Vestibular symptoms and relations with postural balance, inner ear function, and long term survival

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1. Abbreviations

ANOVA: Analysis of variance

BPPV: Benign paroxysmal positional vertigo

CI: Confidence interval

COP: Center of pressure

cVEMP: Cervical vestibular evoked myogenic potentials

dB: Decibel

CDP: Computerized dynamic posturography

HIT: Head impulse test

HR: Hazard ratio

Hz: Hertz

kHz: Kilohertz

ICD-11: International classification of diseases, 11th edition

ICVD: International classification of vestibular disorders

MRI: Magnetic resonance imaging

OR: Odds ratio

oVEMP: Ocular vestibular evoked myogenic potentials

PPPD: Persistent postural-perceptual dizziness

SCDS: Superior canal dehiscence syndrome

SOT: Sensory organizational test

TIA: Transitory ischemic attack

VEMP: Vestibular evoked myogenic potentials

VNG: Videonystamography

VOR: Vestibuloocular reflex

2. Scientific environment

This work was carried out at the Norwegian National Advisory Unit on Vestibular Disorders and at the Department of Clinical Medicine at the University of Bergen under the supervision of Frederik Kragerud Goplen and co-supervisors Hans Jørgen Aarstad and Stein Helge Glad Nordahl. The National Advisory Unit on Vestibular Disorders is closely linked with the vestibular testing laboratory at the Department of Otorhinolaryngology at Haukeland University Hospital where patients are evaluated for suspected vestibular disorders. Patients are referred to the department from general practitioners in the region around Bergen (population approx. 500,000) and from specialists around the country if advanced vestibular evaluation is needed. All patients with vestibular schwannomas in Norway (pop 5.4 mill) are referred to the Norwegian National Unit for Vestibular Schwannomas, which is a collaboration between the Department of Otorhinolaryngology and the Department of Neurosurgery at Haukeland University Hospital. The study was made possible by extensive work performed in the late 1990s and into the early 2000s when patients referred to vestibular testing at Haukeland University hospital were thoroughly examined and both clinical findings and patient reported symptoms were documented in a systematic way.

3. Abstract

Background: Dizziness and unsteadiness are common symptoms that can be caused by pathologies in various organ-systems. In the general population such symptoms are associated with increased mortality, but it is not known if this increased mortality is caused by vestibular pathology. Today, many of the common vestibular diagnoses depend on patient-reported symptoms alone, and the evidence base for evaluating and treating patients with dizziness has been described as low.

Aim: To critically evaluate which symptoms reported by dizzy patients provide useful information, and further to evaluate the interrelations between posturography, inner ear function, and long-term survival.

Material and methods: A cohort of patients examined from 1992 to 2004 at an otolaryngology department for suspected vestibular disorder.

Results: While most patients (72.1%) chose only one timing category, fewer than half the patients (47.1%) describe their complaints with only one type of dizziness. Vomiting was associated with increased risk for caloric asymmetry (Odds ratio 1.60, 95 % CI 1.24–2.06). A 10-dB increase in hearing loss in the best-hearing ear was associated with a 6.0% increase in path length measured on a balance platform. The standardized mortality ratio was 1.03 (0.94–1.12). Periodic or short attacks of dizziness were associated with reduced mortality with a hazard ratio of 0.62 (0.50–0.77) and 0.76 (0.63–0.93), respectively. Both self-reported and unsteadiness on posturography were associated with increased mortality with a hazard ratio of 1.30 (1.08–1.47) and 1.44 (1.14–1.82).

Conclusions: The timing of vestibular symptoms and a differentiation between nausea and vomiting should be targeted when interviewing patients. The type of dizziness provides additional information but does not appear useful for categorization. The association between hearing and postural balance was not explained by unilateral vestibular disorders. Vestibular pathology is probably not the main cause of the increased mortality seen among patients with vestibular symptoms and balance problems in the general population. Further studies exploring cause of death related to vestibular symptoms, hearing, and postural balance are advocated.

4. Sammendrag (*Abstract in Norwegian)*

Bakgrunn: Svimmelhet og balanseproblemer er vanlige symptomer som i befolkningsstudier har vært assosiert med økt dødelighet, men det er ikke kjent om det er sykdommer i balanseapparatet som forårsaker denne økte dødeligheten. Kunnskapsgrunnlaget for å vurdere og behandle pasienter med svimmelhet har vært vurdert som dårlig og ofte er det kun pasientens beskrivelse av symptomer som danner grunnlaget for å diagnostikken.

Mål: Å evaluere hvilke symptomer som gir nyttig informasjon, og undersøke sammenhenger mellom balanse, funksjonen av det indre øre og langtidsoverlevelse.

Materialer og metode: En gruppe pasienter henvist for vurdering med tanke på vestibulær sykdom i perioden mellom 1992 og 2004.

Resultater: De fleste pasienter (72,1%) valgte kun en tids-kategori for å beskrive sine symptomer, mens mindre enn halvparten (47,1%) valgte kun en type svimmelhet. Oppkast var assosiert med økt risiko for asymmetri på kalorisk prøve (odds ratio 1,50. 95% konfidensintervall 1,24-2,06). 10-dB økning i hørselstap på det best hørende øret var assosiert med 6,0% økning i kurvelengde. Standardisert mortalitetsrate var 1,03 (0,94-1,12). Periodiske eller korte anfall av svimmelhet var assosiert med redusert dødelighet med hasard rate på henholdsvis 0,62 (0,50-0,77) og 0,76 (0,63-0,93). Pasient-rapportert ustøhet og ustøhet målt ved posturografi var assosiert med økt dødelighet med hasard rate på 1,30 (1,08-1,47) og 1,44 (1,14 – 1,82).

Konklusjon: Det bør fokuseres på tidsaspektet av vestibulære symptomer og det bør skilles mellom oppkast og kvalme. Hvilken type svimmelhet pasienten opplever gir noe tilleggsinformasjon, men virker ikke å være nyttig for å kunne gruppere pasienter. Vestibulær sykdom kunne ikke forklare sammenhengen mellom hørsel og balanse i denne studien og vestibulær sykdom ser ikke ut til å være hovedårsaken til den økte dødeligheten blant personer med svimmelhet og balanseplager i den generelle befolkningen. For å finne årsakssammenhenger er det behov for ytterligere studier på dødsårsaker blant pasienter med vestibulære symptomer, vestibulær sykdom, dårlig balanse og nedsatt hørsel.

5. List of Publications

1. Berge JE, Nordahl SHG, Aarstad HJ, Gilhus NE, Goplen FK. Evaluation of Self-reported Symptoms in 1,457 Dizzy Patients and Associations with Caloric Testing and Posturography. Otology & Neurotology. 2020 Aug 14;41(7):956–63.

2. Berge JE, Nordahl SHG, Aarstad HJ, Goplen FK. Hearing as an Independent Predictor of Postural Balance in 1075 Patients Evaluated for Dizziness. Otolaryngology–Head and Neck Surgery. 2019 Sep 23;161(3):478–84.

3. Berge JE, Nordahl SHG, Aarstad HJ, Goplen FK. Long-Term Survival in 1,931 Patients with Dizziness: Disease- and Symptom-Specific Mortality. Laryngoscope. 2021 Jun 20;131(6).

4. Berge JE, Goplen FK, Aarstad HJ, Storhaug TA, Nordahl SHG. The Romberg Sign, Unilateral Vestibulopathy, Cerebrovascular Risk Factors, and Long-Term Mortality in Dizzy Patients. Frontiers in Neurology 2022;13

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7. Introduction

7.1 Background

The vestibular sense is not something we are conscious of in everyday life, and Aristotle did not include it, nor did he include the sense of proprioception, in his classic "five" senses (figure 1) (1). Still, they are both important for balance and movement and we become highly conscious of the vestibular system when it is affected by disease.

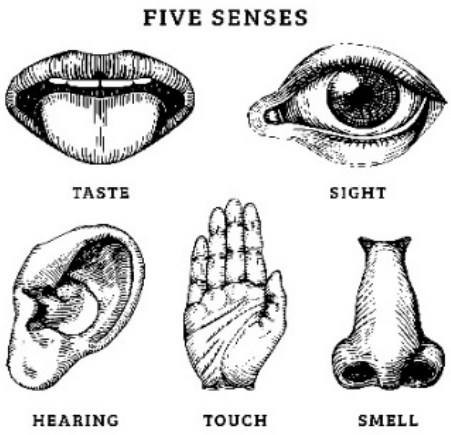

Figure 1. The five senses described by Aristotle, Colourbox.com

Dizziness and poor balance are very common in the general population, somewhat more so in women, and increase in prevalence with age, as shown in figure 2.

Even if these are common symptoms, they should not be considered trivial because people with dizziness or balance problems have twice the mortality of people without such symptoms (2).

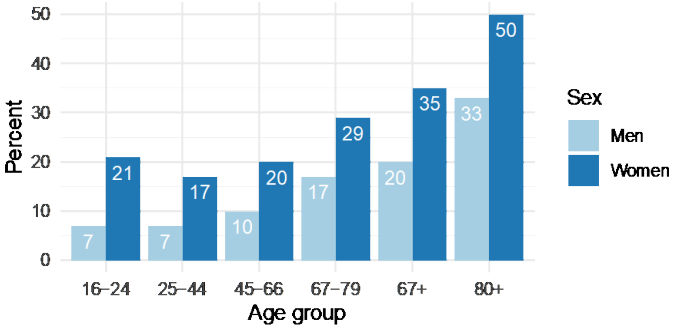

Figure 2: Dizziness or poor balance. Problems lasting 3 months according to self-reported prevalence in the Norwegian population by age and sex. Statistics Norway Health Survey 2019 (www.ssb.no)

Other consequences of vestibular symptoms include impaired quality of life (3), reduced social activity (3), and, in many cases, long-term absence from work (4). Balance and walking problems have been found to cause a greater loss in quality-adjusted-life-years than falls among older adults(5).

Patients presenting with these common and potentially dangerous symptoms can be difficult to diagnose, and many present-day clinicians will probably agree with the quote by famous neurologist W.B. Matthews from 1963*: 'There can be few physicians so dedicated to their art that they do not experience a slight decline in spirits when they learn that their patient's complaint is giddiness. This frequently means that after exhaustive enquiry it will still not be entirely clear what it is that the patient feels wrong and even less so why he feels it."*(6)

However, since the days of W.B. Matthews, there have been major developments in our understanding of common vestibular disorders including benign paroxysmal positional vertigo, postural-perceptual dizziness, and vestibular migraine. In addition, our ability to measure the function of the vestibular system and to treat its disorders has also increased dramatically. Nevertheless, the conclusion from a review in 2010 was that the evidence base for evaluating and treating patients with dizziness was low(7), and there are still challenges with diagnosing patients with vestibular symptoms today.

