constructs and other PROMs. These hypotheses are visually summarized in Figure 2, which illustrates the expected direction (positive or negative) and strength (weak or moderate) of the correlations. Each arrow in the figure represents a hypothesized association. Constructs from the adapted BVQ were correlated with relevant measures (e.g., HUI-3, DHI, HADS) to evaluate conceptual alignment and

establish convergent validity. The hypotheses and the strength of correlation coefficients were analyzed using either Pearson correlation or Spearman's rank-order correlation, based on the normality of the data distribution. Correlation coefficients were categorized as very strong (>0.90), strong (0.70–0.90), moderate (0.50–0.70), weak (0.30–0.50), or very weak/absent (<0.30). A p-value significance level was set at 0.05 (36).

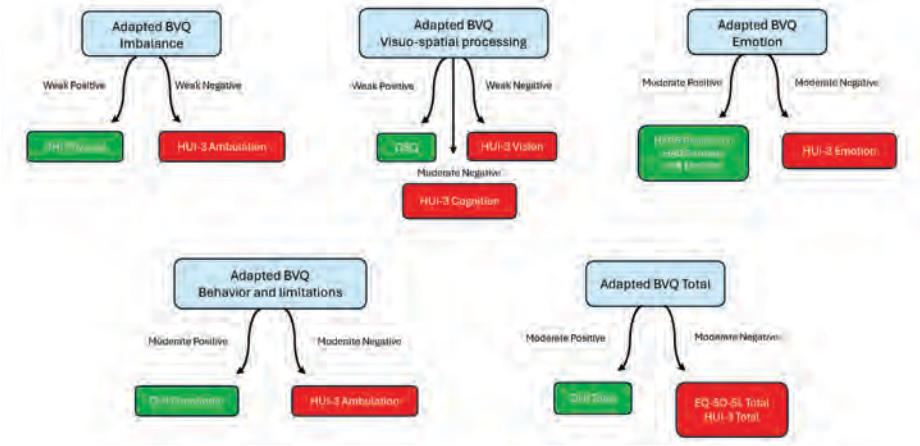


Figure 2. Predefined hypotheses for convergent validity between adapted BVQ and other PROMs

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2.4.1.3 *Known groups validity*

Known groups validity was assessed comparing mean (adapted) BVQ scores across predefined categories, expected to show distinct score patterns. Specifically, four groups were classified based on DHI scores: no handicap (0–15 points), mild handicap (16–34 points), moderate handicap (36–52 points), and severe handicap (54+ points). It was hypothesized that individuals reporting more severe dizziness-related limitations, reflected by higher DHI scores, would also demonstrate elevated BVQ scores, in contrast to those with minimal or no perceived handicap. To test this hypothesis, statistical differences in BVQ scores among the four DHI severity levels were analyzed using either a one-way analysis of variance (ANOVA) or the Kruskal-Wallis test, depending on the distribution of the data. Where significant differences were detected, post-hoc comparisons were performed using the Bonferroni correction. A p-value less than 0.05 was considered statistically significant (37).

2.4.2 *Structural Properties*

The score distributions for each BVQ item were illustrated using stacked bar charts. Floor and ceiling effects were assessed by examining the proportion of respondents who selected the minimum or maximum possible scores. An item was considered to exhibit a

floor or ceiling effect if 15% or more of participants reported the lowest or highest score, respectively (38).

2.4.3 *Reliability*

2.4.3 *Internal consistency*

Cronbach's alpha was calculated for each (adapted) BVQ construct individually to assess the internal consistency of the items within each construct. A low Cronbach's alpha indicated weak or no correlation among items within the same construct, while a very high value suggested that the items measured the same concept. An optimal Cronbach's alpha was considered to be within the range of 0.70 to 0.95 (39).

2.4.3.2 *Test-retest reliability*

During the second testing phase, patients were invited to complete the preliminary BVQ again seven days after the initial administration, in order to evaluate test–retest reliability. To quantify the consistency of responses over time, the intraclass correlation coefficient (ICC) was computed for each item. A two-way mixed-effects model based on absolute agreement was used to calculate the ICC values along with their corresponding 95% confidence intervals. An ICC value of 0.70 or higher was interpreted as indicating good reliability.

2.5 Ethical considerations

This study was conducted in compliance with the legislation and ethical standards on human research, adhering to the principles of the Declaration of Helsinki (amended version 2013). The study protocol was approved as non-WMO (Wet Medisch-Wetenschappelijk Onderzoek) research by the medical ethical testing committee of the University Maastricht/ academic hospital Maastricht (UM/MUMC+) as well as receiving consent from the advisory board of the MUMC+ (METC 2024-0183). Written informed consent was obtained from all patients participating in this study.

3 RESULTS

A total of 100 patients diagnosed with UVH [55% male, mean age 64.1 ± 10.8 years (range: 29–90 years)] completed a set of PROMs, with 98% participating online and 2% completing paper-based questionnaires. The etiologies of UVH were distributed as follows: 33% infection or inflammation, 22% neoplasm, 19% Menière's disease, 10% idiopathic, 5% vestibular migraine, 5% overlapping Meniere's disease and vestibular migraine, 3% iatrogenic causes, and 1% metabolic, autoimmune disorders, or benign recurrent vertigo.

Additionally, 28% of patients developed secondary persistent postural-perceptual dizziness (PPPD), and 10% had secondary benign paroxysmal positional vertigo (BPPV). The duration of symptoms varied widely, ranging from 5 months to 30 years. All patients underwent video head impulse testing (vHIT), 67 patients had left-sided UVH, and 33 had right-sided UVH. Similarly, caloric testing indicated left-sided involvement in 59 patients and right-sided involvement in 34 patients, while 7 patients could not undergo caloric testing due to conditions such as a radical cavity, closed ear canal, or surgical occlusion. The mean absolute caloric responses (sum of warm and cold irrigations) were 49.3 ± 14.9 on the healthy side and 7.6 ± 5.4 on the pathological side, with a mean interaural asymmetry of 73.7 ± 31.6%. The mean horizontal vHIT vestibulo-ocular reflex (VOR) gain was 0.93 ± 0.08 on the healthy side and 0.47 ± 0.14 on the pathological side, resulting in a mean VOR gain asymmetry of 34.18 ± 13.42%.

3.2 Construct validity

3.2.1 *Confirmatory and exploratory factor analyses*

The CFA conducted on a predefined model, developed during the initial content validation phase, did not achieve an adequate model fit. As a result, all 50 Likert-scale items from the initial model were subjected to an EFA using oblique rotation (direct oblimin) to reassess the underlying structure. The KMO measure of sampling adequacy was 0.91, indicating excellent sampling adequacy for factor analysis. Additionally, Bartlett's test of sphericity confirmed the appropriateness of the correlation matrix, yielding a significant result [$X^2(1225) = 5273.66$, $p < 0.001$]. The scree plot suggested a four factor structure for the 50 Likert-type items (Supplementary Figure S1). Applying a factor loading threshold of >0.60, the EFA resulted in a 16 item solution, which explained 65% of the variance (Table 1 and Supplementary Table S2). The resulting constructs were identified as "Imbalance", "Emotion", "Behavior and limitations", and a newly emerged construct, "Visuo-spatial processing". This fourth construct incorporated two items previously linked to oscillopsia and three items from the cognition domain of the original BVQ. Further details regarding item retention, removal, and statistical results from the EFA are provided in Supplementary Tables S2–S4.

Table 1. Adapted BVQ constructs, items, and response options for patients with chronic UVH

Construct/Item		Answer scale
Imbalance		
1	I experience imbalance during daily activities.	1 (never) – 6 (always)
2	I experience imbalance when walking on uneven surfaces (like in the woods, at the beach or in the snow).	1 (never) – 6 (always)
3	I experience imbalance when walking in reduced light.	1 (never) – 6 (always)
4	I experience imbalance while changing positions (such as crouching, bending down, reaching or standing up).	1 (never) – 6 (always)
Visuo-spatial processing		
5	I have blurred vision while walking.	1 (never) – 6 (always)
6	I have blurred vision while travelling (such as being on a train, bus, car or on a bike).	1 (never) – 6 (always)
7	I easily get lost in new places.	1 (never) – 6 (always)
8	I find it difficult to judge distances.	1 (never) – 6 (always)
9	I find it difficult to concentrate.	1 (never) – 6 (always)
Behavior and limitations		
10	I avoid daily life activities.	1 (never) – 6 (always)
11	I avoid performing vigorous activities.	1 (never) – 6 (always)
12	I avoid travelling.	1 (never) – 6 (always)
13	I need to perform daily activities slower.	1 (never) – 6 (always)
Emotion		
14	I feel happy.	1 (never) – 6 (always)
15	I worry a lot.	1 (never) – 6 (always)
16	I feel sad.	1 (never) – 6 (always)

A CFA was subsequently conducted on the adapted version of BVQ model. The overall goodness-of-fit indices indicated an acceptable model fit. The chi-square test was significant [$X2(98)= 218.56$, ($N=100$), $p < 0.001$]. Although the RMSEA value (0.10) exceeded the commonly accepted threshold for a good fit (≤0.08), the model demonstrated acceptable fit based on other indices, including CFI (0.90), TLI (0.88) and SRMR (0.06). These results suggested that the model sufficiently represented the underlying data structure, despite the RMSEA value being slightly higher. Furthermore, inter-construct correlation coefficients ranged from 0.54 to 0.68, remaining below the 0.80 threshold, thereby providing evidence for discriminant validity. A graphical depiction of the structural equation model for the 16-item version is shown in Supplementary Figure S2.

3.2.2 *Convergent validity*

Several significant correlations were obtained between the adapted version of BVQ scores and measures of health and dizziness-related quality of life.

1. The adapted BVQ total score showed a strong negative correlation with HRQoL as measured by the EQ-5D-5L index score (Spearman's rho = −0.77, $p < 0.001$), and the HUI-3 overall utility score (Pearson's r = −0.72, $p < 0.001$).
2. The adapted BVQ total score was strongly positively correlated with the DHI total score (Pearson's r = 0.89, $p < 0.001$).
3. The adapted BVQ emotion construct had a moderate correlation with anxiety and depression levels measured by the HADS Anxiety and Depression subscales (Spearman's rho = 0.56 and 0.69, $p < 0.001$, respectively). It also a moderate positive correlation with the DHI emotional subscale (Spearman's rho = 0.54, $p < 0.001$). There was a moderate negative correlation between the adapted BVQ emotion construct and the HUI-3 emotion score (Spearman's rho = −0.59, $p < 0.001$).
4. The visuo-spatial processing scores of the adapted BVQ showed a strong positive correlation with the Oscillopsia Severity Questionnaire (OSQ) total scores (Spearman's rho = 0.76, $p < 0.001$). Additionally, it showed a moderate negative correlation with the HUI-3 cognition score (Spearman's rho = −0.58, $p < 0.001$), and weak negative correlation with HUI-3 vision attribute utility score (Spearman's rho = −0.43, $p < 0.001$).
5. The adapted BVQ imbalance construct was moderately positively correlated with the DHI physical subscale (Spearman's rho = 0.59, $p < 0.001$), and showed a weak negative correlation with the HUI-3 ambulation score (Spearman's rho = −0.48, $p < 0.001$).
6. Scores in the adapted BVQ behavior and limitations construct showed a strong positive correlation with the DHI functional subscale (Spearman's rho = 0.85, $p < 0.001$), and a moderate negative correlation with the HUI-3 ambulation attribute utility score (Spearman's rho = −0.63, $p < 0.001$).

3.2.3 *Known groups validity*

A statistically significant difference in total adapted BVQ score was observed across the DHI severity groups, as indicated by one-way ANOVA [$F(3) = 70.32$, $p < 0.001$]. Subsequent Bonferroni-adjusted post-hoc analyses confirmed that the total BVQ score differed significantly between all groups (Figure 3 and Supplementary Tables S5, S6).

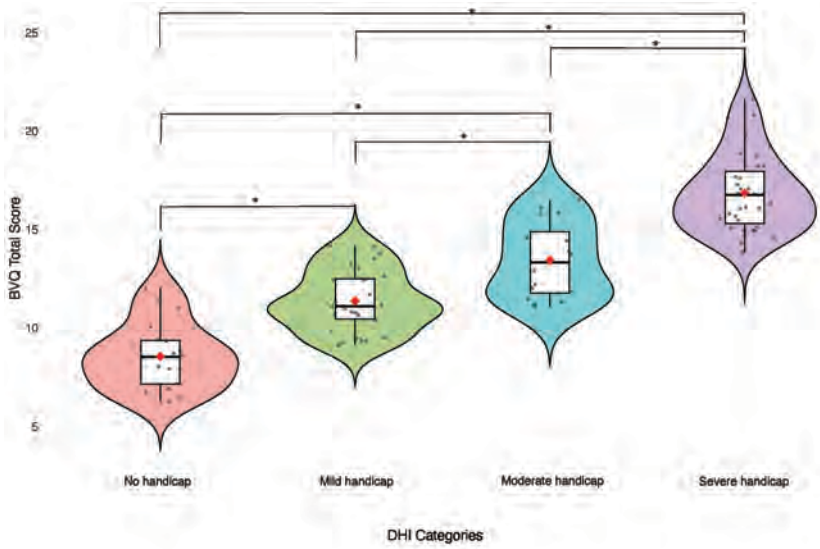


Figure 3. Violin plots illustrating the total adapted BVQ scores by DHI-based handicap groups. Squares within each violin plot indicate mean scores. Asterisks (*) illustrate statistically significant differences. The wider sections of violin plots indicate a higher data density, whereas narrower sections reflect lower data density.

3.3 Structural properties

The structural properties analysis confirmed that all items covered the complete spectrum of response options (Figure 4), with no missing values observed. Floor effects were identified in items related to visuo-spatial processing (items 8, 9, 17, and 18), emotion (item 33), and behavior and limitations (items 36, 42, and 47). Ceiling effects were observed in items assessing imbalance (items 2, 3, and 7) and behavior and limitations (item 47).