Several factors may explain why the diagnosing patients with dizziness or vertigo is challenging. First, there is a wide range of possible causes from many different organ systems, and these range from benign to potentially life-threatening conditions. Secondly, many patients find it difficult to describe their symptoms and the physicians find it difficult to interpret what the patient is describing. Thirdly, vestibular tests often have limited diagnostic sensitivity and specificity on their own and need to be applied to patients with certain well-defined symptoms.

In most cases an interview is necessary to extract the diagnostic elements necessary to determine a diagnosis, to rule-out other causes, and to determine if other examinations are needed. As illustrated by table 1, specific anamnestic information is

required for most of the common vestibular diagnoses. For two of the most common diagnoses, vestibular migraine and persistent postural-perceptual dizziness (PPPD), it is the patient history alone that determines the diagnosis.

Table 1. Elements required in diagnostic criteria published by the International Classification of Vestibular Disorders (ICVD)

Diagnosis	Patient-reported symptoms[a]	Clinical findings[a]	Imaging[a]	Laboratory testing
Benign Paroxysmal Positional Vertigo(8)	X	X	-	-
Vestibular migraine(9)	X	-	-	-
Persistent Postural-Perceptual Dizziness(10)	X	-	-	-
Menières disease(11)	X	-	-	X
Vestibular neuritis/acute unilateral peripheral vestibulopathy (12)	X	X	-	X[b]
Bilateral vestibulopathy(13)	X	-	-	X
Superior canal dehiscence syndrome(14)	X	X[c]	X[c]	X[c]
Vestibular schwannoma	-	-	X	-
Mal de débarquement syndrome(15)	X	-	-	-
Orthostatic dizziness/vertigo (16)	X	-	-	X
Vestibular paroxysmia(17)	X	-	-	-

[a] Clinical findings, symptoms and imaging may be necessary to diagnose comorbidities or other causes of the patients' complaints
[b] May be necessary if the bed-side tests are unclear
[c] At least one of these

When so much of the diagnostics are based on vestibular symptoms it is important to know what these symptoms represent and to critically evaluate if these symptoms present reliable information. The following sections will include a description of the anatomic and physiological basis for the vestibular and postural systems.

7.1.1 The vestibular system

The main functions of the vestibular system are considered to be maintaining a steady gaze during head movements, balance control, and detection of self-motion and orientation of the head in relation to gravity (18). The semicircular canals, the otolith organs, the vestibular nerve, the vestibular nuclei, the vestibulo-cerebellum, and the vestibular cortex are defined as the major structures of the vestibular system (18). The vestibular system has also been defined more broadly as the sensory inputs, central processing, and motor outputs that relate to balance (19). However, "balance" is a wide term that has many meanings. In this thesis the first definition of the vestibular system is used.

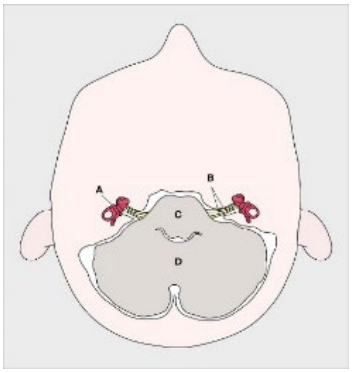

Figure 3: Position of the labyrinth in the inner ear. A. The labyrinth. B. The vestibular and cochlear nerve. C. The brainstem. D. The cerebellum.
Frederik Kragerud Goplen. https://snl.no/vestibul%C3%A6re_sykdommer

7.1.2 The vestibular end organs and vestibular nerve

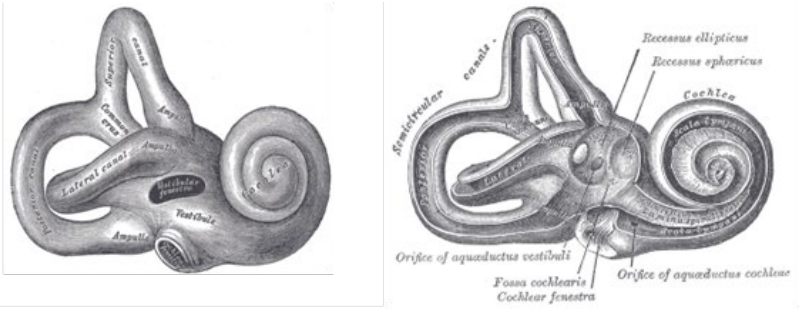

Figure 4: The right osseous labyrinth, lateral and inferior view. Drawing from Gray's Anatomy (1918), 20th edition

The vestibular sensory organs are located in the labyrinth (figure 3,4) and consist of three semicircular canals and two otolith organs – the utricle and the saccule (20). The semicircular canals are oriented orthogonally, and each canal is mirrored by a

corresponding canal on the opposite side of the head (20) The motion sensors in the labyrinth are hair cells that act as mechanoreceptors to detect displacement (18,21).

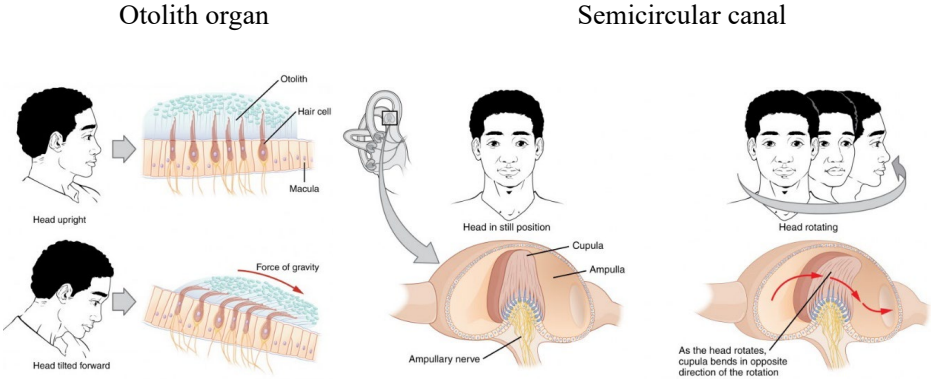

Figure 5: Illustration of head tilt and rotation with corresponding effect on the otolith and semicircular canals. OpenStax College. Anatomy & Physiology, Connexions Website. http:enx.orgcententcoll114961.6, Jun 19, 2013

The otolith organs (the saccule and utricle) have a gelatinous mass with heavy calcium carbonate crystals (otoliths) on top. Movement or tilting will cause a shift in the gelatinous mass and consequently a deflection of the cilia on the hair cells (21,22)(figure 5). The semicircular canals are considered to be more recent phylogenetic developments and consist of fluid-filled canals with a sensory area called the cupula where hair cells can detect deflections of the cupula due to movements in the fluid caused by rotation (18,21,23). Tilt is reported to activate both the otoliths and the semicircular canals, and the semicircular canals provide additional information on rotation (18) while translation is thought to only activate the otolith organs (21).

The sensitivity of the hair cells to translation, rotation, tilts, and sound does not appear to depend so much on the type of hair cell, but rather on the orientation and plane in which the hair cells are built into gelatinous structures in the specific organs, namely the cupula in the semicircular canals, the macula in the vestibule, and the organ of Corti in the cochlea (18,21).

One important functional aspect of the hair cells is that they are mechano-receptors with a resting potential that can be both increased and decreased, and the potential for excitation is larger than the potential inhibition (24). Therefore, the hair cell has been called a mechano-receptor with asymmetric sensitivity (18). In the semi-circular canal all hair cells are oriented in the same direction so that all hair cells are either inhibited or excited from a specific stimulus (18,25).

The signals from the vestibular sensory organs are transmitted by the superior and inferior branch of the vestibular nerve to the brainstem where the signals are further distributed in the central nervous system (25).

7.1.3 Central vestibular pathways

The central vestibular pathways in humans are very complex, and certain elements might be relevant when trying to understand how patients experience and describe their vestibular symptoms and how vestibular function can be tested.

One feature is that neurons that receives input from the vestibular nerve can send direct projections to motor neurons (26). This is the exemplified by the very fast vestibuloocular reflex (VOR) that is crucial in gaze stabilization. This allows a person to keep their eyes on a target while the head is moving. The VOR is a three-neuron reflex-arc from the semicircular canal through the vestibular nerve to the brainstem, and further to the extraocular muscles. This reflex initiates compensatory eye-movements within approximately 7–10 ms (27).

Compared to the peripheral vestibular sensory organs, the central vestibular pathways become much more complex in higher vertebrates, probably to take advantage of other input such as vision and proprioception to maintain equilibrium (21). This illustrates a second feature of the vestibular system that the first stage of central processing is already very multimodal, receiving somatosensory, visual, proprioceptive, and motor input from numerous areas of the brainstem, cerebellum, and cortex (26,28). For instance, as we move through the environment, large field visual motion induces reflexive eye movements to maintain stable gaze relative to the visual space. These compensatory eye movements are termed the optokinetic reflex

(26), and in fact most secondary vestibular neurons appears to be driven by optokinetic visual stimulation in addition to vestibular stimulation (28). This optokinetic reflex has been described to be dependent on both brainstem and cortical input and to work synergistically with the vestibuloocular reflex to maintain gaze stability. Usually, the central nervous system receives information from proprioception, vision, and the vestibular organs that is congruent (29) and thereby to some degree receives redundant information.

A third feature is flexibility in the central vestibular pathways where humans and primates can attenuate or suppress the three-neuron VOR by voluntarily redirecting the gaze when they voluntarily move their eyes or head in order to explore the environment (26). To discriminate passive from active movement is essential in order to perform accurate movements with perceptual stability, but how the brain matches various input to discriminate this is not completely understood (30).

The vestibular system also has the capability to adapt both to changes in the environment and to disease or damage. In early life the VOR needs to adapt to a growing head, and as people get older it also compensates for lowered sensitivity of the vestibular apparatus and the use of corrective lenses for nearsightedness (26). One impressive demonstration of this plasticity of the VOR was the experiment by Gonshor and Melville Jones where a functional reversion of the VOR was seen in healthy subjects after wearing prisms that reversed the horizontal vision for 27 days (31).

A final characteristic of the central vestibular system is that there does not appear to be a single primary cortical area processing only vestibular information (26,32) and this differs from the other sensory systems such as the visual, somatosensory, and auditory system (32). Even though tracer studies in primates (33) and imaging studies (34) have indicated a vestibular cortical system, the regions of the cortex receiving vestibular input also seems to receive and interpret other sensory information (32,33).

Even though all the interactions in the human brain that process information from the vestibular system are not fully understood (29) it is evident that vestibular processing

integrates multimodal information and is very adaptive (26), but without reaching or requiring conscious awareness in everyday situations.

7.1.4 The auditory system

The cochlea contains the hearing organ in the inner ear (figure 4) (20). The organ of Corti, which is the auditory transducer, contains inner and outer hair cells, nerve endings, and supporting cells. Sound transmitted via the oval window induces a travelling wave in the basilar membrane, and this creates a relative movement and bending of the hairs of the hair cells (35). The bending of hair cells opens mechanotransducer ion channels producing a change in potential. The travelling wave is tuned to a sharp peak by the active mechanical action of the outer hair cells. The active amplification is non-linear and most active for low intensity stimuli, thus increasing the functional range of the auditory system (35).

The cochlear nerve transmits auditory stimuli to the cochlear nucleus in the brainstem. Auditory nerve fibers are responsive to tone stimuli, and in the absence of other stimuli they are only excitatory and not inhibitory (35). In 1930 Wever and Bray performed an experiment with an anesthetized cat where they attached an electrode to the auditory nerve and connected this to an amplifier and microphone in a soundproof room 16 meters away. This experiment showed how sound is transmitted through the ear and to the auditory nerve in a very conserved manner, including a correlation of frequency between impulse and stimuli, and this differs from other sensory organs. When the cat died, the transmission stopped, thus illustrating how this is an active process (36).

From the cochlear nucleus the stimulus is further transmitted via the other subcortical nuclei to the cerebral cortex (37). The central auditory system has multiple pathways that overlap and run in parallel. It has been suggested that the complexity of this system has evolved in order to maintain the ability to detect variations over microseconds (as is important in sound localization) in addition to the ability to extract stimuli via lateral inhibition to detect dominant features from the background (37). In addition, a centrifugal system transmitting information from the central

auditory structures to the periphery in order to enhance significant stimuli at other stages of the auditory system has been described (37).

7.1.5 Hearing, comorbidities, and survival

Several studies have investigated the relationship between hearing loss, morbidity, and mortality. Hearing loss has been associated with cognitive decline (38) and increased loneliness (39), which might lead to subsequent physical and mental deterioration. Further, hearing loss has been associated with both a substantial decline in mobility over the next year (40) and with falls (41). In a Korean national cohort, there was increased mortality among patients with severe to profound hearing loss (42). In this population, death from trauma had the highest odds ratio even though hearing loss was also associated with many other causes of death including infection, metabolic, neoplastic, circulatory, and respiratory disorders. In an Icelandic study, older men with hearing impairment had increased cardiovascular-related mortality, but this effect was not significant for women (43) and a Swedish study found increased mortality for circulatory disorders among persons with disability due to otological disorders (44). A relationship between cardiovascular risk factors and hearing has been established, but the relevance of this relationship has been disputed (45,46).

However, the causal relationship between hearing loss and other health problems and mortality has not yet been determined (47). Several possible hypotheses have been presented including common auditory and vestibular dysfunction (47), cardiovascular disease causing a reduction in the blood flow to the cochlea with subsequent atrophy of the stria vascularis (45) and vascular dementia being a common pathway with both age-related hearing loss and frailty (48).

7.1.6 Postural balance

Humans are capable of a bipedal stance and walking. These are complex tasks, and one might expect the vestibular apparatus to be the main sensory organ for a steady stance. However, it does not appear to be quite so simple. To stand upright on two

feet and move around is a task that requires the neural integration of both visual, proprioceptive, and vestibular information (33,49–51).

When standing still, body sway is detected by proprioception and visual and vestibular input that is processed by the central system and corrective movement is effectuated by the muscles (52). In addition to this active torque, postural balance is probably also maintained by passive torque (generated by muscle tone without delay) and by feedforward predictive mechanisms (52). The various systems of postural control appear to be mutually interactive, and the functional range of the systems overlap, thus permitting them to compensate in part for each other's deficiencies (53).

Postural control has also been related to cognitive function, and reaction times increase when persons are standing versus sitting (54). The effect of attention and cognitive function on simple balance-tasks is small among younger individuals, but for older individuals even simple postural challenges are more attentionally challenging and secondary tasks can be deleterious for postural balance (55).

The relationship between hearing and postural balance is also being increasingly recognized. It has been shown that humans can use auditory cues to maintain balance (56–59) and that noise causes increased visual dependence to maintain stability (57). Among older adults without vestibular disorders there is a positive association between hearing loss and postural control (60). There are also indications that hearing aids may improve postural balance (61).

As indicated in the former section on central vestibular pathways, the sensory systems can produce conflicting information and the control of postural must be adaptive and flexible such that information from the sensory systems can be reweighted depending on the situation (62,63). For instance, in a crowd where the surroundings are moving the visual information is unreliable and does not correlate with vestibular and somatosensory information, and on sand the ground is soft and does not provide accurate proprioceptive information. One example of how the brain uses available information is how just light touch of the finger can dramatically

improve postural stability both in healthy controls and in patients with vestibular loss (64).

Additionally, a rapid re-weighting of sensory information is necessary when walking from a well-lit area into a dark area. It has been reported that such rapid re-weighting can be affected by disorders in the central nervous system such as Alzheimer's disease (50).

Everyone will have their own unique set of constraints and resources available to control posture, and it is hypothesized that each individual person will have their own unique strategy dependent on the postural challenge at hand (50).

However, the complex interplay and the foundational theory of postural function are not clear on the contribution of sensory, central, and motor components (49,65). With such a multifaceted postural function, it is also evident that a multitude of neurological diseases and disorders of the visual, proprioceptive, vestibular, or motor control systems can lead to balance problems (66).

7.2 The significance of patient-reported symptoms in the diagnosis and prognosis of vestibular disorders

7.2.1 Nomenclature of vestibular symptoms

Considering the complex vestibular pathways described in the previous paragraphs, it is not surprising that the description and interpretation of vestibular symptoms is challenging. However, much of the diagnostics on vestibular disorders depend on just these symptoms and therefore it is important to know if these symptoms provide reliable information.

The terminology on vestibular symptoms has been confusing with many considering "dizziness" an umbrella term including other terms such as vertigo (67) , while some authors describe exactly the opposite (68).

Over the last decades much work has therefore been done to standardize the nomenclature for vestibular symptoms. In 2006, the Classification Committee of the Bárány Society had its first meeting to establish the International Classification of Vestibular Disorders (ICVD) with the aim to provide evidence-based consensus and standardization regarding syndromes, diseases, diagnostic procedures, and treatments. The work is performed by subcommittees where both otolaryngologists and neurologists are represented (69). Multiple consensus documents have been published, and the first of these "Classification of vestibular symptoms: Towards an international classification of vestibular disorders" from 2009 defined the vestibular symptoms of dizziness, vertigo, postural symptoms, and vestibulovisual symptoms (table 2) (19).

Table 2:

Primary vestibular symptom definitions in the International Classification of Vestibular Disorders

Dizziness -Spontaneous dizziness -Triggered dizziness	The sensation of disturbed or impaired spatial orientation without a false or distorted sense of motion.
Vertigo -Spontaneous vertigo -Triggered vertigo	The sensation of self-motion (of head/body) when no self-motion is occurring or the sensation of distorted self-motion during an otherwise normal head movement.
Vestibulovisual symptoms -External vertigo -Oscillopsia -Visual lag -Visual tilt -Movement-induced blur	Visual symptoms that usually result from vestibular pathology or the interplay between visual and vestibular systems. These include false sensations of motion or tilting of the visual surround and visual distortion (blur) linked to vestibular (rather than optical) failure.
Postural symptoms -Unsteadiness -Directional pulsion -Balance-related near fall -Balance-related fall	Balance problems related to maintenance of postural stability, occurring only while upright (seated, standing, or walking).

Adapted from Bisdorff AR, Staab JP, Newman-Toker DE. Overview of the International Classification of Vestibular Disorders. *Neurol Clin*. 2015;33(3):541-550

However, despite this extensive work the description of vestibular symptoms is still challenging. In a recent study by Sommerfeldt and colleagues there were differences between how patients and providers interpreted the term “dizziness (70). This indicates that the definitions from the consensus document are not well known and not always intuitive for patients or for practitioners. In that study participants were asked “what is dizziness”, and multiple responses were possible. Approximately half of the patients reported “disoriented” compared to only 13% of otolaryngologists and 36% of non-otolaryngologists. Notably, none of the predefined responses matched exactly with the definition from the Bárány Society.

7.2.2 Patients’ description of dizziness and vertigo – types of symptoms

Historically, some experts have argued that the first triage of patients with dizziness should be based on whether the patient experiences “true vertigo” or something else, like impending fainting or unsteadiness. This has been attributed (71) to an influential paper published by Drachman and Hart 1972 where they examined 125 patients with dizziness (72). They interviewed and examined the patients and classified their complaints into four different types – spinning vertigo, impending fainting, loss of balance, and lightheadedness – and found this to be relevant for the diagnoses of the patients. Variations on this approach is still recommended in recent papers on vestibular diagnostics (73,74), and it is employed in emergency departments and in primary care (75–77). However, the original paper by Drachman and Hart has been criticized (71) based on the finding that patients change their responses when asked repeatedly (low reliability) (78,79), that they report several types of dizziness (80), and that a given response may represent a variety of disorders (low validity) (79,81,82). For instance, it has been shown that patients with cardiologic and neurologic disorders can experience spinning vertigo (83), women and men describe their vestibular symptoms differently (79), and younger patients may be more prone to describe true vertigo while older patients tend to report unsteadiness or falling (84). The implication of these findings is that the differentiation of vertigo and dizziness might be less clinically relevant than previously thought (85).

In epidemiology, vertigo, dizziness, and balance problems are often combined (2,86). However, postural symptoms are defined as a distinct category in the ICVD with unsteadiness as the preferred term for postural instability (19). Whether it is clinically relevant to differentiate between unsteadiness and other vestibular symptoms is not well studied.

7.2.3 Time-course of vestibular symptoms

Due to the formerly mentioned inconsistencies in how patients describe their type of symptoms, several authors have recommended not focusing on types of dizziness at all, but rather the *timing* of the symptoms (77,81,87–90). This approach allows for a categorization of vestibular diagnoses as clinical syndromes (85):

1. Acute vestibular syndrome: disorders that present with a single episode of acute onset and persisting symptoms such as vestibular neuritis or stroke.