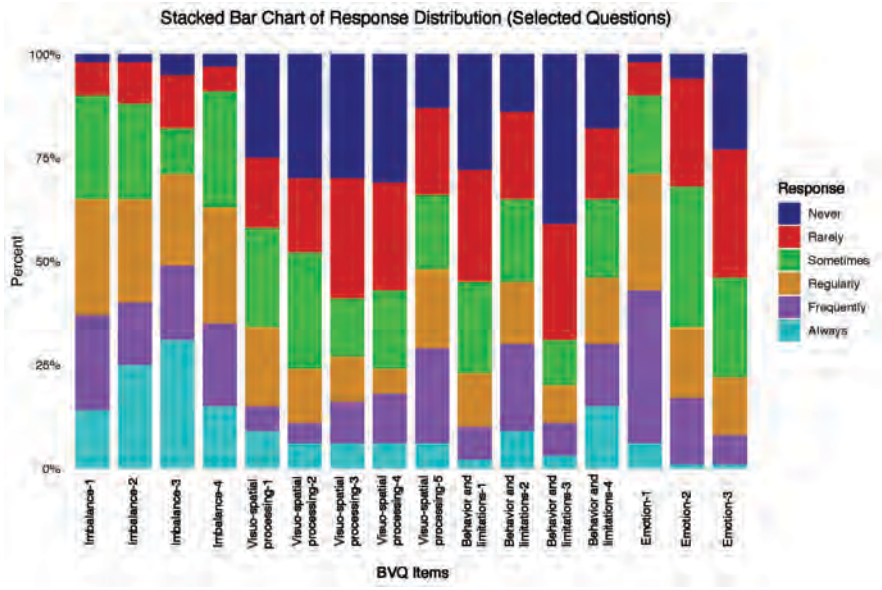


Figure 4. Stacked bar chart of response distribution of the adapted BVQ in chronic UVH patients.

3.4 Reliability

3.4.1 *Internal consistency*

Each of the adapted BVQ constructs exhibited Cronbach's alpha coefficients between 0.70 and 0.95, which reflects strong internal consistency and indicating that the items within each scale were homogeneously related. Detailed reliability coefficients for each construct are presented in Table 2.

Table 2. Internal consistency of adapted BVQ in patients with chronic UVH (Cronbach's alpha per construct)

Construct	Cronbach's alpha[a]
Imbalance	0.93 (0.90-0.95)
Visuo-spatial processing	0.90 (0.87-0.93)
Behavior and limitations	0.85 (0.89-0.92)
Emotion	0.87 (0.81-0.91)

3.4.2 *Test–retest reliability*

Sixty percent of participants completed the test–retest evaluation, with a mean age of 64.5 years (SD = 10.4; range: 29–90), and 53% identifying as male. The average time interval between the initial and follow-up assessments was 7±2 days. The ICCs for both the Likert-

scale and VAS items demonstrated strong test–retest reliability, as all items surpassed the commonly accepted threshold of 0.70, except for the final item, which showed a slightly lower ICC of 0.61 (Table 3). Mean scores and standard deviations for individual items remained highly consistent, which indicated minimal variation between the two assessments.

Table 3. Intraclass correlation coofficient (ICC) for adapted BVQ test (T1) and retest (T2) in patients with chronic UVH (N = 60).

Item	T1	T2		
	Mean±SD	Mean±SD	ICC	95%
Imbalance				
1	3.93±1.20	3.85±1.25	0.73	0.58-0.83
2	4.03±1.38	4.11±1.42	0.79	0.67-0.87
3	4.11±1.62	4.00±1.48	0.77	0.64-0.86
4	4.00±1.31	3.95±1.33	0.73	0.58-0.83
Visuo-spatial processing				
5	2.85±1.57	2.85±1.57	0.80	0.68-0.87
6	2.58±1.47	2.71±1.56	0.80	0.68-0.87
7	2.48±1.42	2.46±1.37	0.82	0.71-0.89
8	2.68±1.57	2.71±1.51	0.89	0.82-0.93
9	3.33±1.41	3.21±1.43	0.82	0.72-0.89
Behavior and limitations				
10	2.48±1.26	2.33±1.09	0.70	0.54-0.81
11	3.35±1.51	3.33±1.58	0.86	0.77-0.91
12	2.25±1.42	2.16±1.16	0.80	0.68-0.87
13	3.38±1.60	3.40±1.57	0.77	0.65-0.86
Emotion				
14	4.10±1.17	4.25±1.24	0.86	0.77-0.91
15	3.11±1.16	3.10±1.18	0.84	0.75-0.90
16	2.41±1.19	2.33±1.06	0.85	0.76-0.91
Visual analog scale items				
17	38.70±28.03	44.36±30.16	0.71	0.55-0.82
18	51.86±29.59	56.71±29.23	0.70	0.55-0.81
19	26.11±27.13	30.73±30.33	0.76	0.63-0.85
20	65.83±21.48	67.71±17.31	0.61	0.42-0.74

4 DISCUSSION

This study provides preliminary evidence for the construct validity and reliability of the adapted BVQ in assessing the impact of chronic UVH. Through EFA, the questionnaire was refined into a 16 Likert-type items model, which demonstrated an acceptable fit in CFA. Additionally, four VAS items were also included. Convergent validity was supported by significant associations with measures of health-related quality of life, dizziness-related handicap, emotional well-being, imbalance, cognition and oscillopsia. Known-groups validity was confirmed by significant differences in adapted BVQ scores across DHI severity levels. Reliability analysis revealed strong internal consistency and robust test-retest reliability, which reinforces the adapted BVQ's suitability for both clinical practice and research in chronic UVH populations.

The main difference between the validated BVQ for BVP and the adapted version for chronic UVH lies in their factor structures and item compositions. While the original BVQ includes 24 items across four constructs, the adapted version comprises 20 items reorganized into revised constructs, such as visuo-spatial processing and behavior and limitations. These changes reflect both statistical results and clinical differences between the two populations.

In the adapted version, several items from the original oscillopsia and cognition constructs were reassigned to the new visuo-spatial processing construct due to conceptual and functional overlap. For example, items like "I have blurred vision while walking" and "I have blurred vision while travelling" involve dynamic visual instability, but also reflect difficulties in processing dynamic visual information during movement. Similarly, items such as "I easily get lost in new places", "I find it difficult to judge distances", and "I find it difficult to concentrate", originally categorized under cognition, are closely linked to spatial orientation and visual interpretation of the environment. The merging of these items likely occurred because patients with chronic UVH tend to experience visual and cognitive symptoms not as separate issues, but as interconnected challenges that affect their ability to navigate and function in daily life. These tasks often require simultaneous processing of visual, spatial, and cognitive inputs. This integration is supported by prior evidence that vestibular input plays a critical role in spatial memory, orientation, and visual stability (40, 41). Therefore, the reorganization into a visuo-spatial processing construct better reflects what chronic UVH patients experience, as presented by previous literature (4).

In the final CFA analysis of the adapted BVQ, most fit indices indicated good model fit. However, RMSEA was unexpectedly high at 1.0, suggesting poor fit. This could be due to the limited sample size or restrictions placed on how items relate to each other (model

constraints) (33, 42). Since RMSEA is sensitive to these factors, it should be interpreted alongside other fit indices.

The findings supported the predefined hypotheses for convergent validity, with the exception of the visuo-spatial processing construct. As expected, the adapted BVQ total scores demonstrated a strong correlation with generic measures such as the EQ-5D-5L and the HUI-3. While a prior study in the BVP population reported moderate correlations (21), the stronger correlations in the present study may represent differences in population characteristics or the adapted structure of the BVQ. These findings suggest that, although the EQ-5D-5L and HUI-3 assess broad health areas, they still capture symptoms like mobility, emotion, and self-care, which are important for patients with chronic UVH. This supports the adapted BVQ's potential to reflect overall health status in this population (16) (manuscript submitted). Furthermore, the adapted version of the BVQ remains a more targeted instrument, as it directly assesses the functional, emotional, and physical challenges unique to this population. When analyzing total scores, the adapted BVQ showed a strong correlation with the total scores of DHI, which confirms its relevance in assessing the impact of chronic UVH. When examining the correlation between specific subdomains, the functional subscale of the DHI exhibited a strong correlation with the behavior and limitations of the adapted BVQ. In contrast, the physical subscale of the DHI showed a moderate correlation with the adapted BVQ imbalance construct. This is particularly crucial, as certain physical items in the DHI assess walking difficulties, which are also a key component of the adapted BVQ imbalance domain. However, not all items in the DHI physical subscale directly address imbalance-related issues. For instance, item such as "Does looking up increase your problem?" is less specific compared to the more targeted content of the adapted BVQ. This finding demonstrates the importance of assessing imbalance as a distinct construct with targeted items tailored to the symptoms and challenges specific to chronic UVH.

Regarding the visuospatial processing construct, while only two of the five items directly address oscillopsia, a strong correlation with the OSQ was observed. This was unexpected, as we initially hypothesized a weak correlation. One possible explanation is that the remaining items may still capture aspects of dynamic visual instability. Alternatively, it may reflect that in chronic UVH, patients experience oscillopsia, cognitive, and visuo-spatial difficulties as overlapping symptoms, rather than as distinct domains (40, 41). These results demonstrate the need for further study on content validity to ensure that each construct clearly represents its intended symptoms.

The adapted BVQ demonstrated strong structural properties, with responses covering the full range of options and no missing data. Ceiling effects were evident in several items,

particularly in imbalance domains, reflecting the prominence of these symptoms in chronic UVH. This is consistent with findings from the original BVQ study in BVP patients (21), where imbalance was also a dominant domain. However, unlike in BVP, where oscillopsia items showed clear ceiling effects, our study revealed floor effects in the visuo-spatial processing construct, which includes two oscillopsia-related items. This difference likely reflects the preserved vestibular function and central compensation in chronic UVH, which reduce the severity and prevalence of oscillopsia (3, 4, 12). Nevertheless, capturing oscillopsia remains important for those chronic UVH patients who do report such symptoms.

Limitations

This study has several limitations. First, the development and content validity phases were not conducted specifically for chronic UVH. Unlike the validated BVQ for BVP, which followed COSMIN guidelines and included expert input and cognitive interviews, the adapted version for chronic UVH has not undergone such a tailored development process. As a result, formal evidence of its content validity is currently lacking. Secondly, there was variability in the time interval between diagnosis of UVH and the administration of the survey, which differed across patients. As a result, potential changes in vestibular function over time cannot be ruled out, which may affect the findings.

5 CONCLUSION

Taking the results of this study into account, this study provides preliminary evidence for the construct validity and reliability of the adapted BVQ in assessing the impact of chronic UVH. It demonstrates solid psychometric properties, and the content originally developed for BVP also appears to capture the symptomatology of chronic UVH. This suggests that the adapted BVQ can help identify the most pertinent items for this population. However, further research should include cognitive interviews and expert panels to establish a PROM specifically tailored for chronic UVH. Afterwards, this established questionnaire can be renamed as Unilateral Vestibulopathy Questionnaire (UVQ).

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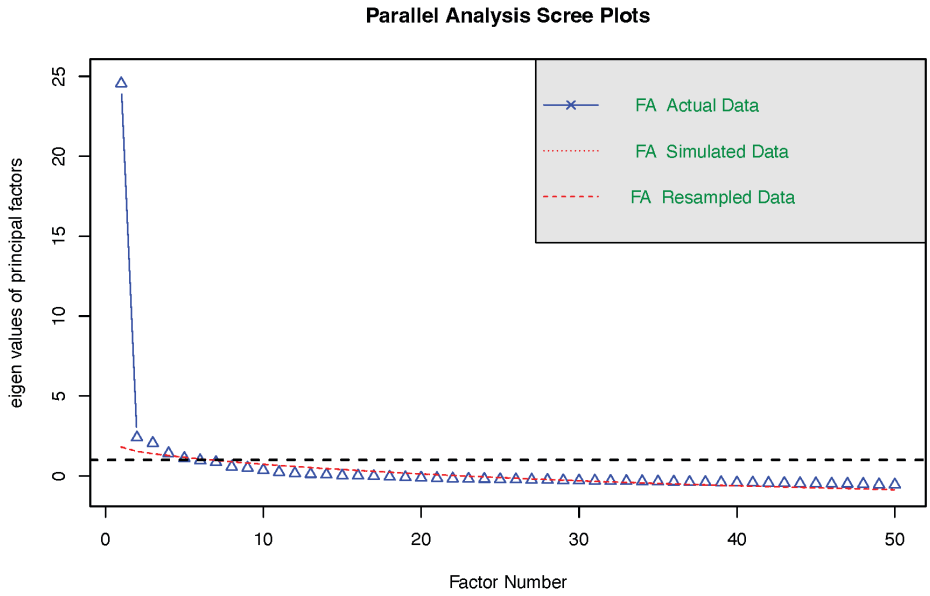
SUPPLEMENTARY MATERIALS

Supplementary Table S1. BVQ constructs, items, and response options after the development and content validity phase (from van Stiphout et al. 2022). The items were developed in Dutch for the Dutch population. These items were translated into English for the purpose of the publication (from van Stiphout et al. 2022).

	Construct/Item	Answer scale
Imbalance		
1	I experience imbalance during daily activities.	1 (never) – 6 (always)
2	I experience imbalance when walking on uneven surfaces (like in the woods, at the beach or in the snow).	1 (never) – 6 (always)
3	I experience imbalance when walking in reduced light.	1 (never) – 6 (always)
4	When walking, I need to pay attention to the ground to avoid falling	1 (never) – 6 (always)
5	I have fallen	1 (never) – 6 (always)
6	I have come close to falling	1 (never) – 6 (always)
7	I experience imbalance while changing positions (such as crouching, bending down, reaching or standing up).	1 (never) – 6 (always)
Oscillopsia		
8	I have blurred vision while walking.	1 (never) – 6 (always)
9	I have blurred vision while travelling (such as being on a train, bus, car or on a bike).	1 (never) – 6 (always)
10	When walking, I have to stand still to recognize faces or the read (road) signs.	1 (never) – 6 (always)
11	I have blurred vision while chewing on my food.	1 (never) – 6 (always)
12	I have blurred vision when quickly turning my head.	1 (never) – 6 (always)
Other physical symptoms		
13	I experience difficulties with fast head movements, like turning my head to the right or left when crossing the street.	1 (never) – 6 (always)
14	I experience light-headedness when standing up fast.	1 (never) – 6 (always)
15	I feel tired.	1 (never) – 6 (always)
Cognition		
16	I must pay close attention to my balance.	1 (never) – 6 (always)
17	I easily get lost in new places.	1 (never) – 6 (always)
18	I find it difficult to judge distances.	1 (never) – 6 (always)
19	I am forgetful.	1 (never) – 6 (always)
20	I find it difficult to concentrate.	1 (never) – 6 (always)
21	I experience difficulties with doing more than one thing at a time.	1 (never) – 6 (always)
22	I experience difficulties with doing things while walking.	1 (never) – 6 (always)
Emotion		
23	I feel happy	1 (never) – 6 (always)
24	I worry a lot	1 (never) – 6 (always)
25	When performing daily activities, I feel confident.	1 (never) – 6 (always)
26	I feel lonely	1 (never) – 6 (always)
27	I am afraid to fall.	1 (never) – 6 (always)
28	I feel I have control over my life.	1 (never) – 6 (always)
29	I am bothered by fast movements surrounding me.	1 (never) – 6 (always)
30	I am bothered by noisy environments.	1 (never) – 6 (always)
31	I am bothered by busy environments surrounding me.	1 (never) – 6 (always)
32	I don’t feel confident when performing daily activities.	1 (never) – 6 (always)