2. Episodic vestibular syndrome: disorders with recurrent symptoms such as vestibular migraine, benign paroxysmal positional vertigo (BPPV), and Meniéres disease

3. Chronic vestibular syndrome: disorders that produce persistent vestibular symptoms over time such as persistent postural-perceptual dizziness (PPPD) and bilateral vestibulopathy

This categorization is now implemented in the International Classification of Diseases, 11th edition (ICD-11) and the International Classification of Vestibular Disorders (ICVD) (85,91). The main paper to support this new classification is the study by Newman-Toker and colleagues from 2007 where they found that timing could be used to group patients because only 16% of the patients chose more than one out of six timing categories. This was much better than what they found for reports on type of dizziness (92). However, it should be noted that when asked repeated questions, 19% of the patients changed their timing-category in this study. Because the focus of that study was on the “type” of dizziness, the details on how patients

reported timing of dizziness were not described and the timing-categories did not correspond to the new categories in ICVD and ICD-11. It therefore seems that the new classification still needs to be critically evaluated in clinical studies.

7.2.4 Triggers of vestibular symptoms

Another element of the patient history that has been emphasized is whether the vestibular symptoms are *triggered* (71,87–89,93). This element has also been included in the ICVD to separate spontaneous vertigo/dizziness from triggered vertigo/dizziness. This was also supported by the Newman-Toker paper in 2007 where triggers showed promising results with only 9% of patients providing inconsistent answers on repeated questioning. However, this was displayed in a table without further discussion in the paper (92).

In the classification by ICVD, triggered symptoms should be time-locked to the stimulus, and in most cases a repetitive, reproducible relationship between the triggering stimuli and symptoms should be present (19). Edlow emphasizes that triggers should be differentiated from exacerbating features that worsen pre-existing symptoms (71). This terminology differs from how the term “trigger” is used when discussing migraine where stress or various foods are considered triggers for attacks (94), but in a more unpredictable and variable way than what is considered a trigger for vestibular disorders.

By implementing triggered vs. spontaneous symptoms, it is possible to further differentiate the acute and episodic vestibular syndromes (examples of diagnoses in italics) (87):

1. Acute vestibular syndrome
    i. Triggered: *Temporal bone trauma, intoxications*
    ii. Spontaneous: *Vestibular neuritis, stroke*
2. Episodic vestibular syndrome
    i. Triggered: *BPPV, orthostatic hypotension*
    ii. Spontaneous: *Vestibular migraine, Meniéres disease*

A study on adolescents with concussions did not find that triggers were associated with etiology (82), and apart from the aforementioned study by Newman-Toker and colleagues from 2007 (92) there do not appear to be any dedicated studies on the diagnostic value of patient-reported triggers in general.

7.2.5 Associated symptoms

Other symptoms that are not directly vestibular in character can also be important. Examples are bone conduction hyperacusis reported by patients with superior canal dehiscence syndrome (SCDS) (14), visual auras or headaches associated with vestibular migraine (9) or fluctuating hearing loss, tinnitus, or aural fullness associated with Menière's disease (11).

Some symptoms were deliberately excluded from the ICVD. This includes symptoms that are less specific to vestibular disorders (syncope, dysarthria, diplopia), neurovegetative symptoms (nausea, vomiting, fatigue, malaise, weakness), and neuropsychiatric symptoms (anxiety, depression) (19). Such symptoms are important to determine if there are comorbidities such as syncope that can be indicative of cardiac disease, and in particular anxiety or depression that is relevant for both the treatment and prognosis of vestibular disorders (95). The neurovegetative symptoms are very common among patients with vestibular disorders, but there is a lack of studies evaluating the diagnostic value of these symptoms.

7.2.6 Different causes of vestibular symptoms, comorbidities, and mortality

In addition to disorders of the vestibular system, there are a multitude of other disorders that can cause similar complaints (83,87) and this must be considered both in diagnosing patients and when trying to understand why vestibular symptoms are associated with mortality.

Historically, isolated vertigo was considered as a benign symptom primarily due to peripheral vestibular disease, but with recent advances in clinical neurotology and imaging there has been an increase in diagnosed strokes in the cerebellum and brainstem among patients with isolated vertigo (96). The prevalence of stroke has

now been reported to be 11% in patients admitted with isolated vertigo or dizziness attacks (97), and in one study the prevalence was as high as 27% in patients with acute transient vestibular syndrome (98). Among patients with isolated “benign” vertigo or dizziness in emergency departments there is reported to be an increased risk of cardiovascular events (99–101) and hypertensive patients with recurrent vertigo have a higher risk of stroke (102). As already mentioned, patients experiencing dizziness or problems with balance in the general population have a two-fold increased mortality, comparable to patients with diabetes mellitus, cardiovascular disease, and cancer (2). However, it is not known if vestibular disorders are the cause of this increased mortality or if it is caused by other disorders that also can cause vestibular symptoms.

7.2.7 Variations in causes of vestibular symptoms

Which diagnoses that are the most common causes of vestibular symptoms will vary depending on the setting, and patients seen in dizziness clinics often satisfy the criteria for more than one vestibular diagnosis at the same time, for example, PPPD in a patient who also suffers from vestibular neuritis or BPPV, migraine, or cervical problems. If only one diagnosis is reported for each patient, this may influence the reported prevalence of diagnoses.

Among elderly patients in general practice, cardiovascular disease has been described as the most common cause of dizziness followed by vestibular disorders and psychiatric illness (103).

In a multidisciplinary clinic for chronic dizziness in Canada, 30% of patients were diagnosed with vestibular cause of the dizziness, 21% were found to have functional dizziness, 15% were diagnosed with central causes including migraine, vestibular migraine, chronic migraine, multiple sclerosis, spinocerebellar ataxia syndromes, or cerebellar ataxia neuropathy vestibular areflexia syndrome, and 9% were diagnosed with multifactorial medical dizziness including orthostasis and diabetic neuropathy (104).

In the US, 3% of all emergency department visits are due to dizziness or vertigo, and among these vestibular causes constituted 33%, cardiovascular causes 21%, respiratory causes 12%, and neurological causes 11% (including a total of 4% of strokes) (105). In Italy, 13% of the neurological consultations in emergency departments are due to dizziness (106).

Adams and colleagues found large geographical variations in vestibular diagnoses within the US, they hypothesized that this variation was due to coding imprecision and nonuniform application of diagnostic criteria (107). This is also seen in other studies where one interdisciplinary dizziness clinic reported 14% somatoform phobic postural vertigo, while another neurotology clinic did not report any patients diagnosed with functional dizziness among 2079 patients (108,109). Richetti-Masterson and colleagues explored prevalence estimates of Meniéres disease and compared this to international estimates (110). They found large geographical variations but could not conclude whether these differences were due to geographical differences in pathology or simply due to geographical variations on how the diagnosis was determined and the prevalence was calculated. Another study found remarkably large variations in the prevalence of vestibular migraine, even in studies that reportedly had used the same diagnostic criteria proposed by the Barany Society (111).

In addition to this, Parker and colleagues performed a systematic review in 2018 that revealed very large variation in the prevalence of vestibular diagnoses, not only between different specialties but also over different time periods (112). Such a large variation over time is more likely caused by variation in how diagnoses are determined rather than variations in pathophysiology over time, and just like the geographical variations this raises questions as to how reliable the diagnostics and diagnostic groups are.

7.2.8 Diagnostic models

In an international survey among emergency physicians, identification of central or serious vertigo was rated as the number 2 priority for the development of new clinical

decision rules, second only to the investigation of the febrile child <36 months (113). Since then, various diagnostic approaches have been suggested, often with easy to remember acronyms and flow-charts. Newman-Toker and Edlow suggested in 2015 the Triage-TiTrATE-Test (Triage Timing Triggers Targeted Examination Test) (87), and Edlow later suggested a similar approach with the mnemonic ATTEST (Associated symptoms, Timing, Triggers, bedside Examination Signs, additional Testing as needed) (71). Other authors have suggested a classification in five different categories using several aspects of information, including timing, type, and triggers of dizziness (114).

The SO-STONED (Symptoms, Often, Since, Trigger, Otology, Neurology, Evolution, Duration) inventory suggested eight dimensions for determining a likely diagnosis, which should be confirmed by clinical, laboratory, and imaging examinations (115). This provides memory aid but is otherwise similar to what Fife describes in which clinicians should do a thorough interview and then use clinical examination and laboratory testing to (sometimes) confirm the diagnosis based on the principle of pattern recognition (116). This approach is probably often used in clinical practice but requires considerable clinical experience.

Questionnaires for use in chronic settings have also been evaluated and shown to have an accuracy of about 80–90% down to about 40% (117–123). However, in these studies the purpose was not to accurately diagnose all vestibular diagnoses, but rather to group patients. This could be useful for establishing the most common diagnoses or in determining what specialist the patient should see (physiotherapist, otolaryngologist, neurologist, psychiatrist), but it is not accurate enough to determine the correct diagnosis or diagnoses for most patients.

7.3 Otovestibular testing in the diagnosis of vestibular disorders

From the previous sections it is evident that the interview is necessary, but not always sufficient, to diagnose patients with dizziness. What then is the role of vestibular testing?

There are no general guidelines on the role of vestibular laboratory testing in diagnosing patients with dizziness, but several authors conclude that it is usually not necessary (73,124). The clinical practice guidelines from the American Academy of Otolaryngology for BPPV and Menière's disease recommend against routine vestibular testing for these diagnoses (125,126).

However, vestibular testing is required for diagnosing bilateral vestibulopathy and presbyvestibulopathy (13,127). VEMP responses are valuable in diagnosing SCDS (14), and audiometry is required to diagnose Menière's disease (11).

Neuroimaging is often used for patients with dizziness, but an evidence-based approach is lacking (128,129). Neuroimaging is essential in diagnosing vestibular schwannomas, SCDS, as well as strokes and disorders in the central nervous system causing dizziness such as multiple sclerosis and tumors in the posterior cranial fossa. However, for BPPV and vestibular migraine imaging does not provide positive diagnostic information, and even for stroke in the posterior fossa presenting with dizziness the sensitivity of MRI performed during the first 24-48 hours is reported to be only 80–85% (93).

However, developments in vestibular testing and imaging have been very important for an increased understanding of vestibular function and pathophysiology, and some of the most important tests are described in the following sections. This thesis concerns itself with the long-term follow-up of a cohort of patients seen for the first time in our department in the 1990s. The discussion will start with the methods available at this time.

7.3.1 Caloric test

The most widely used vestibular test has for many years been the caloric test with bithermal irrigation, and this has been considered the gold standard up to the present day (130–133). The caloric test was described by Robert Bárány and was considered one of the main discoveries that led to his Nobel prize in 1914 (134). It is considered to be a test mainly of the horizontal semicircular canals (135) and the superior vestibular nerve, even though some stimulation of the vertical canals has also been

reported (136). The test was introduced in clinical practice by protocols such as the one described by Fitzgerald and Hallpike in the 1940s (137). They described a protocol that measured the duration of nystagmus in bithermal irrigation.

The caloric test is performed by irrigating the ears first with warm water at 44°C and then with cold water at 30°C (138) . During the 1950s this diagnostic test was further improved by the introduction of electro-nystagmography where the maximum slow-phase velocity of nystagmus could be quantified (139) and which is also possible in the more recently developed video-nystagmography. This quantification made it possible to calculate the difference in excitability between the two sides more accurately. Jongkees' and colleagues described in the early 1960s a formula to calculate this difference in excitability (140) also called side difference (138) or unilateral weakness (138).

Jongkees' formula for calculating side difference and canal paresis in bithermal caloric irrigation (140):

$$\frac{(WR + CR) - (WL + CL)}{WR + CL + WL + CR} \times 100$$

WR = warm right, CR = cold right, WL = warm left, CL = cold left

Currently there are protocols for performing the test published by both the British Society of Audiology (139) and the American National Standards Institute (141). Thermal stimulation with air instead of water may be used in cases of tympanic membrane perforations or other ear conditions with increased risk of ear infections. However, air stimulation gives weaker responses and is less desirable for the patients (142)

Head rotation is the natural stimulus to elicit the VOR, but head rotations will always stimulate semicircular canals on one side while inhibiting those on the opposite side. The caloric test has therefore been considered important in being able to assess the function of one vestibular end organ at a time (138).

7.3.2 Posturography and balance testing

An assessment of postural balance is an integral part of evaluating patients with vestibular symptoms. The Romberg test is the best-known test of postural stability. It is often considered a positive Romberg sign when a patient can stand with feet together and eyes open but falls with eyes closed (143). Moritz Heinrich Romberg (1795–1873) is credited with discovering this phenomenon after his description of tabes dorsalis, a form of neurosyphilis with degeneration of nerve fibers in the posterior column and dorsal root of the spinal cord that carries sensory information (144–146). A traditional understanding is that postural balance in static conditions is mainly a measure of proprioception (147) and the Romberg sign is also generally attributed to reduced proprioceptive function, but bilateral vestibular loss, acute unilateral vestibular loss, and pathology of the cerebellum have also been mentioned as possible causes (145).

Increased postural sway is often seen in the acute phase of vestibular disease (148), but in the compensated phase sway may return to normal as long as the subject is standing on a firm surface(149). Performing the test on a pliant surface such as foam has by many been considered a specific test of vestibular function (143,150), but this has been contradicted by Jacobson and colleagues who found that this test has a very low sensitivity for vestibular impairments and is rather a measure of balance function dependent on the central integration of multiple sensory inputs and motor outputs (133).

More complex clinical tests like the Berg Balance Scale have been developed to measure balance in the clinical setting, but these tests tend to have a ceiling effect for younger patients (151). If, on the other hand, the test is too difficult, there is a floor effect for patients with disturbances (151).

Instrumental balance tests have therefore been developed to obtain better accuracy with less tendency for ceiling and floor effects. The force platform has been a widely used tool in assessing standing balance in a quantitative way (152). Static posturography consists of a static force platform connected to a computer that measures the center of pressure (COP) and provides measures of its displacement during the trial. The test can be performed with eyes open or eyes closed with a foam cushion under the feet during various head movements or cognitive tasks (figure 6). This has been shown to be a convenient method to assess postural balance, and it provides quantifiable data (49,153,154). Displacement of the COP depends on the gravitational force and the corrective forces exerted on the platform by the patient by isometric muscular contractions in order to maintain a steady posture (155). Sway path is the path the COP travels during a trial, and it is considered a valid measure of balance and the shorter the length the better the postural stability (49).

Figure 6. Static computerized posturography. Photo: K. S. Nilsen

A further development of the static posturography technique is dynamic posturography or computerized dynamic posturography (CDP), and the most commonly employed is the sensory organizational test (SOT) that is considered the gold standard by some authors (156). This test consists of six conditions where the surface in the first three test conditions is static but in the next

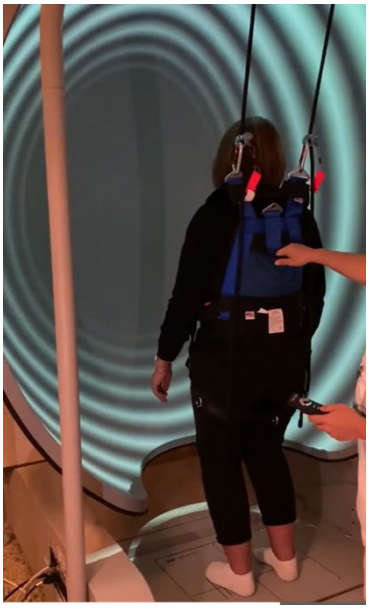

Figure 7. Dynamic computerized posturography measured at Haukeland University Hospital

three conditions is referenced by how the patient sways in the anterior-posterior direction (figure 7). In conditions 2 and 4 the patient closes their eyes, while in test 3 and 6 the visual surrounding sways along with the patient's movement in the anterior-posterior direction (157). This paired movement of the vision and the surface diminishes the ability to use other sensory information than the vestibular input (158). Therefore, the results in test conditions 5 and 6 have been considered a measure of vestibulospinal function (156,158,159). However, several other studies have not been able to show this (160,161). Balance testing with multisensory perturbations such as the SOT has been shown to be necessary in order to evaluate the balance function in patients with bilateral vestibulopathy because these patients may not show deficiencies in the simpler test situations (162).

Several authors have suggested that posturography may be useful to predict falls (49,163–166), but others have questioned this (152,167). Our group has shown that unsteadiness on posturography can predict the future growth of vestibular schwannoma (168). Unsteadiness may be linked to progressive vestibulopathy caused by a growing tumor, as opposed to the more stable situation allowing for central compensation in a stationary tumor.

It appears that postural balance is a function that depends on many bodily functions including the effects of adaptation, rehabilitation, and training, and it is therefore not surprising that posturography is in general not a diagnostic test, but rather a supplement to more specific vestibular tests.

7.3.3 Other tests of vestibular function

This thesis is based a cohort of patients who were examined in our clinic in the 1990s and early 2000s. Since that time, several other vestibular tests have been developed and have gained widespread use, particularly the video-based head impulse test and vestibular evoked myogenic potentials (VEMP). In combination these can provide a test of all the sensory end organs of the vestibular system.

Video-head impulse testing (vHIT) is a test of the vestibuloocular reflex that allows for specific testing of each semicircular canal (169). The patient wears a pair of

goggles with a high-speed camera and accelerometer. As the patient tries to keep their eyes focused on a point in front, the examiner performs rapid head movements in the planes of the specific semicircular canals. The ratio of compensatory eye movements to head movements are then calculated (gain) and pathologic saccades can be identified. vHIT is a test of the high-frequency function of the semicircular canals and VOR (132).

VEMP testing averages myogenic responses thought to be dependent on the saccule and utricle (170). There are two common types of VEMP testing, namely cervical VEMP (cVEMP) and ocular VEMP (oVEMP). cVEMP has been found to depend mostly on the integrity of the saccular macula and the inferior division of the vestibular nerve, and it is performed by sending sound or vibration stimuli to the ear and recording the EMG over the ipsilateral sternocleidomastoid muscle (170,171). The oVEMP is used clinically to test the function of the utricle and the superior division of the vestibular nerve and is measured over the extraocular muscles after stimulation of the contralateral ear with sound or vibration (171).

7.3.4 Test of hearing function

Pure tone audiometry is the standard test of hearing function in which hearing thresholds are determined by measuring the lowest intensity at which sound can be heard at a specific frequency (172). In clinical practice this means that the patient responds to the stimuli 50% of the time (173). It is a subjective measure of hearing, and if the patient is unable or unwilling to cooperate, objective measures such as otoacoustic emissions or auditory evoked responses can be used (172). The World Health Organization grades hearing loss according to the average hearing thresholds calculated from the frequencies 500, 1000, 2000 and 4000 Hz in the best-hearing ear (Table 3) (174).

Table 3. Grades of hearing impairment

Grade of impairment	Corresponding audiometric value * (better ear)	Performance	Recommendations
0 No impairment	25 dB or better	No or very slight hearing problems. Able to hear whispers.	
1 Slight impairment	26-40 dB	Able to hear and repeat words spoken in normal voice at 1 meter	Counselling. Hearing aids may be needed.
2 Moderate impairment	41-60 dB	Able to hear and repeat words spoken in raised voice at 1 meter	Hearing aids usually recommended.
3 Severe impairment	61-80 dB	Able to hear some words when shouted into better ear.	Hearing aids needed. If no hearing aids available, lip-reading and signing should be taught.
4 Profound impairment including deafness	81dB or greater	Unable to hear and understand even a shouted voice.	Hearing aids may help understanding words. Additional rehabilitation needed. Lip reading and sometimes signing essential.

* The audiometric values are averages of values at 500, 1000, 2000 and 4000Hz

Adapted from: World Health Organization. Grades of hearing impairment. https://www.who.int/pbd/deafness/hearing_impairment_grades/en/, Accessed January 1, 2019.

Audiometry is essential in the diagnosis of many inner ear disorders, including Menière's disease, labyrinthitis, perilymphatic fistula, inner ear trauma, SCDS, vestibular schwannoma, and other cerebellopontine angle tumors. In Meniéres disease, an audiometrically documented sensorineural hearing loss of at least 30 dB for at least two contiguous frequencies below 2000 Hz is required for a definite diagnosis (11). For patients with suspected SCDS, low-frequency negative bone-conduction thresholds on pure tone audiometry are one of the three signs indicative of a "third mobile window" in the inner ear (14).

8. Objective

The main objective of the study was to critically evaluate which symptoms reported by dizzy patients provide useful information, and to evaluate the interrelations between posturography, inner ear function, and long-term survival.

Much of the diagnostics of patients with dizziness rely on patient-reported symptoms. However, vestibular symptoms can originate from many organ systems, and they are difficult to interpret. We hypothesized that relevant vestibular symptoms could predict objective measures such as postural balance, vestibular asymmetry and long-term survival. We also hypothesized that unsteadiness was associated with reduced hearing and that this association was mediated by vestibular function. We further hypothesized that the increased mortality among patients with vestibular symptoms was mainly caused by other comorbidities and not primarily vestibular disorders.