Supplementary Table S1. *Continued*

Construct/Item		Answer scale
33	I feel sad.	1 (never) – 6 (always)
34	I am embarrassed by my balance problems.	1 (never) – 6 (always)
Behavior and limitations		
35	I feel limited in daily life activities.	1 (never) – 6 (always)
36	I avoid daily life activities.	1 (never) – 6 (always)
37	I feel limited when performing vigorous activities.	1 (never) – 6 (always) – N/A
38	I avoid performing vigorous activities.	1 (never) – 6 (always) – N/A
39	I feel limited when performing moderate activities.	1 (never) – 6 (always)
40	I avoid performing moderate activities.	1 (never) – 6 (always)
41	I feel limited in travelling.	1 (never) – 6 (always)
42	I avoid travelling.	1 (never) – 6 (always)
43	I feel limited when driving a car.	1 (never) – 6 (always) – N/A
44	I avoid driving a car.	1 (never) – 6 (always) – N/A
45	I feel limited in my social activities.	1 (never) – 6 (always)
46	I avoid social activities.	1 (never) – 6 (always)
47	I need to perform daily activities slower.	1 (never) – 6 (always
Social life		
48	My symptoms negatively affect my close relationships.	1 (never) – 6 (always)
49	People don't understand my problem.	1 (never) – 6 (always)
50	I need the help of other people to perform daily activities.	1 (never) – 6 (always)
VAS scale questions		
51	How limited do you feel in daily life? The scale below is numbered from 0 to 100. 0 means that you are not limited in daily life. 100 means that you are extremely limited in daily life. Mark an X on the scale to indicate how much you feel limited in daily life.	Scale 0 (not limited in daily life) – 100 (extremely limited in daily life)
52a	What is the most important problem you would like to have improved? Please fill in your answer here:	Open answer
52b	How much does this problem affect your life (see the answer you filled in at question 52a)? The scale below is numbered from 0 to 100. 0 means the problem does not affect your life. 100 means the problem affects your life extremely. Mark an X on the scale to indicate how much you suffer from this symptom.	Scale 0 (no suffering) – 100 (extreme suffering)
53	How hopeful are you that you will get better? The scale below is numbered from 0 to 100. 0 means you are not hopeful that you will get better. 100 means you are extremely hopeful that you will get better. Mark an X on the scale to indicate how hopeful you are that you will get better.	Scale 0 (not hopeful) – 100 (extremely hopeful)
54	How would you rate your health today? The scale below is numbered from 0 to 100. 0 means your health is extremely bad. 100 means your health is extremely good. Please note: the scale below is marked from 'extremely bad' (0) to 'extremely good' (100). Mark an X on the scale to indicate how you feel today.	Scale 0 (extremely bad) – 100 (extremely good)



Supplementary Figure S1. Scree plot indicating that four factors would be suitable for the 50 Likert-type items of the BVQ.

Supplementary Table S2. Eigenvalues, percentages of variances and cumulative percentages for the 4 factors from the exploratory factor analysis

Total variance explained			
Factor	**Eigenvalue**	**% of variance**	**Cumulative %**
1	25.04	50.08	50.08
2	2.90	5.80	55.88
3	2.59	5.18	61.06
4	1.96	3.92	64.98

Supplementary Table S3. Exploratory factor analysis with the items of the adapted BVQ in patients with chronic UVH

Items	Factors				Constructs
	1	2	3	4	
BVQ-Q1	0.82				Imbalance
BVQ-Q2	0.81				
BVQ-Q3	0.84				
BVQ-Q7	0.80				
BVQ-Q36		0.78			Behavior and limitations
BVQ-Q38		0.82			
BVQ-Q42		0.76			
BVQ-Q47		0.68			
BVQ-Q8			0.77		Visuo-spatial processing
BVQ-Q9			0.75		
BVQ-Q17			0.73		
BVQ-Q18			0.85		
BVQ-Q20			0.73		
BVQ-Q23				-0.68	Emotion
BVQ-Q24				0.63	
BVQ-Q33				0.63	

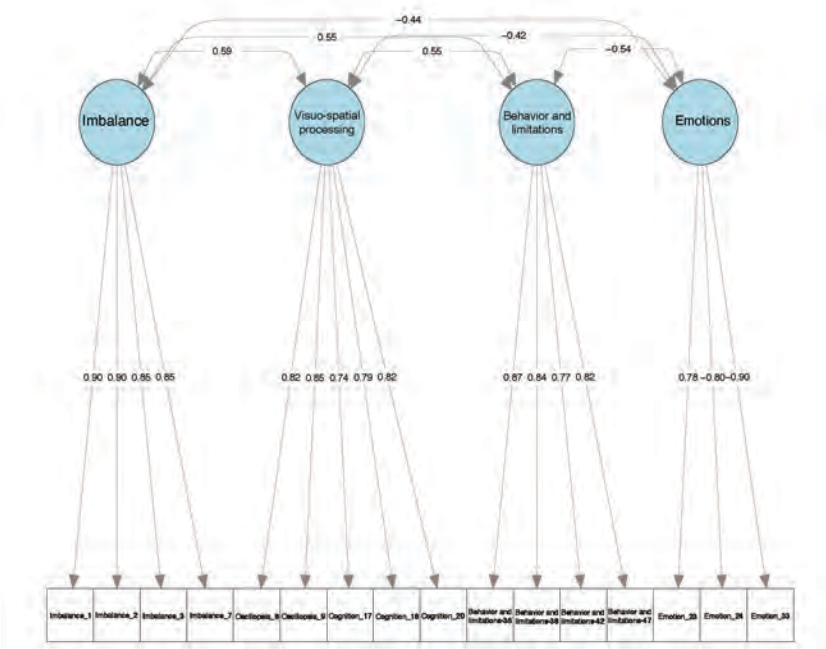
Supplementary Table S4. Adapted version of the BVQ following the Exploratory Factor Analysis (from van Stiphout et al. 2022). The items were developed in Dutch for the Dutch population. These items were translated into English for the purpose of the publication (from van Stiphout et al. 2022). Removed items are shown in red.

Construct/Item		Answer scale
Imbalance		
1	I experience imbalance during daily activities.	1 (never) – 6 (always)
2	I experience imbalance when walking on uneven surfaces (like in the woods, at the beach or in the snow).	1 (never) – 6 (always)
3	I experience imbalance when walking in reduced light.	1 (never) – 6 (always)
4	When walking, I need to pay attention to the ground to avoid falling	1 (never) – 6 (always)
5	I have fallen	1 (never) – 6 (always)
6	I have come close to falling	1 (never) – 6 (always)
7	I experience imbalance while changing positions (such as crouching, bending down, reaching or standing up).	1 (never) – 6 (always)

Construct/Item		Answer scale
Oscillopsia		
8	I have blurred vision while walking.	1 (never) – 6 (always)
9	I have blurred vision while travelling (such as being on a train, bus, car or on a bike).	1 (never) – 6 (always)
10	When walking, I have to stand still to recognize faces or the read (road) signs.	1 (never) – 6 (always)
11	I have blurred vision while chewing on my food.	1 (never) – 6 (always)
12	I have blurred vision when quickly turning my head.	1 (never) – 6 (always)
Other physical symptoms		
13	I experience difficulties with fast head movements, like turning my head to the right or left when crossing the street.	1 (never) – 6 (always)
14	I experience light-headedness when standing up fast.	1 (never) – 6 (always)
15	I feel tired.	1 (never) – 6 (always)
Cognition		
16	I must pay close attention to my balance.	1 (never) – 6 (always)
17	I easily get lost in new places.	1 (never) – 6 (always)
18	I find it difficult to judge distances.	1 (never) – 6 (always)
19	I am forgetful.	1 (never) – 6 (always)
20	I find it difficult to concentrate.	1 (never) – 6 (always)
21	I experience difficulties with doing more than one thing at a time.	1 (never) – 6 (always)
22	I experience difficulties with doing things while walking.	1 (never) – 6 (always)
Emotion		
23	I feel happy	1 (never) – 6 (always)
24	I worry a lot	1 (never) – 6 (always)
25	When performing daily activities, I feel confident.	1 (never) – 6 (always)
26	I feel lonely	1 (never) – 6 (always)
27	I am afraid to fall.	1 (never) – 6 (always)
28	I feel I have control over my life.	1 (never) – 6 (always)
29	I am bothered by fast movements surrounding me.	1 (never) – 6 (always)
30	I am bothered by noisy environments.	1 (never) – 6 (always)
31	I am bothered by busy environments surrounding me.	1 (never) – 6 (always)
32	I don't feel confident when performing daily activities.	1 (never) – 6 (always)
33	I feel sad.	1 (never) – 6 (always)
34	I am embarrassed by my balance problems.	1 (never) – 6 (always)
Behavior and limitations		
35	I feel limited in daily life activities.	1 (never) – 6 (always)
36	I avoid daily life activities.	1 (never) – 6 (always)
37	I feel limited when performing vigorous activities.	1 (never) – 6 (always) – N/A

Supplementary Table S3. *Continued*

Construct/Item		Answer scale
38	I avoid performing vigorous activities.	1 (never) – 6 (always) – N/A
39	I feel limited when performing moderate activities.	1 (never) – 6 (always)
40	I avoid performing moderate activities.	1 (never) – 6 (always)
41	I feel limited in travelling.	1 (never) – 6 (always)
42	I avoid travelling.	1 (never) – 6 (always)
43	I feel limited when driving a car.	1 (never) – 6 (always) – N/A
44	I avoid driving a car.	1 (never) – 6 (always) – N/A
45	I feel limited in my social activities.	1 (never) – 6 (always)
46	I avoid social activities.	1 (never) – 6 (always)
47	I need to perform daily activities slower.	1 (never) – 6 (always
Social life		
48	My symptoms negatively affect my close relationships.	1 (never) – 6 (always)
49	People don't understand my problem.	1 (never) – 6 (always)
50	I need the help of other people to perform daily activities.	1 (never) – 6 (always)



Supplementary Figure S2. A visual representation of the structural equation model of the 16-item adapted BVQ in patients with chronic UVH: Results of the final CFA

Supplementary Table S5. Mean total adapted BVQ scores by DHI-based handicap groups according to the total score classification

DHI classification	No handicap[a] N=19	Mild handicap[b] N=30	Moderate handicap[c] N=17	Severe handicap[d] N=34	ANOVA	
Mean BVQ	8.5±1.7	11.4±1.5	13.4±1.9	16.8±2.0	F(3)=58.9	p<0.001

[a]Patient scores ranging from 0 to 14 points for DHI total score were considered having no self-perceived dizziness related handicap.
[b]Patient scores ranging from 16 to 34 points for DHI total score were considered having mild self-perceived dizziness related handicap.
[c]Patient scores ranging from 36 to 52 points for DHI total score were considered having moderate self-perceived dizziness related handicap.
[d]Patient scores equal to or higher than 54 points for DHI total score were considered having severe self-perceived dizziness related handicap.

Supplementary Table S6. Bonferroni-corrected post-hoc results for adapted BVQ scores by DHI handicap groups

DHI categories		Mean BVQ total score difference	p value
No handicap	Mild handicap	-2.18	0.004
	Moderate handicap	-3.97	<0.001
	Severe handicap	-7.55	<0.001
Mild handicap	Moderate handicap	-1.78	0.038
	Severe handicap	-5.36	<0.001
Moderate handicap	Severe handicap	-3.58	<0.001

7

CHAPTER 7

Vestibular implants: The present status and future prospects

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ABSTRACT

Vestibular implant (VI) is a device designed to restore peripheral vestibular function in patients with bilateral vestibulopathy. It comprises three key components: gyroscopes and/or accelerometers, an external processor, and an implanted stimulator. The VI compensates for bilateral vestibular loss, by electrically stimulating the vestibular system. Candidates for implantation typically experience disabling chronic symptoms such as unsteadiness and oscillopsia. Multiple research groups demonstrated the feasibility of the vestibular implant in humans. It was shown that a VI is able to partially restore the vestibulo-ocular reflex, otolith responses, and improve quality of life.

1 INTRODUCTION

Bilateral vestibulopathy (BVP) is a heterogeneous condition that frequently results from bilaterally decreased peripheral vestibular function (1, 2). BVP may be diagnosed using criteria determined by the Bárány Society (3), which include a combination of vestibular symptoms and vestibular test results. The most reported symptoms in BVP patients are chronic unsteadiness and oscillopsia (4, 5). However, the vestibular system also contributes to various other activities such as spatial orientation and motion perception (6, 7). Besides these physical symptoms, BVP patients also report that their vestibular loss has a negative impact on their cognitive and social functioning (8). Consequently, BVP can decrease quality of life and have adverse socioeconomic effects (4, 9). The current documented prevalence of BVP ranges between 28-81 in 100 000 adults, but this might be an underestimation (10, 11). It can present with various clinical pictures, and is therefore often misdiagnosed (10, 12).

BVP can have many different etiologies such as meningitis, hereditary conditions, autoimmune disorders, neurodegenerative diseases, or ototoxicity (e.g., aminoglycosides) (12-14). Finding the true cause for BVP can be challenging. A definite or probable etiology may only be established in 49% to 80% of the cases. In other cases, the etiology remains idiopathic (15, 16). Unfortunately, currently there is no adequate treatment for restoring vestibular function. Treatment of BVP is mainly focused on rehabilitation strategies, generally using physiotherapy (17). However, despite intensive balance training and vestibular exercises, they often have a low yield, and BVP can not be treated adequately in most cases (17). In the 1960s, it was demonstrated by Cohen and Suzuki that compensatory eye movements and postural responses could be elicited by selective electrical stimulation of the ampullary branches of the vestibular nerve in monkeys and cats (18, 19). Ever since the first signs of success by (20), research has shown that rotational cues can be transmitted to the central nervous system by electrical stimulation of the vestibular nerves (21-25).

Based on the results obtained in animal studies and the growing success of cochlear implants (CIs), the concept of a vestibular implant (VI) arose. The aim of the VI, similar to a CI, is to bypass the dysfunctional sensory end-organ by directly stimulating its sensory nerves. This neuroprosthesis was developed and implanted during several clinical trials since 2007 (26). In this chapter, the general aspects of the VI will be discussed.

The Vestibular System

The inner ear, located in the temporal bone, consists of the vestibular organ and the cochlea. The vestibular organ contains five sensory structures, which are able to sense

head accelerations and gravity. Three semicircular canals (SCCs, i.e., the lateral, superior and posterior) capture rotational accelerations around three orthogonal axes. Two otolith organs (i.e., the utricle and saccule) mainly sense linear accelerations and gravity. By regulating the firing rate of the vestibular nerves, these five sensory structures supply head motion information to the central nervous system, leading to several reflexes and self-motion perception (27).