The specific objectives for each paper were:

Paper 1: Describe how patients report their vestibular symptoms in a clinical symptom questionnaire and determine whether these symptoms predict caloric asymmetry and postural balance.

Paper 2: Determine how postural balance is related to hearing levels and caloric asymmetry.

Paper 3: Determine whether vestibular symptoms and diagnoses predict long-term survival.

Paper 4: Describe the relationship between unsteadiness, canal paresis, cerebrovascular risk factors, and long-term mortality

9. Material and Methods

9.1 Design and setting

This thesis used data from a cohort of patients examined at the vestibular and balance laboratory at the Department of Otorhinolaryngology, Head and Neck Surgery, Haukeland University Hospital. In the period from 1992 to 2004 the clinic maintained a standardized procedure for patients referred for suspected vestibular disease, including a questionnaire and the same method for static posturography and vestibular testing. Most patients were referred from primary or secondary care physicians within a catchment area of approximately 500,000 inhabitants. However, the clinic also received some patients from a larger area of approximately 4.5 million inhabitants with certain disorders that require highly specialized care, including patients with vestibular schwannoma, patients requiring surgical treatment for Menière's disease, and patients with complicated or long-lasting vertigo with suspected vestibular origin. Divers and aviators that were referred for work-related health examinations were not included in this study. The literature review for this thesis was completed on October 20, 2021.

9.2 Ethics

The study was approved by the Regional Committee for Medical and Health Research Ethics (REK 2012-1075). Patients alive at follow-up were informed of the study by mail and given the opportunity to withdraw.

9.3 Baseline data and diagnosis

A questionnaire on symptoms and former medical history was answered by patients before undergoing clinical examination by an otolaryngologist and further testing. The examinations included pure-tone audiometry, speech recognition, static posturography, and electronystagmography or video-nystagmography with

measurements of ocular smooth pursuit, saccadic pursuit, spontaneous and positional nystagmus, and bithermal caloric tests. For patients with more than one consultation in the clinic, data from the first visit were used in the analyses.

The patient records were reviewed by two of the supervisors for this thesis, Stein Helge Glad Nordahl and Frederik Kragerud Goplen. Based on the available information, patients were diagnosed according to a predefined set of diagnostic groups: (I) peripheral vestibular, (II) central nervous, (III) traumatic, or (IV) other. Each group contained more specific diagnoses. In case of several diagnoses, the vestibular diagnosis was considered to be the primary diagnosis if present. If no vestibular diagnosis was reported, then the most relevant of the other diagnoses were chosen as the primary diagnosis for the statistical analyses.

9.3.1 Static posturography

In this study static posturography was performed with a commercially available force platform (Cosmogamma®, AC International, Cento, Italy). This platform measures 40 cm × 40 cm × 8 cm and contains three strain gauge pressure transducers connected to a computer to calculate the COP with a sampling frequency of 10 Hz. Patients were asked to stand on the platform with their heels 7 cm apart with an angle of the feet at their own preference and arms along the side. The same test was performed twice, first with eyes open and focusing on a small target approximately 2 meters ahead, then with eyes closed.

Test conditions were standardized for the posturography with the same visual environment and minimal disturbing noise. Posturography was performed prior to other testing that might cause dizziness or fatigue (electronystagmography/caloric tests). No training and only minimal instruction was needed. The path length in millimeters (also called sway path) described by the COP while standing quietly for 60 seconds was recorded. This is a continuous variable with theoretical values ranging from zero to several thousand. Zero indicates a very stable situation with absolute immobility while increasing values show increasing unsteadiness. A recording time of 60 s was used because body sway patterns in most cases reaches

their plateau within this time (175). In paper I and II, the path length was used as a continuous variable in the analyses. In paper IV we categorized patients into four groups with low, low-median, median-high, and high postural instability. In addition, a dichotomized variable was created using normative values for posturography from a former study (176) where path lengths greater than 895 millimeters with eyes open or 1665 millimeters with eyes closed were considered pathologic. If the path length was pathologic either with eyes open or eyes closed the patient was categorized as "unsteady", otherwise the patient was considered "steady".

9.3.2 Bithermal caloric testing

The caloric response (maximum slow phase velocity of nystagmus) to irrigation of each ear canal with warm and cold water (44°C and 30°C degrees) was recorded using electro- or video-nystagmography. Asymmetry between the two ears was calculated using Jongkees' formula, and values ≥25 % were considered abnormall (138).

9.3.3 Questionnaire

The medical history was assessed using a standardized questionnaire with items on disease-specific symptoms as well as general health and comorbidity. An abbreviated translation of the questionnaire can be found in the appendix of paper 2. Vestibular symptoms were then categorized according to time course, dizziness quality, accompanying symptoms, and triggers. In cases where the patient needed assistance in completing the questionnaire, this was provided by the patient's family if they were present, by laboratory personnel, or by the examining physician.

9.3.4 Statistical analysis

Categorical variables were reported as absolute and relative frequencies and were compared using the $\chi 2$ or Fisher's exact test as appropriate. Continuous variables were compared using Student's t-test for normally distributed variables or Mann–Whitney U-test for non-normally distributed variables. Path lengths were positively skewed and were therefore log-transformed before regression analyses, t-tests, and

tests for Pearson's correlation coefficient. Back-transformation was performed to obtain geometric means. For the regression analysis of path lengths, coefficients represented the ratios of geometric means. For survival data, Kaplan–Meier curves were used to illustrate differences between diagnoses and selected symptoms, and statistical differences between curves were tested by log-rank tests. Cox proportional hazards regression models were used to calculate crude and adjusted hazard ratios (HRs). Forward regression analyses were used to create final models identifying the patient-reported factors significant for path-length, asymmetric caloric response, diagnoses, and survival. The assumptions of proportional hazards and specifications were checked using graphical methods, link tests, and tests based on Schonfeld residuals.

Data on vital status and time of death were retrieved from the Norwegian National Registry on June 28, 2019. The Norwegian age and sex-specific mortality data were used as a reference population to calculate the standardized mortality ratio (observed number of deaths/expected number of deaths) for the study population by indirect standardization in which the stratum weights were defined as the distribution in the study population.

Statistical analyses for paper 1, II and III were performed using Stata v15 (StataCorp., College Station, TX, StataCorp). Statistical analyses for paper IV were performed using the Epi(177) and popEpi(178) packages in R 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria). Two-sided p-values < 0.05 were considered statistically significant.

10. Results

10.1 Paper 1, Self-reported symptoms, caloric testing, and posturography

In this paper we evaluated how patients reported their symptoms and how these symptoms were associated with caloric asymmetry and posturography. A total of 1457 patients were included in this study. Table 4 shows the frequency of reported symptoms and figure 8 shows how many different responses individual patients had within each symptom category.

A majority (72.1%) of the patients reported only one category of timing, and 47.1% reported only one type of dizziness, while 12.3% of the patients reported both spinning and rocking dizziness and 30.4% had caloric asymmetry.

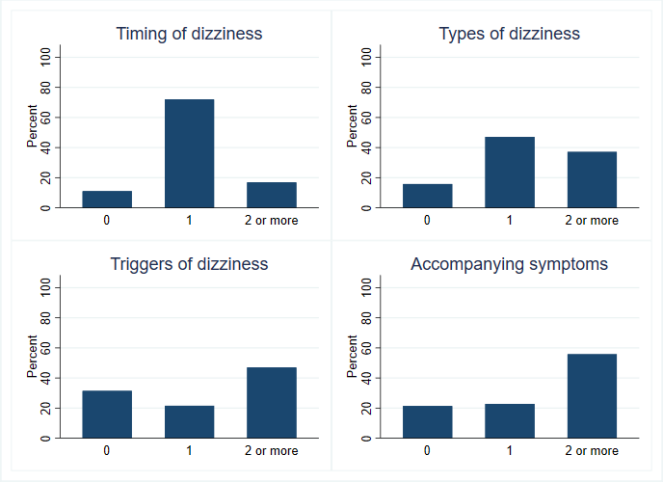

Figure 8. Percentage of patients reporting 0, 1, and 2 or more symptoms in each category of symptom.

10.1.1 The association between patient-reported symptoms and caloric asymmetry

Patients who reported vomiting or chronic hearing loss had increased risk for caloric asymmetry in adjusted analyses (odds ratios (OR) = 1.60 ($p < 0.001$) and OR = 1.59 ($p = 0.002$), respectively). Patients with short attacks of dizziness (OR = 0.60 ($p < 0.001$)), periodic dizziness (OR = 0.76 ($p = 0.034$)), rocking dizziness (OR = 0.74 ($p = 0.021$)), or syncope (OR = 0.60 ($p = 0.049$)) had reduced risk for caloric asymmetry. None of the triggers were associated with caloric asymmetry.

Table 4: Frequency of reported symptoms among 1457 patients (%).

Multiple choices were possible.

Timing of dizziness:		Tinnitus:	
Short attacks	675 (46%)	During dizziness attacks	100 (7%)
Periodic	565 (39%)	Independent of dizziness attacks	419 (29%)
Constant	298 (21%)	Hearing loss:	
Other, free text	7 (0.5%)	During dizziness attacks	57 (4%)
Types of dizziness:		Independent of dizziness attacks	254 (17%)
Spinning	705 (48%)	Triggers of dizziness:	
Rocking	457 (31%)	Positional change	536 (37%)
Other, free text	343 (24%)	Sleep deprivation	210 (14%)
Walking on pillows or floating	297 (20%)	Neck movements	445 (31%)
Drop-attacks/vestibular falls	164 (11%)	Light or darkness	119 (8%)
Accompanying symptoms:		Sound	152 (10%)
Syncope	101 (7%)	Psychological factors	408 (28%)
Headache	428 (29%)	Medication	22 (2%)
Nausea	813 (56%)	Infection / fever	52 (3%)
Vomiting	388 (27%)	Other, free text	258 (18%)
Visual disturbances	438 (30%)	None	284 (20%)
Near-fainting	228 (16%)		
Other, free text	193 (13%)		
None	129 (9%)		

10.1.2 Association between patient-reported symptoms and postural balance

Constant dizziness was associated with a 15.5% ($p < 0.001$) increase in sway in adjusted analyses. Dizziness triggered by light or darkness was associated with an increased postural sway of 14.0% ($p = 0.026$), dizziness triggered by sound was associated with an increased postural sway of 13.9% ($p = 0.014$), and dizziness

triggered by visual disturbances was associated with an increased postural sway of 9.1% ($p = 0.013$). Female sex and attacks of dizziness were associated with a 12.8% ($p < 0.001$) and 12.2% ($p < 0.001$) reduction in postural sway, respectively.

10.1.3 Caloric response and path length

There was no correlation between caloric asymmetry and postural sway.

10.2 Paper 2, Hearing as a predictor of postural balance

In this paper we evaluated how hearing level was associated with static postural balance among 1075 patients. Many of the patients had unilateral vestibular disorders, and we therefore evaluated the two ears separately in order to determine the effect of ear disorders.

Path length increased with increasing hearing loss as illustrated by figure 9.

ANOVA analyses revealed that hearing and path lengths with eyes open and closed varied depending on the primary diagnosis of the patient. However, the Romberg quotient of the path length did not vary significantly between the diagnostic groups.

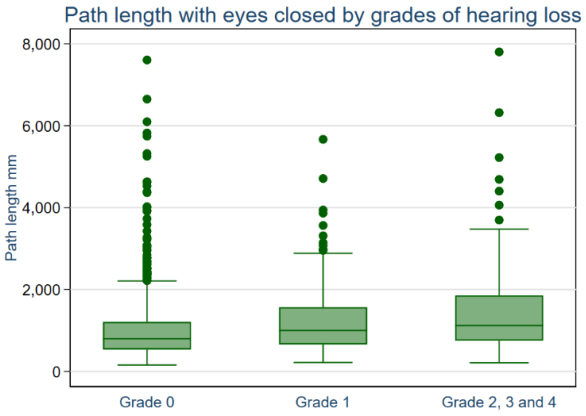

Figure 9. Path length with eyes closed for 1075 dizzy patients by grades of hearing impairment. Path length of quiet standing with eyes closed by World Health Organization grades of hearing impairment. Boxes display the median and interquartile range.

Regression analysis adjusted for age and sex found that a 10-dB increase in hearing loss in the best-hearing ear was associated with a 6.0% increase in path length with eyes closed (95% CI 2.9%–9.3%, $p < 0{,}001$). A 10-dB increase in hearing loss in the worst-hearing ear was associated with a 2.0% (95%CI, 0%–4.1%, $p = 0.040$) increase in path length with eyes closed.

The effect of a 10-dB increase in hearing loss in the best-hearing ear after adjusting for diagnoses was a 7.3% (95% CI, 4.14%–10.7%) increase in path length and a 4.0% (95% CI, 1.89%–6.17%) increase in the worst-hearing ear.

Vestibular asymmetry was not significantly associated with path length after adjustment for hearing, sex, and age, neither for the best nor the worst-hearing ear ($p = .884$ and $p = .981$, respectively).

In regression analyses for path length with eyes closed adjusted for age, sex, hearing, and comorbidities, there was no significant effect of diabetes, former heart disease, former stroke/transitory ischemic attack (TIA), or hypertension.

10.3 Paper 3. Symptom and disease-specific long-term survival

A total of 1931 patients were included in this study. We compared the mortality of the cohort with the Norwegian population and performed analyses on how symptoms and diagnoses predicted long-term survival in the cohort.

For the entire cohort the 5 and 10-year mortality rates were 4.3% and 10.1%, respectively. The standardized mortality ratio was 1.03 (95% CI 0.94–1.12) illustrating no significant difference from a Norwegian population of the same age and sex distribution.

Figure 10 shows Kaplan-Meier unadjusted survival estimates and illustrates how patients reporting periodic dizziness or dizziness triggered by sound have better survival compared to the other patients, and patients with self-reported unsteadiness have poorer survival.

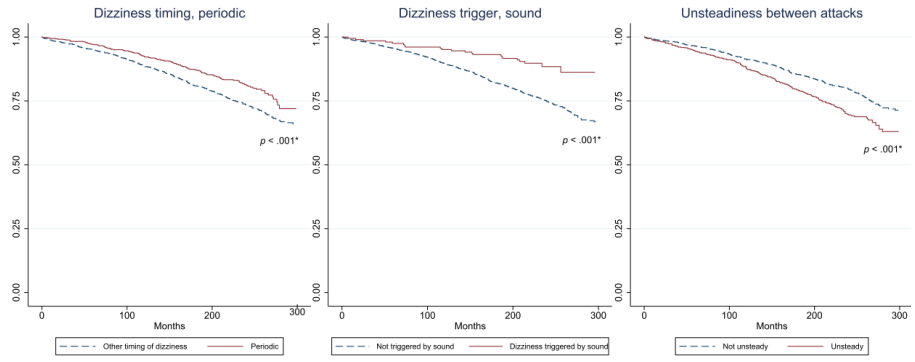

Figure 10. Kaplan-Meier unadjusted estimates by patient-reported symptoms in 1,931 patients with dizziness. *p-value from log-rank test. From Berge et al. "Long-Term Survival in 1,931 Patients With Dizziness: Disease- and Symptom-Specific Mortality", Laryngoscope, 2021.

In stepwise Cox regression analysis of patient-reported symptoms adjusted for age, sex, cardiovascular disease, and diabetes mellitus, we found that periodic or short attacks of dizziness were associated with reduced mortality (HR 0.62 (0.50–0.77)) and HR 0.76 (0.63–0.93), respectively). Unsteadiness between dizziness attacks was

associated with increased mortality (HR 1.30 (1.08–1.57)), while dizziness triggered by sound was associated with decreased mortality (HR 0.59 (0.38–0.91)).

Spinning vertigo was associated with improved survival in analyses adjusted for age, sex, and comorbidities (HR 0.80 (0.67–0.96)), but it was not significant in the stepwise Cox regression analysis that included other patient-reported symptoms.

Figure 11 shows unadjusted survival according to the cause of dizziness. Cox-regression analysis adjusted for age, sex, and cause of dizziness showed increased mortality among patients with cerebrovascular causes of dizziness (HR 1.56 (1.11–2.19)) compared to that in patients with BPPV.

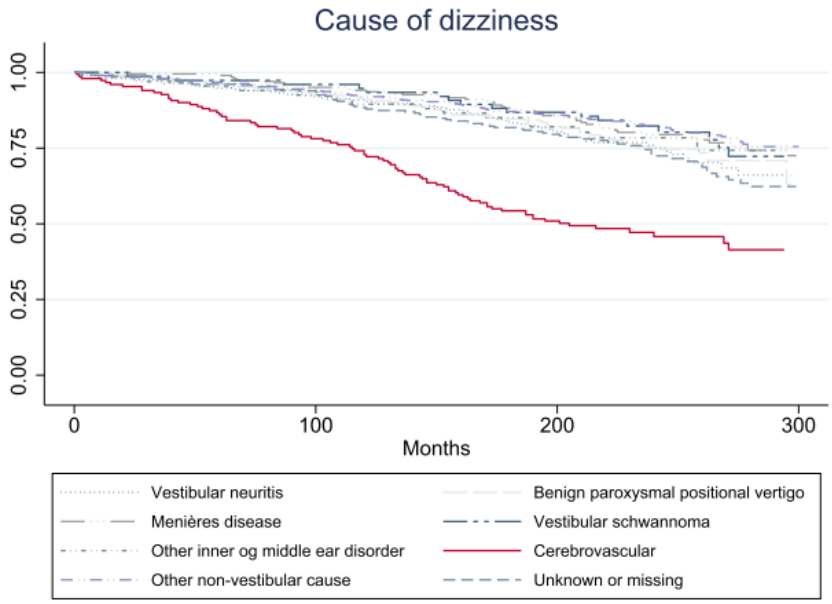

Figure 11. Kaplan-Meier unadjusted estimates according to cause of dizziness in 1,931 patients with dizziness. *p-value from log-rank test. From Berge et al. “Long-Term Survival in 1,931 Patients With Dizziness: Disease- and Symptom-Specific Mortality”, Laryngoscope, 2021.

Patients reporting one or more triggers of dizziness had reduced mortality in the unadjusted analysis (HR 0.71 (0.60–0.86)), but this was no longer significant after adjusting for age, sex, and comorbidities (HR 0.83 (0.69–1.00)).

10.4 Paper 4. Unsteadiness, caloric test, and mortality in patients with dizziness

In this study we evaluated the relationship between unsteadiness, canal paresis, cerebrovascular risk factors, and long-term mortality. A total of 1561 patients 18–75 years of age were included in this study. Patients were classified as steady or unsteady based on static posturography test results with eyes open or eyes closed. Unsteadiness was associated with diabetes, higher age, heart disease, hypertension, and cerebrovascular dizziness.

Follow-up time ranged from 17 to 29 years (mean 22 years, SD 2.9 years). The observed number of deaths in the study population was 336 over a total of 31,335 person-years, which did not differ significantly from the expected number of 350 deaths in the Norwegian general population matched for age, sex, and calendar years (standardized mortality ratio: 0.96, 95% CI: 0.86–1.07).

In Cox regression analyses, we found that unsteadiness on static posturography was a significant predictor of mortality independent of age, sex, self-reported comorbidities, and clinical diagnosis of dizziness of suspected cerebrovascular origin with an adjusted HR of 1.44 (95%CI: 1.14–1.82). Self-reported diabetes and stroke or TIA were also significant predictors in the adjusted analysis.

Kaplan-Meier analysis of survival related to four increasing levels of postural instability is shown in figure 12. The two groups with median-high or high postural

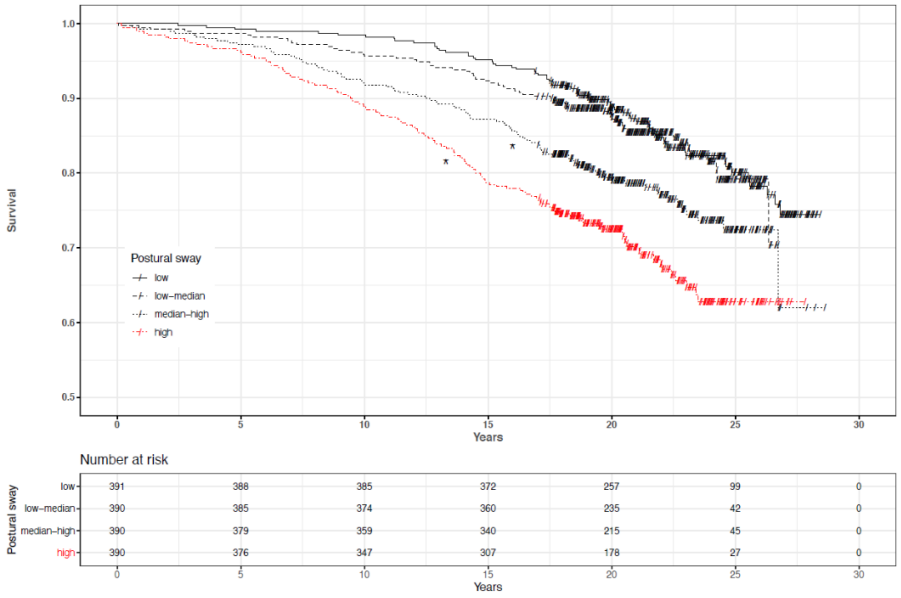

Figure 12. Kaplan-Meier estimates of survival by postural sway

sway had decreased survival compared to the group with low postural sway ($p < 0.005$).