The vestibular nerves can be divided into regular-firing nerve fibres and irregular-firing nerve fibres which have different characteristics. Irregular-firing nerve fibres, when compared to regular-firing nerve fibres, are more sensitive to natural stimulation of the end organs and to electrical stimulation of the efferent system (28). The regular-firing nerve fibres have a resting discharge firing rate (baseline firing rate) of about 90 action potentials per second (pps). Head movements can change this firing rate. For example, a yaw rotation to the left leads to an increase in the firing rate of the nerve fibres in the lateral SCC (excitatory response). Depending on the velocity, the firing rate can go up to around 400 pps (29). In contrast, this movement in the right side leads to a decrease in the firing rate of these nerve fibres (inhibitory response). Depending on the velocity, the firing rate can become as low as 0 pps (30). The lateral SCC on the contralateral side shows an inverse response to the same movements. The two vestibular organs work in unison to provide information about head movements to the brain (push-pull system).

The motion-controlled modulation of the firing rate provides necessary information for several processes. The vestibulo-ocular reflex (VOR) generates compensatory eye movements upon head movements, providing gaze stabilization in dynamic situations, such as during walking and running. The vestibulospinal reflex (VSR) and vestibulocollic reflex (VCR) generate rapid compensatory body and neck movements to enable postural control and balance (31). Additionally, the vestibular system contributes to self-motion perception and spatial navigation. These processes require a complex integration of inputs not only from the vestibular system but also from the visual and somatosensory system (32, 33). Finally, the multiple vestibular projections are known to influence emotions, memory and cognition (7, 34). For more details about the anatomy and physiology of the vestibular system, see Chapter X.

2 GENERAL ASPECTS OF THE VESTIBULAR IMPLANT

The aim of the VI is to restore vestibular function by detecting head motion information and processing this into electrical signals that stimulate the vestibular nerves. By directly stimulating these nerves, it bypasses the vestibular end-organs and is able to restore

vestibular function in BVP patients (35). Although different designs exist, the VI generally consists of four key components:

1. Gyroscopes and/or accelerometers, which sense head motion
2. An external motion processor that converts head motion signals into electrical signals for stimulation
3. An external antenna sends electrical signals to implanted stimulator by radio frequency
4. Electrodes implanted in the vestibular organ directly stimulate the vestibular nerves. (See Figure I.). This figure was created in collaboration with the "Swiss Foundation For Innovation And Training In Surgery".

The implanted stimulator generally consists of electrodes inserted into the SSC or otolith organs or a combination of both. The electrical signals modulate the firing rate and/or amplitude of the vestibular nerve fibres. This information is perceived as a head movement by the central nervous system. Through this process, the vestibular function can be artificially restored (36). In order to restore vestibular function and hearing function at the same time, a VI can also be combined with a cochlear implant, which is then referred to as a vestibulocochlear implant (VCI). (See Figure I.) Most VI prototypes have been based on modified commercially available cochlear implant types.

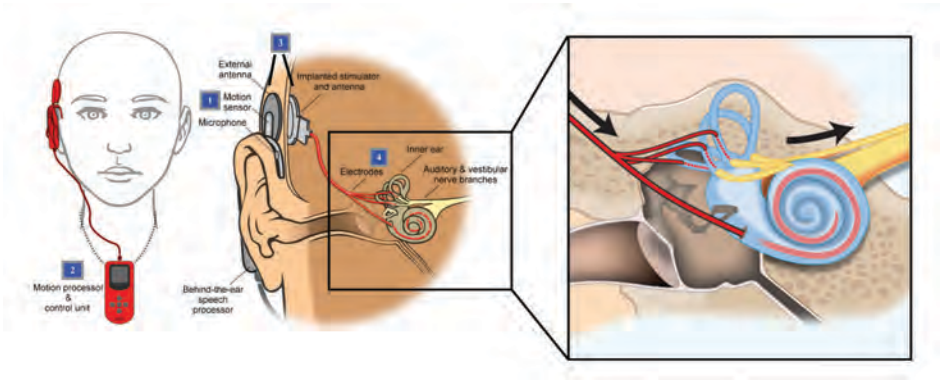


Figure 1. Vestibulocochlear implant (VCI). A) A VCI comprises vestibular and cochlear implant parts. The VI part includes four main components. **1)** Motion sensor (gyroscopes) senses head motion. **2)** External motion processor converts head motion signals into electrical signals for stimulation. **3)** External antenna sends electrical signals to implanted stimulator by radio frequency. **4)** Electrodes implanted in the vestibular organ directly stimulate the vestibular nerves. In order to restore vestibular function and hearing function at the same time, a VI can also be combined with a cochlear implant, which is referred to as VCI. This figure was created in collaboration with the "Swiss Foundation For Innovation And Training In Surgery"

2.1 Fundamentals of the Vestibular Implant

In order to restore vestibular function with the VI, a baseline firing rate is created using electrical stimulation (26, 37). This baseline firing rate can then be modulated to generate vestibular responses (38, 39). In the case of SCC stimulation, these responses include, among others, eye movements in both directions along each SCC plane.

2.1.1 *Modification of the baseline firing rate*

Human VI research is currently limited to unilateral vestibular implantation. Unilateral stimulation leads to an asymmetry in response since the natural baseline firing rate (90 pps) is below the middle of the stimulation range (0-400 pps). This causes a stronger excitatory response compared to the inhibitory response. For this reason, baseline stimulation of a vestibular implant can artificially be set higher (supraphysiological baseline) (22, 40, 41). Using a supraphysiological baseline, corresponding to 50% of the total dynamic range, increases the inhibitory responses but reduces the excitatory responses, leading to a more symmetrical response.

This (supraphysiological) baseline firing rate will initially be interpreted by the brain as an excitatory stimulus, resulting in nystagmus. Furthermore, symptoms of vertigo and/or nausea can occur (26). These undesired symptoms mainly disappear within 30 minutes of continuous baseline stimulation due to adaptation (26). Turning off the device after baseline adaptation can again initiate vertigo, nausea, and nystagmus, but in the opposite direction (26, 42). The central nervous system (CNS) is, however, able to adapt and habituate to switching between both conditions (electrical stimulation on and off) which is often referred to as “dual state adaptation” (26, 42, 43). This implies that after several off-to-on and on-to-off transitions of electrical stimulation, the intensity of the nystagmus becomes less, and adaptation to the new baseline happens more quickly. Eventually, (almost) no significant undesired nystagmus is triggered anymore by transitions between VI conditions “on” and “off”. (26, 41, 44). The adaptation time gradually becomes longer if the device remains deactivated for longer periods (42). Dual state adaptation would allow VI recipients to switch their device on or off without any significant side effects (e.g., when changing batteries, taking a shower, or sleeping).

2.1.2 *Motion modulation*

After adaptation to the supraphysiological baseline firing rate has been established, motion-based modulation is applied. The baseline firing rate is modulated up and down depending on the direction and velocity of the head movements. For example, when a patient (with a VI on the right side, adapted to the supraphysiological baseline) makes a yaw rotation to the right, stimulation of the right lateral ampullary nerve increases. The amount of increase depends on the velocity of the movement: a slow head movement

leads to a smaller increase in stimulation than a fast head movement. A head movement in the opposite direction (to the left in this case) leads to an inverse response. The amount of increase (or decrease) of stimulation for a given angular velocity is called the "modulation sensitivity", and it can artificially be set for each electrode.

Motion modulation around a (supraphysiological) baseline firing rate can be executed with pulse rate modulation, pulse amplitude modulation, or a combination of both (26, 38, 45). (See Figure II). Pulse rate modulation is similar to the natural neural coding of the vestibular system (46). However, recent studies have demonstrated that pulse amplitude modulation is more effective than pulse rate modulation in evoking eye movements (37, 45). Animal studies showed that co-modulation evokes significantly larger eye movement responses than amplitude or rate modulation alone (38, 45, 47).

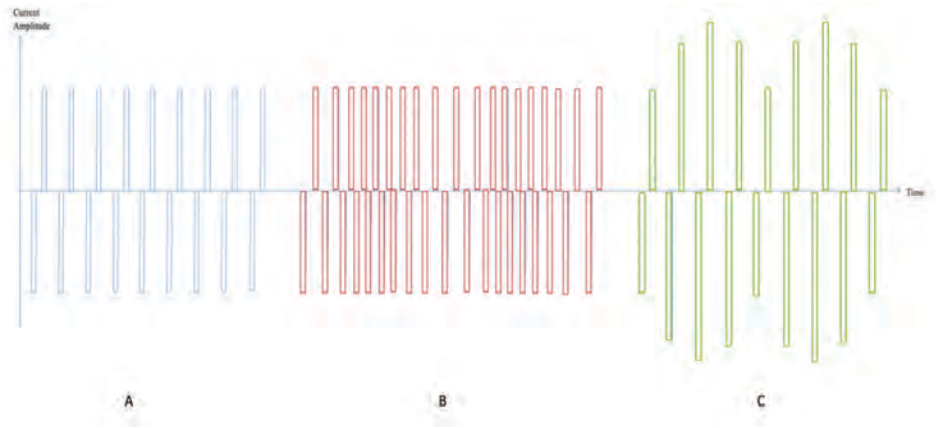


Figure 2. Baseline stimulation with motion modulation. Motion modulation can consist of pulse rate modulation and/or pulse amplitude modulation. **A)** Unmodulated baseline– Electrical stimulation by cathodic-first, charge-balanced, biphasic, rectangular pulses; **B)** Pulse rate modulation - The amplitude of the electrical stimulation remains the same, but the frequency of pulses is altered over time; **C)** Pulse amplitude modulation - The frequency of the electrical stimulation remains the same, but the amplitude of pulses is altered over time.

3 ELECTRICAL STIMULATION

The optimal electrical stimulation paradigm is not yet determined. The most commonly used pulse shape is the charge-balanced, biphasic, rectangular, cathodic-first current pulse (26, 48-50). Stimulation parameters (current intensity, pulse rate, phase width, current range, etc.) can vary depending on the research setting (51).

The fitting process of VI shows similarities with the fitting of a CI. First, the dynamic range is determined by finding the lower and the upper stimulation threshold. This is done by increasing the stimulation step by step. The lowest current level where a vestibular response can be observed is considered the lower threshold. The vestibular response can be the onset of nystagmus or the perception of a vestibular sensation. As a next step, the current level is further increased until stimulation causes discomfort to the patient (upper comfortable level) or leads to stimulation of off-target nerves (upper threshold, e.g., facial nerve stimulation). Lower and upper thresholds are determined for each of the electrodes separately and are patient specific. The available dynamic range, i.e., the range between lower and upper stimulation level, can vary between electrodes. It can, for example, be as wide as 550 µA or as narrow as 25 µA (36). Electrode position, the integrity of the targeted neurons and interpatient variability of anatomy and physiology are parameters known to influence the dynamic range of stimulation (36).

4 CANDIDACY EVALUATION

In the past, research teams used different implantation criteria for their subjects (36, 52, 53). Recently, in order to facilitate better comparison between studies, research teams jointly published an opinion statement about vestibular implantation criteria. These VI implantation criteria are shown in Table I., adapted from van de Berg et al. (54).

The VI-implantation criteria include severe loss of vestibular function based on disabling chronic symptoms (chronic imbalance and oscillopsia) together with objective signs of decreased or absent vestibular function in both ears. In contrast to the diagnostic criteria of BVP (55), the caloric test, the rotatory chair test and the video head impulse test, all need to show abnormalities. Furthermore, not only the lateral SCC but also vertical SCCs should also show deficits. Vestibular-evoked myogenic potentials are included on indication. The main reasons for these changes to the diagnostic criteria of BVP are:

1. Vestibular implantation can cause damage to vestibular structures in the inner ear, which might be irreversible. The diagnosis should therefore be verified by more than one vestibular test.
2. Implantation is not restricted to the lateral semicircular canals but can also include the other SSCs and otolith organs. Therefore, impairment of the structures to be implanted should be demonstrated.
3. VI surgery can impair residual vestibular function (e, g. by surgical plugging of the SCCs and/or inducing local trauma). VI-implantation should not damage the vestibular system more than it can restore (56, 57).

In the future, based on study-related outcomes, these criteria might be revised for clinical use, and other indications for implantation might be evaluated as well (e.g., unilateral vestibulopathy).

Table 1. Vestibular implantation criteria for research

A. Chronic Vestibular Syndrome with the following disabling symptoms	Unsteadiness when walking or standing	[1]Movement-induced blurred vision or oscillopsia during walking or quick head/body movements	[*]Worsening of unsteadiness in darkness and/or on uneven ground			
B. Symptoms greatest during head movement						
C. Major criteria for bilaterally reduced or absent angular VOR function[2]	Bilaterally pathological lateral angular VOR gain≤0.6 and at least bilaterally one vertical angular VOR gain <0.7, measured by the video-HIT or scleral-coil technique	Reduced caloric response (sum of bithermal max. peak SPV on each side ≤6◦/sec for 30 sec water stimuli or <10◦/sec for 60 sec water or air stimuli)	Reduced lateral angular VOR gain≤0.1 upon sinusoidal stimulation on a rotatory chair (0.1 Hz, Vmax = 50◦/sec) and a phase lead >68◦ (time constant <5 sec)			
C'. Obligatory for otolith implantation	Bilaterally absent cVEMP and oVEMP responses					
D. Minor criteria for bilaterally reduced or absent angular VOR function[3]	Bilaterally pathological VOR gains of at least two semicircular canals <0.7, measured by the video-HIT or scleral-coil technique	Reduced caloric response (sum of bithermal max. peak SPV on each side <10◦/sec for water and air stimuli of ≥30 sec)	Reduced lateral angular VOR gain <0.2 upon sinusoidal stimulation on a rotatory chair (0.1 Hz, Vmax = 50◦/sec)			
E. Symptoms are not better accounted for by another disease						
F. Additional requirements	Age 18 years and above	BVP results most likely from a peripheral origin	Vestibular function and symptoms are unlikely to significantly improve, according to the duration of symptoms and clinicians' estimations	Patent vestibular end-organ and intact vestibular nerve	Ability to use the device and follow a personalized rehabilitation program	Ability to undergo the surgery
G. No current psychological or psychiatric disorder that could significantly interfere with use or evaluation of the VI						

1 At least one of these two symptoms should be applicable

2 At least one item has to be met

3 In case only one or two major criteria (C) are met, (and also criterion C' is matched in case of otolith stimulation), the remaining test(s) should comply with the following items

5 SURGICAL APPROACHES

Basically, two surgical approaches have been used for vestibular implantation: the intralabyrinthine approach and the extralabyrinthine approach (57). Both surgical approaches have been successfully carried out and have been shown to selectively stimulate the ampullary nerves.

The most commonly used approach is the intralabyrinthine approach (40, 41, 43, 58-60). In this approach, a cortical mastoidectomy is performed, the labyrinth is opened, and electrodes are inserted in the semicircular canals and/or the otoliths nearby the sensory epithelium. (See Figure III). Advantages of this approach are that the surgery is less challenging for most surgeons, and middle ear structures are preserved (50, 56, 61). Risks and challenges include possible sensorineural hearing loss due to opening the labyrinth and inserting electrodes, and difficulty in getting the electrodes as close as possible to the sensory epithelium (48, 58, 62)

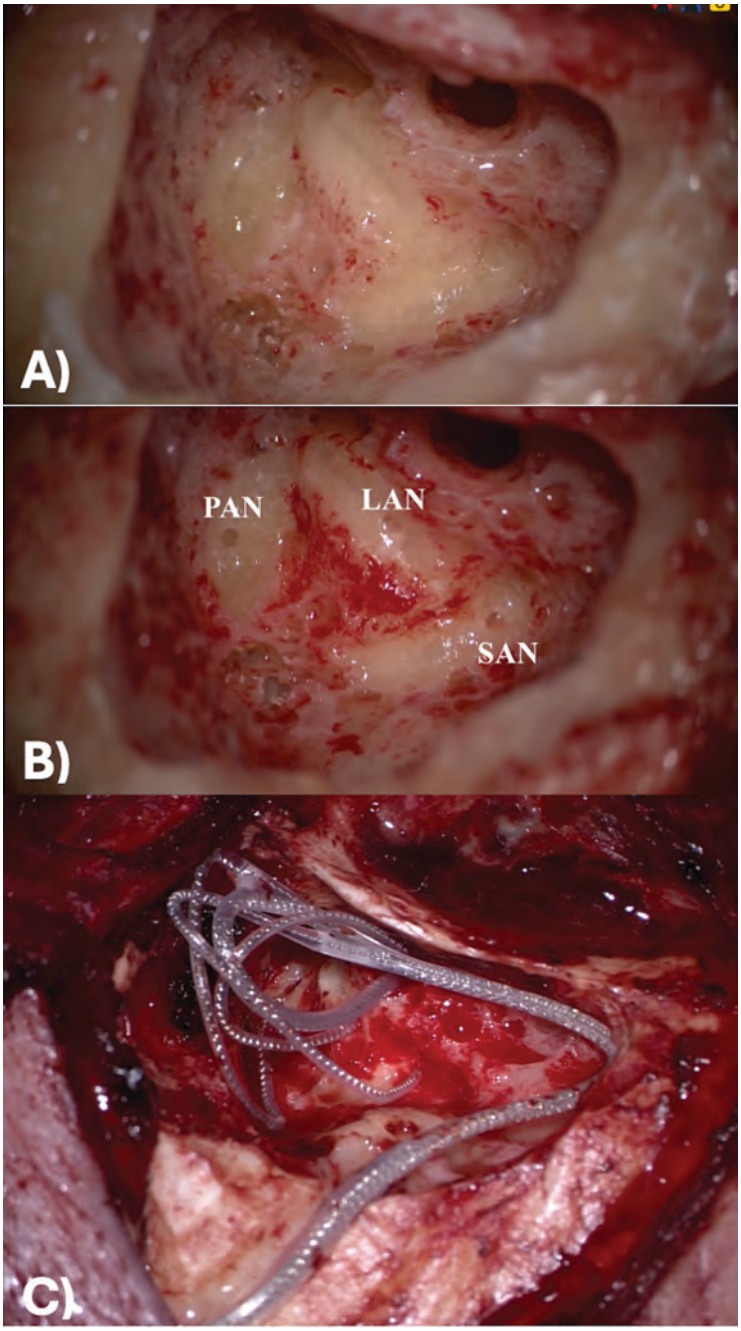


Figure 3. Stepwise images during vestibular implant surgery using the intralabyrinthine approach. **A)** Semicircular canals are blue-lined adjacent to their ampullary nerves. **B)** Fenestrations are performed for each semicircular canal (SAN, LAN, PAN) to allow selective intralabyrinthine access. **C)** Electrodes are inserted in the semicircular canals nearby the sensory epithelium. Abbreviations**:** SAN, Superior Ampullary Nerve; LAN, Lateral Ampullary Nerve; PAN, Posterior Ampullary Nerve

In the extralabyrinthine approach, the electrodes are directly placed on the posterior, lateral and superior ampullary nerves close to the labyrinth without opening the semicircular canals and the vestibule. This approach consists of two pathways: 1) the posterior ampullary nerve (PAN) access, and 2) the superior ampullary nerve (SAN) and lateral ampullary nerve (LAN) access. The PAN access is reached by drilling the round window niche. The PAN is identified, and an electrode is placed in contact with the nerve. The LAN and SAN pathway is created by removing the head of the malleus and the incus. By drilling superiorly from the facial nerve, the SAN and LAN can be identified, and an electrode is placed in contact with the nerves. It should be noted that the LAN and SAN cannot yet be stimulated separately since they are located very close to each other. The main advantage of this approach is the fact that the labyrinth does not need to be opened, minimizing the risk of sensorineural hearing loss. Risks and challenges of the extralabyrinthine approach include accidentally opening the labyrinth (causing a sensorineural hearing loss), facial nerve damage, inability to correctly fixate the electrodes or failure to reach the nerve canals (mainly applicable to the PAN approach) (56).

6 INTRAOPERATIVE MEASUREMENTS

During VI surgery, intraoperative monitoring is performed to evaluate the integrity of the implant and to provide appropriate placement of the electrodes (63). It seems that electrode placement should be as close as possible to the sensory epithelium of the ampulla (64). Several strategies are being investigated to achieve optimal electrode position:

1. Fluoroscopy, a real-time radiation-based imaging technique, can be utilized to improve the placement of the electrodes into the SSCs. It has been previously applied in CI surgery to provide direct feedback on the location of the CI electrodes (65). In this way, electrodes are visualized within the SCCs in real-time, enabling more precise placement of the electrodes in the SCCs (66). (See Figure IV.)
2. Eye movement responses as a result of direct electrical stimulation can be observed during surgery. By manipulating the electrode position until the favorable eye movements (correct magnitude and angle) are obtained, the best electrode position can be determined. However, general anaesthesia is known to alter and suppress the nystagmic response. Surgery under local anaesthesia may improve this procedure so that it can be used to indicate optimal placement.

3. The synchronous response of the vestibular nerve fibres (67, 68) can be used to characterize the direct effect of vestibular electrical stimulation at a certain electrode position. This neural potential is referred to as the vestibular electrically evoked compound action potential (veCAP), in analogy with the auditory eCAP in CI's. These measures can be performed intraoperatively as well as postoperatively (fitting information and follow-up tool). Anaesthetics may have less impact compared to eye movement responses, but current spread between electrodes can hamper (direct) interpretation of the results.

Until now, no strategy has been proven to be infallible. Further research is currently being conducted to optimize these strategies as well as to possibly find alternatives.

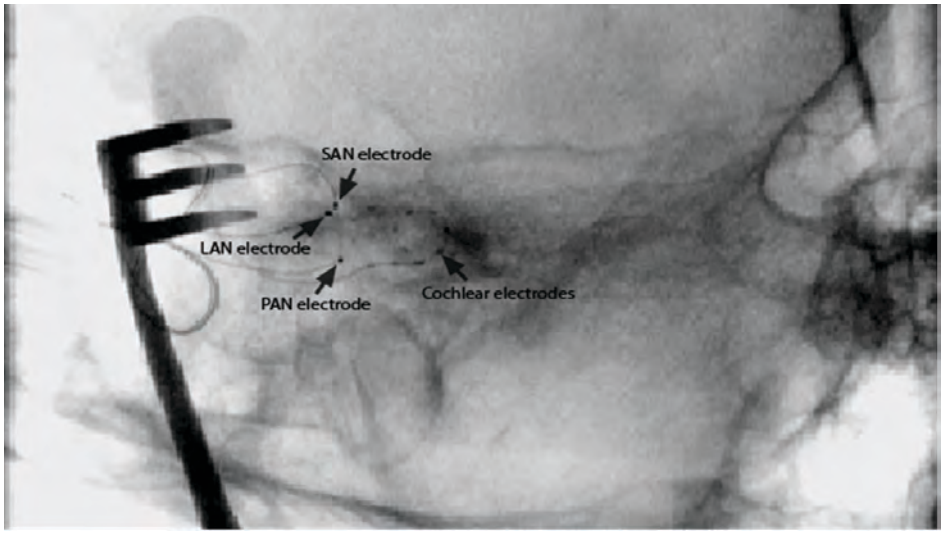


Figure 4. Fluoroscopy**.** A real-time radiation-based imaging technique. Black dots represent electrode contacts in each semicircular canal as well as the cochlear array. Abbreviations: SAN, Superior Ampullary Nerve; LAN, Lateral Ampullary Nerve; PAN, Posterior Ampullary Nerve

7 OUTCOMES WITH VI

In the 1960s, it was demonstrated that a nystagmic response could be generated in monkeys by electrical stimulation of the vestibular nerves. Since the beginning of this century, many feasibility studies on animals have demonstrated the effectiveness of chronic electrical stimulation (38, 69, 70) and how different stimulation parameters can be optimized (44, 71). After obtaining promising results from animal studies, studies on

humans were initiated. Results obtained in individuals fitted with a vestibular implant prototype are discussed below.

a) Vestibular Reflexes

The VOR, VCR and VSR have all been used to evaluate the effect of VI stimulation. Regarding the VOR, it was found that it is possible to (partially) restore the low and high-frequency VOR with a VI in patients with BVP (37, 72) (See Figure V). The electrically evoked VOR increases with increasing stimulation, it shows a natural frequency-dependency (73), and the eye movements can be aligned with the plane of the stimulated canal, although misalignment can occur (52).

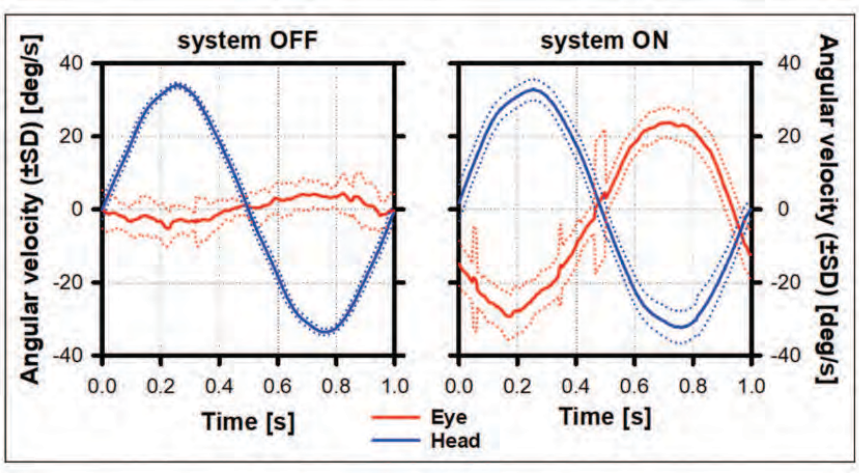


Figure 5. Vestibulo ocular reflex restoration with vestibular implant. Vestibular ocular reflex gain is almost absent (eye velocity (in grey) around zero) with the vestibular implant turned OFF (left panel) while it normalizes (eye velocity (grey) mirroring head velocity (black)) when the vestibular implant is turned ON (right panel). (Obtained from (Perez Fornos et al., 2014))

As for VSR and VCR, it was demonstrated that it is possible to generate controlled postural responses with a VI in patients with BVP (74, 75). In general, these results indicate that electrical stimulation of the vestibular end-organ in humans enables both compensatory eye movements and compensatory body and neck movements, potentially restoring gaze stabilization and postural control, respectively.

b) Functional Improvements

One of the main symptoms of BVP is oscillopsia, the loss of visual acuity during head movements (76). Visual acuity in dynamic conditions (like head movements), referred to as

"dynamic visual acuity" (DVA), can be compared to the visual acuity in static conditions (77). Measuring DVA allows the above-mentioned improvement in VOR gain to be evaluated on a more functional level. It was found that VI stimulation significantly improved dynamic visual acuity when walking and during fast-passive head movements (78-80).

Alongside oscillopsia, imbalance is also an often-reported symptom of BVP (76). Therefore, posture and gait have been examined to investigate whether the electrically evoked VSR and VCR can result in functional benefits for the patient. Outcome measures for posture (Bruininks-Oseretsky Test of Motor proficiency) and for gait (Dynamic Gait Index) in long-term users of a VI prototype indicated improvement compared to a control situation without electrical stimulation (81). These results demonstrate the potential of the VI to improve balance.

c) Subjective outcomes

Various subjective outcome measures have been used in order to demonstrate the effects of a VI in daily life. Regarding qualitative measurements, more stable vision and increased postural responses were reported by VI recipients. Besides, some patients reported that the VI increased their ability to perform daily life activities safely (e.g abandoning the use of walking sticks, increased ability to walk in darkness, increased ability to walk on uneven ground, and being able to carry weight) (52). As for the quantitative measurements, improvements were demonstrated by the quality of life questionnaires (Short Form 36, Health Utility Index 3) (81). In general, patients report an increased quality of life.

d) Undesirable consequences of VI

Apart from the positive results obtained in VI trials, hearing loss is an often-reported side-effect of VI implantation surgery. Most likely due to a combination of the surgical drilling and the insertion of electrodes into the inner ear, hearing loss was reported for most patients with functional hearing in the implanted ear prior to surgery (68, 81). Efforts are being made to reduce this risk by investigating different surgical strategies (e.g., the extralabyrinthine approach) and soft-surgery techniques. Due to this risk, several research groups are currently only implanting patients with complete hearing loss in the ear to be implanted. In this light, the Geneva-Maastricht and Washington (82) groups are using a combined vestibular and cochlear implant (VCI) to restore both modalities simultaneously (39).

8 FUTURE PROSPECTIVES

The VI concept presented in this chapter has the potential to be the first clinically available treatment aimed at restoring vestibular function loss. Although promising, several aspects can still be improved.

Regarding the surgery, the overall goal is to get the VI electrodes as safe as possible at the desired location, using a technique which does not require extensive training. Therefore, the implant design and surgical techniques should allow easy placement of the electrodes, with one of the main goals being the preservation of inner ear structures and therefore hearing function. Intra-operative monitoring (either imaging-based, via neural monitoring or VOR-based) might facilitate this goal.

Accurate neural stimulation is vital for the functioning of a VI. A more extensive understanding of the physiology of the vestibular neurons and their response to electrical stimulation, together with central vestibular processing within reflex and perception pathways, is probably important to optimize the stimulation algorithms. Although previous research in animals indicated the capacity of the brain to adapt to suboptimal (i.e. misaligned) stimulation (49), mapping the electro-dynamics inside the inner ear might create a better understanding on how to improve stimulation algorithms, including current steering and the influence of spatial and temporal coding of the stimulus signal.

Another aspect is to improve or create outcome measures to evaluate the vestibular system. This will aid in substantiating any claims on VI efficacy while also giving insights into the complex integration of sensory modalities for balance and motion perception. This also includes subjective outcome measures explicitly aimed at the BVP population to quantify symptoms, disease burden and overall quality of life.

Besides the above-mentioned goals, future efforts will be aimed at the usability of the device and its effective integration into standard clinical practice. This includes increasing the wearability and concealability of the device, improving battery life and making it easy to use, both for patients and clinicians. Furthermore, VI-specific rehabilitation programs need to be developed.

Currently, the VI is mainly aimed at patients with severe BVP, but other indications for VI implantation (e.g., uncompensated unilateral vestibulopathy) and the possible added value of bilateral vestibular implantation will be evaluated in the future.

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8

CHAPTER 8

General discussion

1 GENERAL DISCUSSION

This thesis aimed at providing insights into chronic unilateral vestibular hypofunction (UVH), regarding chronic symptoms (chapter 2, 3, and 4), etiologies, co-morbidities (chapter 4 and 5) clinical subtypes, diagnostics (chapter 2, 4, and 5), quality of life (QoL) (chapter 2, 3, 4, 5 and 6) and vestibular implants as a potential future treatment (chapter 7).

1.1 Chronic symptoms

Chronic dizziness and unsteadiness were the most common symptoms of chronic UVH, as consistently shown across chapters 2, 3, and 4. These findings suggest that vestibular compensation, particularly when initiated during the (sub)acute phase, does not always lead to full symptom resolution (1-4). While compensation mechanisms are often sufficient in static conditions, they may be insufficient in dynamic conditions (5). This may explain why some patients continue to experience long term symptoms despite vestibular intervention. Unfortunately, current vestibular tests are not yet capable of accurately assessing the extent of central compensation, making it difficult to predict which patients will develop chronic symptoms. Moreover, the symptom profile in chronic UVH extends beyond chronic dizziness and imbalance. For example, oscillopsia was reported by approximately 20% of patients (6-8), which indicate partial preservation of gaze stability through residual vestibular input and central adaptation. Beyond these core symptoms, patients described other reported complaints such as visually-induced dizziness, tiredness, cognitive and emotional disturbances. However, many of these symptoms are non-specific and may reflect co-morbid conditions or underlying etiologies (e.g., Menière's disease, migraine, PPPD, or metabolic disorders) rather than UVH itself (9). This highlights the multifactorial nature of symptom presentation in chronic UVH. Importantly, such symptoms are not always captured in standard clinical assessments, and patients may struggle to articulate or associate them with their vestibular condition. This demonstrates the need for a structured history-taking in chronic UVH cases (10).

1.2 Etiologies

The most frequent etiology of chronic UVH varied across chapters: Menière's disease was predominant in chapters 2 and 4, while infection/inflammation and neoplasms were more common in chapter 5. These differences likely stem from variations in diagnostic approaches and clinical settings. For example, when caloric testing was used, Menière's disease was more frequently identified (11, 12), whereas vHIT-based diagnoses more often pointed to acute unilateral vestibulopathy/vestibular neuritis or neoplasm (13). Selection bias also plays a role. ENT specialists are more likely to assess patients with concurrent hearing and balance symptoms, which increases the detection of disorders like Menière's disease or genetic inner ear conditions. Additionally, tertiary centers tend to manage more

complex or advanced cases compared to primary care. Overall, the reported etiologies of chronic UVH are influenced by both diagnostic criteria and the healthcare context in which patients are evaluated.

1.3 Co-morbidities

In addition to the primary diagnosis of chronic UVH, various secondary diagnoses and co-morbid conditions may emerge. Chapter 4 and 6 revealed that the most frequently reported secondary vestibular diagnoses were benign paroxysmal positional vertigo (BPPV) (21-10%) and Persistent-postural perceptual dizziness (PPPD) (19-28%). These conditions can either develop as a consequence of UVH or co-occur independently, which often leads to overlapping symptoms that complicate diagnosis and treatment (14). Recognizing these co-existing or sequential conditions is crucial for accurate diagnosis and tailored management. The presence of persistent symptoms despite standard treatment should prompt further evaluation (15). Therefore, a structured approach to assessment, including targeted history-taking and appropriate screening, is essential to address the full spectrum of symptoms in this patient population (10).

Chapter 3 and 4 revealed most frequently reported co-morbidities were hypertension (34-53%) and non-migraine headache (20-36%). While these rates appear elevated, it is important to consider that both conditions are also highly prevalent in the general population. For instance, population-based data from the Netherlands indicate a hypertension prevalence of approximately 31%, based on 2019 estimates from the World Health Organization (16), and non-migraine headache affects roughly 30% of individuals (17). Therefore, the presence of these co-morbidities in the current sample may, at least in part, reflect background population rates rather than disorder-specific associations. However, this aspect alone does not fully capture the complexity of the relationship between co-morbidities and chronic UVH. Some conditions, such as hypertension or diabetes, may contribute to vestibular dysfunction through vascular mechanisms, while others like depression or anxiety can both exacerbate vestibular symptoms and emerge as a consequence of chronic dizziness. Additionally, autoimmune disorders may play a modulating role in the development of chronic UVH, either directly or through their association with other vestibular pathologies such as Menière's disease or vestibular migraine (18). As a result, although population prevalence must be considered, the potential pathophysiological interactions between co-morbidities and chronic vestibular dysfunction should further be investigated.

1.4 Symptoms patterns (clinical subtypes)

Chapter 4 highlights that most chronic UVH patients exhibited symptoms patterns aligned with their underlying etiology (e.g., recurrent vertigo in Menière's disease). However, it is

worth noting the heterogeneity of clinical subtypes in chronic UVH, especially in idiopathic and slowly progressive cases where vertigo is absent. This raises important concerns regarding potential mis- or underdiagnosis (19). In clinical practice, UVH is often associated with acute vertigo episodes; therefore, patients who do not report such symptoms may be overlooked or misclassified. For instance, idiopathic cases without vertigo may be mistaken for non-vestibular conditions, such as anxiety, or functional disorders. Furthermore, the overlap between slowly progressive and idiopathic UVH demonstrates the diagnostic challenge in distinguishing these subtypes without clear biomarkers or standardized criteria. These findings call for a more structured diagnostic approach, including detailed vestibular testing and longitudinal symptom tracking, to capture the full spectrum of UVH and reduce the risk of missed or delayed diagnoses (10).

1.5 Diagnostics

Currently, no universally accepted diagnostic criteria exist for chronic UVH. This lack of consensus creates ambiguity in both clinical and research settings, particularly when relying on caloric or vHIT outcomes. Each test assesses different aspects of vestibular function. Caloric testing reflects low-frequency function, while vHIT targets high-frequency responses (20). This difference often results in diagnostic discrepancies between both tests (21). Each test also has its own challenges. For instance, a patient with bilaterally reduced caloric responses could be misdiagnosed as having UVH if only interaural asymmetry is considered without evaluating absolute response values (22). VHIT on the other hand, despite being quick and patient-friendly, may miss subtle deficits due to its lower sensitivity in UVH detection (20). Additionally, current test protocols predominantly focus on horizontal canal function, often neglecting otolith organs, even though otolith dysfunction appears common, especially in conditions like PPPD (23, 24). These limitations highlight the need for a consensus on diagnostic criteria for chronic UVH. This should include a multimodal and comprehensive diagnostic approach to more accurately assess the full spectrum of vestibular dysfunction.

Imaging can play a supportive role in selected cases of chronic UVH, particularly when ruling out structural pathologies such as vestibular schwannoma. However, in over half of the patients who underwent imaging, no abnormalities were detected (Chapter 4). This demonstrates the importance of using imaging based on clinical indications, rather than as a routine diagnostic tool. Clear clinical guidelines could help minimize unnecessary scans, reduce healthcare costs, and avoid patient burden.

Regarding the previously mentioned diagnostic criteria, the initial classification of chronic UVH in this thesis was based on caloric test results, using an asymmetry threshold of >25% in Chapter 4. However, due to the discrepancy between the caloric test and vHIT (21), more

stringent criteria were introduced to improve diagnostic specificity in Chapter 3, 5 and 6. For vHIT, a pathological gain was defined as <0.7 on the affected side and a normal gain as >0.8 on the healthy side. Additionally, an interaural gain asymmetry threshold of ≥18% was applied. According to the Bárány Society, a VOR gain <0.7 on the affected side and/or a side difference >0.3 between ears is indicative of acute unilateral vestibulopathy/vestibular neuritis (25). However, the side difference criterion becomes significant only when the gain on the affected side exceeds 0.7. After all, a large asymmetry with bilaterally low gains may suggest bilateral vestibulopathy (e.g., gains of 0.25 and 0.55 exceed the 0.3 threshold but indicate bilateral vestibulopathy rather than UVH). In contrast, the ≥18% asymmetry threshold used in this study corresponds to a comparable gain difference (e.g., 0.65 vs. 0.95 yields 23% asymmetry and a 0.3 difference), while also fulfilling stricter gain criteria (affected side <0.7, healthy side >0.8). This approach improves diagnostic specificity and ensures consistent identification of true unilateral hypofunction.

1.6 Quality of life (QoL)

QoL in patients with chronic UVH was explored using qualitative and quantitative approaches across different chapters of this thesis. The qualitative approach (Chapter 3) involved semi-structured interviews to capture patients' experiences and perceived impact on daily life, while the quantitative approach (Chapters 2, 4, 5, and 6) relied on PROMs, including the DHI, HADS, and EQ-5D-5L.

Regarding the qualitative findings, Chapter 3 revealed that patients with chronic UVH experience symptom triggers such as stress, physical exertion, driving, visually complex environments, and crowded spaces. These challenges frequently lead to avoidance behaviors and fear of falling. While many adopt coping strategies like slowing movements or avoiding triggers, these can reinforce maladaptive patterns which can be linked to PPPD (26). Additionally, emotional and social consequences such as frustration, isolation, and reduced family dynamics demonstrate the broad impact of chronic UVH. Quantitative findings across Chapters 2, 4, 5, and 6 further support this broad impact. In Chapter 2, a meta-analysis showed that while various interventions can alleviate symptoms, approximately 30% of patients still continue to report moderate disability, indicating limited benefit from vestibular interventions. Chapter 4 confirmed these findings in a large clinical cohort (n=251), where over 80% of patients reported moderate-to-severe handicap on the DHI, and 20–25% exhibited clinically significant anxiety and depression based on HADS scores. Chapter 5 provided additional evidence by comparing chronic UVH with bilateral vestibulopathy, showing that although bilateral vestibulopathy patients generally report more severe impairments, those with chronic UVH experience a moderate-to-severe disability in QoL, which is often underestimated in clinical practice. Although variations in study design and population characteristics (e.g., tertiary referral bias) may influence these rates, the

overall picture is consistent: a substantial proportion of chronic UVH patients experience long-term functional and emotional limitations. Therefore, evaluating QoL in chronic UVH requires a multidimensional approach that not only considers physical symptoms, but also the psychological and social burden. Integrating psychological support and patient-centered rehabilitation strategies into clinical care, may improve outcomes in this population.

In chapter 4, the QoL was also examined in relation to several clinical and demographic factors (n=193). These factors included symptom duration, the presence of secondary diagnoses (e.g., PPPD), clinical subtypes (e.g., presence of vertigo attacks), co-morbidities (e.g., migraine), hearing status, and vestibular test results (e.g., caloric responses). Together with these factors, QoL outcomes were assessed using the DHI, HADS, and EQ-5D-5L questionnaires. Among the factors associated with reduced QoL in chronic UVH patients, the presence of PPPD was consistently linked to worse outcomes across all measures. This aligns with previous literature and likely reflects the persistent, unpredictable, and activity-triggered nature of PPPD symptoms, which are difficult to manage or avoid (27, 28). The uncertain pathophysiology and limited treatment options for PPPD may further contribute to its burden.

In contrast, no significant association was found between migraine and QoL in this population, which may be due to the assessment of patients outside active migraine episodes (29). Although factors such as symptom duration, hearing status, and different clinical subtypes were expected to influence QoL, no significant associations were found in this study. One possible explanation is the high degree of variability in individual coping mechanisms and compensation capacity, which may mitigate the impact of these clinical features on perceived handicap. For example, some patients may adapt well to long-standing symptoms, while others report significant impairment even with shorter symptom duration (30). Similarly, hearing loss might have a variable effect depending on communication needs, social support, or the presence of assistive devices (e.g, hearing aids (31)). A decreased QoL was not linked to a specific clinical subtype. This suggest that individual perception, psychological resilience, and contextual factors may play a crucial role in determining QoL than the clinical characteristics alone. Furthermore, the observed mismatch between objective vestibular test results and patients' subjective complaints reinforces the need for assessing potential psychological, psychiatric, or functional contributors to symptom burden, rather than relying solely on laboratory findings.

While quantitative tools such as the DHI, HADS, and EQ-5D-5L are widely used to assess QoL in chronic UVH, they have limitations in capturing the full range of patient experiences. Furthermore, clear and standardized symptom definitions are essential to avoid misdiagnosis and improve care (32). As shown in Chapter 3, several symptom domains, such as vision

problems, memory issues, and difficulties with multitasking, were commonly reported in interviews but not reflected in PROM scores. This gap indicates the restricted scope of standardized PROMs and the value of qualitative methods in revealing less common, yet impactful symptoms. By comparing interview data with PROM content using the ICF framework, it became clear that current tools may underestimate the emotional, cognitive, and functional burden of UVH. Therefore, the development of a UVH-specific PROM is warranted to ensure a more accurate assessment of symptomatology and daily impact.

In this context, the Bilateral Vestibulopathy Questionnaire (BVQ), originally developed and validated for bilateral vestibulopathy (33, 34), was examined as a potential tool to assess the symptom burden in chronic UVH. Due to the overlap in symptoms between bilateral vestibulopathy and chronic UVH, the BVQ appeared relevant in capturing various physical, cognitive, and emotional complaints reported by chronic UVH patients. In Chapter 6, the full-length 50-item version of the BVQ was used to explore symptom patterns in this population (33), which ultimately led to the development of a adapted 20-item version. Psychometric analyses of this adapted version provided preliminary evidence for its construct validity, high internal consistency, and acceptable test–retest reliability in chronic UVH. However, unlike the version validated for bilateral vestibulopathy, the adapted BVQ was not developed following the COSMIN framework and has not yet undergone expert panel review or cognitive interviews to ensure formal content validity (35). This is a critical limitation, as it means the instrument may not yet fully capture the complete range of experiences in chronic UVH Therefore, future research should complete the content validation process to refine and formally establish a chronic UVH-specific PROM, potentially to be named the Unilateral Vestibulopathy Questionnaire (UVQ).

1.7 Vestibular implants as a potential future treatment for chronic UVH

In Chapter 7, the current status and future prospects of vestibular implants (VI) were discussed, with a primary focus on its application in patients with severe bilateral vestibulopathy, who suffer from profound functional impairment and limited treatment options. Currently, VI is mainly aimed at this population; however, emerging evidence and clinical observations suggest that other patient groups, such as those with chronic UVH, may also benefit from a VI. While these patients retain function in the contralateral ear, a subset of patients experiences persistent chronic symptoms that do not respond adequately to conventional vestibular intervention. This raises important questions about expanding the clinical indications for VI beyond bilateral vestibulopathy. Future research should explore whether selected UVH patients with chronic symptoms and poor central compensation could achieve functional improvements with targeted vestibular stimulation. Such an expansion of indications would require careful patient selection, ethical considerations, and tailored stimulation strategies, but could ultimately help more patients benefit from vestibular implants.

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9

CHAPTER 9

Summary

SUMMARY

Vestibular compensation and rehabilitation lead to recovery in many patients with unilateral vestibular hypofunction (UVH). However, a subset of patients fails to achieve full recovery of symptoms. This observation forms the basis of this thesis: Chronic UVH is a multidimensional clinical condition that has a significant impact on patients' quality of life (QoL). Furthermore, current assessment tools are not sufficient to capture the health impact of chronic UVH on daily life. To investigate these aspects, a multi-method approach was carried out. This included a systematic review, a qualitative approach, a retrospective cohort analysis, cross-sectional comparisons, and psychometric validation. Across these studies, key aspects of chronic UVH were investigated, including symptomatology, etiologies, clinical subtypes, diagnostic challenges, and impact on QoL. Therefore, the goal of this thesis is to enhance the understanding of chronic UVH. This could lead to more effective clinical management strategies.

Chapter 2 presents a systematic review synthesizing the full spectrum of chronic symptoms in patients with chronic UVH. It also illustrates the effects of vestibular interventions on symptoms. An analysis of 47 studies revealed a wide range of symptoms, with chronic dizziness (98%) and imbalance (81%) being the most frequently reported. These symptoms were followed by visually induced dizziness and symptoms worsening with head movements. In addition to vestibular symptoms, non-vestibular complaints such as tiredness, cognitive dysfunction, and autonomic disturbances were also prevalent. Oscillopsia was the least commonly reported symptom (22%). Vestibular rehabilitation led to significant reductions in perceived handicap. Nevertheless, a subset of patients (~30%) continued to experience moderate disability. This suggests the need for alternative treatments, such as vibrotactile feedback or vestibular implants. This chapter also demonstrated the limited ability of existing assessment tools to fully capture the health impact of chronic UVH on daily life. A qualitative study investigating these symptoms, was therefore needed.

In response, **Chapter 3** presents a qualitative study based on semi-structured interviews with chronic UVH patients, analyzed within the framework of the International Classification of Functioning, Disability and Health (ICF). Results showed 16 physical, 4 cognitive, and 5 emotional symptoms, with crucial challenges in daily life, including difficulties with driving, in darkness, and with sleep. Additionally, fear of falling was reported. Patients adopted various coping strategies, such as moving cautiously and avoiding complex visual environments. Importantly, several domains, such as visual sensitivity, multitasking, and memory-related issues, were not adequately represented in commonly used PROMs. This demonstrated the need for a chronic UVH-specific assessment tool.

Chapter 4 reports findings from a retrospective cohort of 251 chronic UVH patients, aiming to classify etiologies, clinical subtypes, and QoL outcomes. Thirteen different etiologies were identified, with Menière's disease being the most common etiology. Secondary diagnoses such as benign paroxysmal positional vertigo (BPPV) and persistent postural-perceptual dizziness (PPPD) frequently co-occurred and contributed to greater disability (21% and 19%, retrospectively). Five distinct clinical subtypes of chronic UVH were described, which indicated the condition's heterogeneity. The presence of PPPD was found as a key predictor of reduced QoL. This finding demonstrates the importance of identifying and addressing co-morbid vestibular conditions in routine clinical evaluation.

Building on the identified need for a chronic UVH-specific assessment tool in Chapter 3, **Chapter 5** compares patient-reported outcomes between patients with UVH and bilateral vestibulopathy (BVP). Data was used from 100 chronic UVH patients and 148 BVP patients. Differences in symptom burden, functional limitations, emotional well-being, and health-related QoL were evaluated. While BVP patients reported more severe symptoms on condition-specific PROMs, both groups exhibited significantly impaired outcomes compared to healthy normative data. These results demonstrate that although BVP is often considered the more debilitating condition, chronic UVH also imposes a significant burden. This burden is often under-recognized in clinic and research setting.

To address the need for a chronic UVH-specific assessment tool, **Chapter 6** evaluates construct validity and reliability of the preliminary version full-length Bilateral Vestibulopathy Questionnaire (BVQ) in a cohort of patients with chronic UVH. Psychometric analyses, including confirmatory and exploratory factor analyses, revealed a refined four-factor structure: imbalance, visuo-spatial processing, behavior and limitation, as well as emotion. This revised 20-item version demonstrated strong construct validity, high internal consistency, and acceptable test–retest reliability. The adapted version offers preliminary evidence for the construct validity and reliability of the adapted BVQ in assessing the impact of chronic UVH. While these findings suggest that the adapted BVQ has potential as a chronic UVH-specific PROM, its development was not originally guided by the COSMIN framework. Crucially, it has not yet undergone expert panel review or cognitive interviews to ensure content validity. Future research should address these gaps to refine the tool into a fully validated, condition-specific questionnaire, potentially to be established as the Unilateral Vestibulopathy Questionnaire (UVQ).

Finally, **Chapter 7** discusses the potential future implications of vestibular implants (VI) for chronic UVH. As an emerging intervention for patients with BVP, the VI has shown promising results in (partially) restoring vestibular function, improving postural control, and enhancing QoL. Although its current use is focused on patients with BVP, findings from

chapters in thesis demonstrate the need for further research into its potential applicability in patients with chronic UVH.

SAMENVATTING

Vestibulaire compensatie en revalidatie zorgen bij veel patiënten met eenzijdige vestibulaire hypofunctie (UVH) voor herstel. Toch lukt het een deel van de patiënten niet om volledig te herstellen van hun klachten. Deze observatie vormt de basis van dit proefschrift: chronische UVH is een aandoening met meerdere dimensies die een aanzienlijke invloed heeft op de kwaliteit van leven van patiënten. Daarnaast schieten de huidige meetinstrumenten tekort in het volledig in kaart brengen van de impact van chronische UVH op het dagelijks functioneren. Om deze aspecten te onderzoeken, is gebruik gemaakt van verschillende onderzoeksmethoden: een systematische literatuurstudie, kwalitatief onderzoek, een retrospectieve cohortanalyse, dwarsdoorsnede-vergelijkingen en psychometrische validatie. In deze studies zijn belangrijke kenmerken van chronische UVH onderzocht, zoals klachtenpatronen, oorzaken, klinische subtypes, diagnostische uitdagingen en de impact op kwaliteit van leven. Het doel van dit proefschrift is dan ook om het inzicht in chronische UVH te vergroten, wat kan bijdragen aan betere behandelstrategieën.

Hoofdstuk 2 bevat een systematische literatuurstudie naar het volledige spectrum van chronische klachten bij patiënten met chronische UVH. Ook wordt het effect van vestibulaire behandelingen op deze klachten beschreven. Analyse van 47 studies laat zien dat chronische duizeligheid (98%) en balansproblemen (81%) het vaakst voorkomen. Andere veelvoorkomende klachten zijn visueel geïnduceerde duizeligheid en klachten die verergeren bij hoofdbewegingen. Naast deze vestibulaire klachten hadden patiënten ook last van vermoeidheid, cognitieve problemen en verstoringen van het autonome zenuwstelsel. Oscillopsie (bewegend beeld bij hoofdbeweging) werd het minst vaak gemeld (22%). Vestibulaire revalidatie verminderde het ervaren beperkingen, maar bij ongeveer 30% van de patiënten bleef sprake van matige klachten. Dit wijst op een mogelijke behoefte aan alternatieve behandelingen, zoals vibratietactiele feedback of vestibulaire implantaten. Ook werd duidelijk dat bestaande meetinstrumenten onvoldoende geschikt zijn om de impact van chronische UVH op het dagelijks leven goed vast te leggen. Daarom was aanvullend kwalitatief onderzoek nodig.

Hoofdstuk 3 beschrijft een kwalitatieve studie, gebaseerd op semigestructureerde interviews met patiënten met chronische UVH. De analyse werd uitgevoerd aan de hand van het International Classification of Functioning, Disability and Health (ICF)-model. Er kwamen 16 lichamelijke, 4 cognitieve en 5 emotionele klachten naar voren, met

belangrijke beperkingen in het dagelijks leven, zoals moeite met autorijden, slecht zicht in het donker en slaapproblemen. Angst om te vallen werd vaak genoemd. Patiënten pasten verschillende copingstrategieën toe, zoals voorzichtiger bewegen en het vermijden van drukke visuele omgevingen. Opvallend was dat bepaalde klachten, zoals visuele overgevoeligheid, moeite met multitasken en geheugenproblemen, niet goed worden weergegeven in bestaande vragenlijsten. Dit onderstreept de noodzaak van een specifiek meetinstrument voor chronische UVH.

Hoofdstuk 4 presenteert de resultaten van een retrospectieve cohortstudie onder 251 patiënten met chronische UVH. Doel was om de oorzaken, klinische subtypes en uitkomsten op het gebied van kwaliteit van leven in kaart te brengen. Er werden 13 verschillende oorzaken geïdentificeerd, waarbij de ziekte van Ménière het vaakst voorkwam. Daarnaast kwamen secundaire diagnoses, zoals benigne paroxysmale positieduizeligheid (BPPD) en persisterende postureel-perceptuele duizeligheid (PPPD), vaak voor en gingen gepaard met een grotere mate van beperkingen (21% en 19%). Vijf klinische subtypes van chronische UVH werden onderscheiden, wat de diversiteit van de aandoening benadrukt. De aanwezigheid van PPPD bleek een belangrijke voorspeller van verminderde kwaliteit van leven. Dit benadrukt het belang van het herkennen en behandelen van bijkomende vestibulaire aandoeningen in de klinische praktijk.

Voortbouwend op de eerder vastgestelde behoefte aan een specifiek meetinstrument, vergelijkt **Hoofdstuk 5** de uitkomsten van patiëntgerapporteerde klachten tussen patiënten met chronische UVH en patiënten met bilaterale vestibulopathie (BVP). Er werd gebruik gemaakt van gegevens van 100 UVH-patiënten en 148 BVP-patiënten. Verschillen in klachten, functionele beperkingen, emotioneel welzijn en gezondheidsgerelateerde kwaliteit van leven werden geanalyseerd. Hoewel BVP-patiënten ernstigere klachten rapporteerden op aandoeningsspecifieke meetinstrumenten, bleken beide groepen duidelijk slechter te scoren dan gezonde referentiepopulaties. Dit laat zien dat chronische UVH, ondanks dat het vaak als minder ernstig wordt beschouwd dan BVP, eveneens leidt tot een aanzienlijke ziektelast die in de kliniek en het onderzoek vaak wordt onderschat.

Hoofdstuk 6 onderzoekt de constructvaliditeit en betrouwbaarheid van de volledige versie van de Bilateral Vestibulopathy Questionnaire (BVQ) bij een groep patiënten met chronische UVH. Psychometrische analyses, waaronder confirmatieve en exploratieve factoranalyses, toonden een verfijnde structuur met vier schalen: balansproblemen, visueel-ruimtelijke verwerking, gedrag en beperking, en emotioneel welzijn. Deze aangepaste versie met 20 items liet sterke constructvaliditeit, hoge interne consistentie en een aanvaardbare test-hertestbetrouwbaarheid zien. Daarmee levert het voorlopige aanwijzingen dat de aangepaste BVQ geschikt kan zijn als een specifiek meetinstrument

voor chronische UVH. De ontwikkeling is echter niet oorspronkelijk uitgevoerd volgens het COSMIN-kader en het instrument heeft nog geen beoordeling door een expertpanel of cognitieve interviews ondergaan om de inhoudsvaliditeit te waarborgen. Toekomstig onderzoek zou deze stappen moeten omvatten om het instrument verder te verfijnen tot een volledig gevalideerde, conditie-specifieke vragenlijst, die mogelijk de naam Unilateral Vestibulopathy Questionnaire (UVQ) kan krijgen.

Tot slot bespreekt **Hoofdstuk 7** de mogelijke toekomstige rol van vestibulaire implantaten (VI) bij chronische UVH. Deze implantaten zijn in opkomst als behandelmethode bij patiënten met BVP en laten veelbelovende resultaten zien op het gebied van herstel van het evenwichtsorgaan, verbetering van balans en toename van kwaliteit van leven. Hoewel ze momenteel vooral bij BVP worden ingezet, onderstrepen de bevindingen in dit proefschrift het belang van verder onderzoek naar de toepassing van VI bij patiënten met chronische UVH.

10

CHAPTER 10

Impact

IMPACT

This thesis addresses significant gaps in understanding chronic UVH. It examines chronic symptoms, etiologies, diagnostics, co-morbidities, QoL impact, and potential future interventions, particularly vestibular implants. The findings across **Chapters 2 to 7** have evident clinical, methodological, and societal implications.

One of the main contributions of this thesis is the clear description of long-term symptoms in patients with chronic UVH. **In Chapter 2**, a systematic review and meta-analysis showed that symptoms like chronic dizziness and imbalance are very common and long-lasting. These results show that even if the brain starts to adapt and compensate early, it does not always fully decrease the symptoms over time. This finding is explored further in **Chapter 3**, where qualitative interviews revealed a broader symptom spectrum, including visual dependency, cognitive issues, emotional distress, and social withdrawal. Together, **Chapters 2 and 3** demonstrate the clinical need for structured history-taking and detailed evaluation of patients with chronic UVH (1). They provide clear evidence for clinicians to look beyond vertigo and consider a wider range of complaints that impact daily functioning.

Another strength of this thesis is the use of both quantitative data and qualitative insights to better understand chronic UVH. **Chapters 2, 4, 5, and 6** used PROMs (like the DHI, HADS, and EQ-5D-5L) to measure symptom severity and its impact on QoL. In contrast, **Chapter 3** used semi-structured interviews to explore symptoms that are often overlooked by standard PROMs. By using the ICF framework, **Chapter 3** revealed additional challenges such as visual sensitivity, memory issues, and problems with multitasking. However, these are not always captured in standard PROMs. By combining both approaches, the thesis provides a complete picture of patient symptomatology and offers a useful model for future research.

Chapter 4 provides important information about the diverse etiologies, clinical subtypes, co-morbidities and QoL impact. This heterogeneity demonstrates the complexity of the chronic UVH and the need for individualized clinical approaches. The identification of common secondary vestibular disorders (such as BPPV and PPPD) and co-morbidities (like hypertension and non-migraine headaches) demonstrates the need for a multidisciplinary approach in managing chronic UVH. Importantly, the finding that patients with PPPD experience significantly reduced QoL, indicates the need for early recognition of PPPD and integrated psychological support during follow-up. These findings do not only expand our clinical understanding of chronic UVH, but also call for a more individualized, symptom-focused, and patient-centered approach in both diagnosis and management. **Chapter 4**

therefore provides important guidance for improving clinical pathways and delivering more tailored interventions to this under-recognized patient population.

Additionally, there are currently no established diagnostic criteria for chronic UVH. This thesis contributes to filling that gap by first identifying the full range of chronic symptoms through both quantitative and qualitative approaches, providing a strong foundation for the symptom-based component of diagnosis. In addition, across different studies, various diagnostic test parameters, such as caloric testing and video head impulse test (vHIT), were systematically explored, which revealed valuable diagnostic patterns. Together, these findings pave the way for the development of future diagnostic criteria for chronic UVH. Furthermore, they support the integration of both symptom profiles and objective test results into a diagnostic framework.

Chapter 5 compared the QoL between patients with chronic UVH and bilateral vestibulopathy (BVP), using the same PROMs across both groups and a healthy control sample. While BVP patients reported more severe deficits overall, chronic UVH patients also experienced moderate-to-severe disability, which is often underestimated by clinicians. This chapter challenges the assumption that chronic UVH is invariably a mild condition that patients fully compensate for. It shows that chronic UVH can have serious impacts on mobility, mental health, and daily participation. This finding has clear translational implications: clinicians must recognize that chronic UVH deserves the same level of attention and individualized rehabilitation efforts as BVP.

Given the overlap between BVP and chronic UVH symptoms, **Chapter 6** examined the applicability of the Bilateral Vestibulopathy Questionnaire (BVQ) in a chronic UVH population. Although the original BVQ was developed for BVP, the full-length version 50-item version was tested in chronic UVH patients and provided preliminary evidence for its construct validity and reliability in this group. This caused the development of a 20-item adapted version tailored to chronic UVH. However, **Chapter 6** also critically reflects that this version was not yet validated through expert consultation or cognitive interviews and therefore lacks formal content validation according to the COSMIN criteria. This recognition is scientifically important: it highlights that, while the adapted BVQ shows promising psychometric properties, it may not fully capture all aspects of chronic UVH. Therefore, future research should include formal content validation to develop a dedicated questionnaire (2), potentially to be renamed the Unilateral Vestibulopathy Questionnaire (UVQ), ensuring it reflects the specific symptomatology and patient experiences of chronic UVH.

Chapter 7 indicates the future potential of vestibular implants (VI), currently indicated for patients with severe BVP. This chapter critically reviewed the evidence base, surgical techniques, and clinical outcomes of VI, and proposed that a subgroup of chronic UVH patients, those with persistent symptoms and poor central compensation, might also benefit from this intervention. Although VIs are not yet approved for the treatment of chronic UVH, **Chapter 7** highlights a promising direction for future clinical and translational research. Furthermore, **Chapter 2** showed through meta-analysis that vestibular interventions can significantly reduce self-perceived handicap. However, for a subset of patients (~30%) who remain symptomatic despite conventional rehabilitation, alternative strategies such as vibrotactile feedback or VIs should be explored. Expanding VI indications to chronic UVH, could potentially restore function and improve QoL in these cases. This would, however, require careful patient selection, ethical considerations, and individualized stimulation protocols. By proposing a new target population, this thesis contributes to the evolving field of vestibular neuroprosthetics and sets the stage for future clinical trials.

In conclusion, this thesis provides a broad and detailed description of the characteristics of patients with chronic UVH. By using six connected research chapters, it helps us better understand clinical characteristics, symptomatology, diagnostic challenges, co-morbidities, and how this disorder affects daily life. It also offers a new (preliminary) methodological tool for assessment and measurement, and points to future therapeutic innovations such as vestibular implants. These findings have several implications: researchers are provided with a foundation for developing validated outcome measures and testing novel interventions; clinicians are encouraged to adopt a more personalized, symptom-focused approach to diagnosis and rehabilitation; and patients are given a stronger voice, as their lived experiences are incorporated into both clinical care and research design. At a broader level, this thesis calls for improved awareness of chronic UVH within healthcare systems and policy frameworks. By addressing an underdiagnosed and often overlooked condition, it might eventually contribute to reducing long-term disability, enhancing QoL, and lowering societal and economic burdens through earlier identification and more targeted care. By providing these connections between research and practice, the knowledge generated by this thesis can be effectively translated into real-world benefits for patients living with chronic UVH.

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APPENDICES

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APPENDICES

List of publications and presentations

LIST OF PUBLICATIONS

1. Zhu M, Willems P, Marcellis R, Senden R, van Stiphout L, **Karabulut M,** Bijnens W, Nefeli K, Janssen M, Pérez Fornos A, Guinand N, van de Berg R, Meijer K, McCrum C. Criterion and discriminant validity of accelerometer-based analysis of step time and step time variability during treadmill walking in people with bilateral vestibulopathy. OSF Preprint.
2. Zhu M, van Stiphout L, Marcellis R, Senden R, **Karabulut M,** Willems P, Janssen M, Pérez Fornos A, Guinand N, Meijer K, van de Berg R, McCrum C. Unperturbed and perturbed gait variability is increased in bilateral vestibulopathy compared to age-sex-matched healthy participants. OSF Preprint.
3. **Karabulut M,** Kutlu S, Viechtbauer W, Melliti A, Meço C, Mohamad A, Ozgirgin ON, Bhandari A, Kingma H, van de Berg R. Co-occurrence of otologic disorders and benign paroxysmal positional vertigo: Systematic review and meta-analysis. Clinical and experimental otorhinolaryngology. 2025. DOI: 10.21053/ceo.2025-00030
4. **Karabulut M**, Avci H, Yalcinkaya E, Kimman M, Viechtbauer W, Mohamad A, Van Rompaey V, Guinand N, Perez Fornos A, Ozluoglu L, Ozgirgin ON, van de Berg R. Chronic unilateral vestibular hypofunction: A qualitative study exploring the full spectrum of symptoms and impacts through the ICF framework. Frontiers in Neurology. 2025;16(5). DOI: 10.3389/fneur.2025.1589404
5. Karabulut EÇ, **Karabulut M**, Kirazlı G, Akmeşe PP. Factors Influencing Satisfaction, Perceived Disability and Handicap among Hearing Aid Users in the Turkish Population. ENT Updates. 2025 May 28;15(2):10
6. Zhu M, van Stiphout L, Volge B, Janssen M, **Karabulut M**, Perez Fornos A, Guinand N, Meijer K, van de Berg R, McCrum C. Dynamic visual acuity assessment on a treadmill: a crosssectional comparison of dynamic visual acuity loss and dropout rate between people with bilateral vestibulopathy and healthy age- and sex-matched participants. Preprint.
7. Melliti A., Bhandari R, Bhandari A, **Karabulut M**, Rikers E, Paredis S, Vanbelle S, van de Berg R. Telemedicine: Inter-Method Agreement Between In-Person Consultations and Video Recordings When Diagnosing Benign Paroxysmal Positional Vertigo. Journal of Clinical Medicine. 2025;14(7):2495. DOI: 10.3390/jcm14072495
8. **Karabulut M**, Viechtbauer W, Van Laer L, Mohamad A, Van Rompaey V, Guinand N, Perez Fornos A, Gerards M-C, van de Berg R. Chronic unilateral vestibular hypofunction: Insights into etiologies, clinical subtypes, diagnostics and quality of life. Journal of Clinical Medicine. 2024;13(18):5381. DOI: 10.3390/jcm13185381
9. Kartal Özcan E, **Karabulut M**, Karakoç K, Müjdeci B. Is there an association between self-reported dual- task performance and fear of falling in older adults? Journal of Aging and Physical Activity. DOI: 10.1123/japa.2023-0267
10. Öztürk H, **Karabulut M**, Baydan-Aran M, Tokgöz-Yılmaz S. Validity and reliability of the ERSA questionnaire in Turkish. Journal of Deaf Studies and Deaf Education. DOI: 10.1093/deafed/enad064.

11. **Karabulut M,** Van Laer L, Hallemans A, Vereeck L, Van Rompaey V, Viechtbauer W, Melliti A, van Stiphout L, Mohamad A, Fornos AP, Guinand N, van de Berg R. Chronic symptoms in patients with unilateral vestibular hypofunction: Systematic review and meta-analysis. Frontiers in Neurology 2023; 14:1177314. DOI: 10.3389/fneur.2023.1177314
12. Van Laer L, Herssens N, Hallemans A, Van Rompaey V, **Karabulut M,** van de Berg R, Vereeck L. The Association Between Physical Activity and Chronic Symptoms After a Unilateral Vestibular Deafferentation: Narrative Review. B-ENT; 19:50-58. DOI: 10.5152/B-ENT.2023.22176
13. Zhu M, van Stiphout L, **Karabulut M,** Fornos AP, Guinand N, Meijer K, van de Berg R, McCrum C. Assessing balance in people with bilateral vestibulopathy using the Mini-Balance Evaluation Systems Test (Mini-BESTest): feasibility and comparison with healthy control data. Journal of Neurology 2023; DOI:10.1007/s00415-023-11795-y
14. Karakoç K, **Karabulut M**, Kartal Özcan E, Müjdeci B. Audiology Students' Opinions Towards COVID-19 Pandemic: Occupational Perspective and Future Expectations. Hearing, Balance, and Communication 2022; 20(2): 72-78. DOI: 10.1080/21695717.2022.2067720
15. Kaya Ş, Şenli FD, Mecit H, Erataç B, **Karabulut M.** A Study on Stress and Resilience among Hearing Impaired People During the COVID-19 Pandemic. International Journal of Clinical Practice. 2021;00:e14861. DOI: 10.1111/ijcp.14861
16. **Karabulut M,** Baş B, Müjdeci B. Evaluation of Dual-Task Performance with Nintendo Wii-Fit Plus in Children with Specific Learning Disabilities. Hearing, Balance, and Communication 2021; 19(2): 126-132. DOI: 10.1080/21695717.2020.1870822
17. Baş B, **Karabulut M,** Müjdeci B. Evaluation of Balance Test Outcomes in Children with Poor Vision. Cyprus Journal of Medical Sciences 2020; 5: 284-288. DOI: 10.5152/cjms.2020.1156

PRESENTATIONS

05/2025	Vestibular Implants: Present Status and Future Prospects. I. Biruni International Health Sciences Congress, Istanbul, Türkiye
05/2025	Vestibular Implants. VI. Otology & Audiology Congress, Istanbul, Türkiye
05/2025	Vestibular Implantation in Practice: Case-Based Reflections and Outcomes. I. OKSUD Audiology Student Congress, Ankara, Türkiye
04/2025	The quality of life in patients with chronic unilateral vestibular hypofunction. Vertigo Academy International (VAI-6), Budapest, Hungary
04/2025	Unilateral vestibular hypofunction. 20th Middle East Academy of Otorhinolaryngology Congress, Dubai, United Arab Emirates
11/2024	3rd International Congress of the Mirko Tos Ear & Hearing Research Center. Preclinical, Clinical, and Innovative Approaches in Inner Ear Diseases: A Multidisciplinary Symposium, Edirne, Türkiye
10/2024	Artificial intelligence applications in vestibular and balance systems and the future. 12th National Congress of Audiology and Speech Disorders, Ankara, Türkiye
09/2024	Chronic unilateral vestibular hypofunction: Insights in etiologies, clinical subtypes, diagnostics and quality of life. World Congress of Audiology, Paris, France
08/2024	Otological disorders in patients with benign paroxysmal positional vertigo (BPPV): A systematic review. BARANY Meeting, Uppsala, Sweeden (Poster Presentation)
08/2024	Chronic unilateral vestibular hypofunction: Insights in etiologies, clinical subtypes, diagnostics and quality of life. BARANY Meeting, Uppsala, Sweeden (Poster Presentation)
02/2024	Unilateral Vestibular Hypofunction. Middle East Vestibular Competency Course, Bahrain
12/2023	Unilateral Vestibular Hypofunction. Ege University I. International Audiology Symposium: Multidisciplinary approach to vestibular diagnosis and assessment. (Hybrid meeting), İzmir, Türkiye
12/2023	The Future of the Vestibular System. I. Gazi Symposium: Functional Perspective on the Vestibular System, Ankara, Türkiye
09/2023	Assessing Quality of Life via Patient-Reported Outcome Measures in Adults with Cochlear Implant Users: A Systematic Review. 7th World Congress of Cochlear Implantation in Emerging Nations, Istanbul, Turkiye
03/2023	Chronic Symptoms in Patients with Unilateral Vestibular Hypofunction. VAI-5, Belgrade, Serbia
05/2022	Chronic Symptoms in Patients with Unilateral Vestibular Hypofunction. BARANY Meeting, Madrid, Spain (Poster Presentation)

APPENDICES

Curriculum Vitae

CURRICULUM VITAE



Mustafa Karabulut was born on October 23, 1994, in Aksaray, Türkiye, and spent his childhood years in Erzurum and Rize. In 2012, he graduated from Erdemli Anatolian High School in Mersin. He received his Bachelor of Science degree in Audiology from Hacettepe University, Ankara in 2016. Between 2016 and 2019, Karabulut completed his Master of Science in Audiology at Hacettepe University, Ankara, Türkiye. During this period, he developed a particular interest in vestibular diagnostics and balance disorders. In 2017, he was awarded a national scholarship by the Turkish Ministry of National Education to pursue graduate-level academic training abroad. From 2017 to 2019, he also worked as a research assistant at Ankara Yıldırım Beyazıt University. As part of the scholarship program, after resigning from this position, he received six months of English language education at Kent State University in Ohio, United States of America in 2019. Motivated by his growing academic interest in vestibular sciences, Karabulut began his PhD in 2020 at Maastricht University Medical Center (MUMC+), Maastricht, Netherlands under the supervision of Prof. Dr. Raymond van de Berg. His doctoral research focused on chronic unilateral vestibular hypofunction, investigating its symptomatology, etiologies, clinical subtypes, diagnostic challenges, and impact on quality of life. During his PhD, he actively contributed to research, teaching, and student mentoring, and presented his work at numerous national and international scientific conferences. Karabulut's academic journey reflects a sustained commitment to vestibular science and a broader aim of improving clinical understanding and care for patients with balance disorders.