Caloric asymmetry was not significantly associated with unsteadiness (chi square: $p = 0.46$) or to mortality (unadjusted Cox HR: 1.04, 95%CI: 0.80–1.34).

11. Discussion

This thesis describes how patients report their symptoms in a questionnaire designed to facilitate history-taking in a specialized clinic for patients with suspected vestibular disorders. It further analyses the associations between symptoms, caloric asymmetry, posturographic instability, hearing, and long-term survival. Patients referred for suspected vestibular disorders have a long-term survival similar to the general population, but there are important differences within the group.

11.1 Patient-reported symptoms

Timing

One of the main findings in this thesis is that the timing of vestibular symptoms seems to be a relevant predictor for vestibular asymmetry, postural balance, long-term survival. When asked to classify their symptoms into three categories – short attacks, periodic, or constant – most patients chose only one of these categories. However, 18% chose more than one option, which is reasonable considering that many patients with episodic vestibular syndromes such as Menière's disease or BPPV also experience symptoms between attacks. This was also very similar to the paper by Newman-Toker et al. where 16% reported more than one category of timing(92).

Several authors have suggested that the timing, rather than the character of vestibular symptoms, may be most relevant in the initial triage of patients with vestibular disorders (74,81,87,88,179) and this is reflected in the International Classification of Diseases 11th revision (ICD-11) as well as in the International Classification of Vestibular Disorders (85,91). No other anamnestic information was as consistently associated with the various outcomes postural balance, vestibular function, and survival, and this supports the suggested classification of patients based on the timing of their symptoms.

Vomiting

We found that vomiting was associated with vestibular asymmetry. This is a new finding because vomiting and nausea are usually analyzed in combination

(117,119,120). Our findings indicate that vomiting is a more specific symptom related to vestibular disorders, and this should be differentiated from nausea. This was also confirmed in a later paper by Strobl and colleagues (180). Our results are from an outpatient setting, and in the acute setting it should be remembered that vomiting is associated with stroke (181).

Type of vestibular symptoms

When asked to characterize their dizziness by selecting one or more options – including spinning, rocking, floating, walking on pillows, or other – most patients (>70 %) selected more than one alternative, which is similar to a previous population-based study that reported 61% selecting more than one alternative (80). An epidemiological study on the general population found a high prevalence of vertigo, and the authors concluded that vertigo was not more specific than unsteadiness or dizziness, and they further postulated that vertigo, dizziness, and unsteadiness represent a spectrum of similar mechanisms and disorders (182). These findings show that these categories are not mutually exclusive and are unsuitable for classification of patients.

We found that a rocking type of dizziness was associated with reduced risk of caloric asymmetry, and spinning vertigo was associated with better survival, but in our study the effect of spinning vertigo on survival was cancelled out when the time aspect of symptoms was included in the model. Our findings supplement a previous study that found that caloric testing correlated with a history of vertigo, while there was no correlation between postural balance and a history of vertigo (160). A French cohort study on hypertensive patients found that patients who reported vertigo had increased mortality from stroke, but this was not seen among patients reporting other types of dizziness (102). This differs from our findings of better survival among patients with vertigo, and it also differs from the findings by van Vugt and colleagues (183). This difference could be explained by the French study being performed on hypertensive patients, and spinning vertigo could also be a symptom of cardiac disease and orthostatic/hemodynamic hypotension (16,83,184). Thus, vestibular symptoms have different implication in different patient populations and settings.

Our findings seem to agree with Newman-Toker and Edlow's suggestions that the timing of symptoms is better for categorizing patients than the type of dizziness symptoms (87). However, because patients reporting rocking dizziness had less asymmetrical vestibular function and patients reporting spinning vertigo had better survival, the type of dizziness also contains relevant information that can be useful in the diagnostic process. The study therefore supports previous studies showing that tests of inner ear function provide supplementary information to that which is obtained by the patient history and questionnaires (185,186).

Triggers of vestibular symptoms

A trigger in the context of vestibular symptoms usually means that there is a reproducible, repetitive relationship between trigger stimuli and vestibular symptoms (19). Common vestibular triggers are head movements as well as other stimuli that may affect the inner ear directly, such as sounds, vibrations, or pressure. Several authors emphasize the importance of differentiating between triggered and spontaneous vestibular symptoms (75,78,87,88), and this is also included in the ICVD (19). Triggers represent a key source of diagnostic information in patients with transient symptoms, while misinterpretation of exacerbation of symptoms by head movements in acute vestibular syndrome is a common cause for misconception (187).

In our study, vestibular symptoms triggered by sound was associated with worse postural balance and better survival. However, this trigger was reported by approximately 10% of the patients, which is much more than the proportion of patients with SCDS and perilymphatic fistula in the cohort. This indicates that reports of this trigger in this study are not specific for these disorders.

Furthermore, we found that patients who reported triggers had better survival in the unadjusted analysis, but this was no longer significant in the adjusted analyses. Most patients reported triggers, and the majority of these reported more than one. It is hard for patients to differentiate between what the clinician considers triggers and factors that exacerbate preexisting symptoms. Even though validation of a telephone interview on detecting vertigo of vestibular origin showed promising results

regarding sensitivity and specificity (118), and recurrent positional vertigo is suggested to be most commonly caused by BPPV (73,188) our findings suggest that patient-reported triggered episodic dizziness or vertigo should be confirmed by clinical testing.

Diagnostic accuracy of questionnaires and patient-reported symptoms

The purpose of this study was not to evaluate the diagnostic accuracy of our questionnaire, but the findings in the study justify a discussion on challenges in developing diagnostic questionnaires and in the interpretation of patient-reported symptoms in general.

Because we have shown that a large proportion of patients reported triggered symptoms, a diagnostic questionnaire would necessitate careful phrasing on triggers. For instance, Kentala and Rauch deliberately excluded questions on positional dizziness stating that "many patients believe that any head position enhances their symptoms, and asking about symptoms induced by head position could be misleading" (123). This corresponds with our findings and illustrates important challenges in diagnosing BPPV by questionnaires.

An additional challenge with questionnaires is patients with several diagnoses, which is very common among patients with dizziness. Some examples are patients with Meniére's disease who are more likely to also have migraine (189), and PPPD is either precipitated by or co-exists with other causes of vestibular symptoms (10). The many possible diagnostic combinations therefore make it challenging to make an accurate automated diagnosing system.

A systematic review from 2021 found 18 different diagnostic tools. In general, there was a higher accuracy as the number of items increased, but the diagnostic repertoire of the tools did not necessarily increase, ranging from 3 to 36 diagnoses/diagnostic groups. This systematic review also included more advanced tools with a combination of patient reported symptoms, laboratory data, and results from clinical testing in order to provide an accurate diagnosis (190). There were various ways of defining precision of the tools, but specificity was generally better than sensitivity

with sensitivity ranging from 50% to 89% for the clinical decision support tools and specificity ranging from 60% to 100%.

In addition, it is also problematic that there is no defined “gold” standard that is used across the various diagnostic tools, and in most cases the diagnostic accuracy is only compared to the “gold standard” being the opinion of a single clinician (190).

As described in the introduction, the vestibular system differs very much from the visual and auditory system when it comes to central pathways. While the other sensory inputs are readily available in our awareness, the vestibular input is not cognitively available in the same manner. The signals from the vestibular end organs go through a process with modulation and multimodal integration, and we do not become aware of this information until there are discrepancies and unexpected information. This provides a physiological explanation for the challenges patients encounter when describing vestibular symptoms and may explain why it is problematic to create mutually exclusive and diagnostically relevant symptom categories such as “vertigo” and “dizziness”. This may be the most important challenge to diagnosing vestibular symptoms based on symptoms alone. It also provides an explanation for why the timing of symptoms may be easier to describe, as this could simply be considered a duration of discomfort or a time-period when “something is wrong”.

The challenges with patient-reported symptoms and questionnaires are important to keep in mind when interpreting epidemiological studies based on questionnaires and telephone interviews. Therefore, epidemiologic studies should include a validation and critical evaluation of the diagnostic accuracy of the method used in the study, and further work to establish objective measures as the basis for vestibular disorders is encouraged.

11.2 The various diagnoses

Because diagnoses evolve over time and many of the vestibular diagnoses depend on patient-reported symptoms, we tried to limit the focus of specific diagnoses. We also

see that because investigations were performed a couple of decades ago, several diagnoses that are reported as the most prevalent diagnoses today such as vestibular migraine and PPPD were not consistently diagnosed in this population. The approach where patient-reported symptoms and objective measures were prioritized over diagnoses are therefore important for the results in this study to stand the test of time. However, some comments should be made on diagnoses.

In this study the most prominent finding with regard to diagnoses was seen among patients diagnosed with cerebrovascular causes of dizziness. This diagnosis was determined by review of the clinical examination, patient history, and results, and usually imaging was not available. Therefore, the diagnosis should be interpreted with caution. However, patients in this diagnostic group had certain characteristics, including impaired postural balance and impaired survival. However, after adjusting for the major risk factors for stroke, i.e. age and patient-reported diabetes, hypertension, atrial fibrillation, and previous stroke or TIA, this increased mortality was no longer seen. However, posturography remained a significant predictor even after these adjustments.

As mentioned earlier, there has been a large variation in the prevalence of various vestibular diagnoses, both in different specialties, in different time-periods, and in different locations (110–112,191). Even though a difference in prevalence can be expected due to different study populations in general practice, neurology departments, and otolaryngology, and some change over time is caused by the introduction of new diagnoses, is it still evident that these variations highlight a scientific and therapeutic problem where patients are not consistently diagnosed over time, by medical specialty, or by location.

An important development during the last years is therefore the formerly mentioned international diagnostic criteria that have been published for several vestibular disorders (8–11,13,16,17,127,192)(8)(9)(17)(10)(11)(13)(16)(127)(192). Well defined international diagnostic criteria should contribute to a more common nomenclature for vestibular disorders. However, the fact that many of the common

vestibular diagnoses do not have objective diagnostic criteria and have unclear pathophysiologic mechanisms illustrates that there is still a need for future work on defining and critically evaluating the various diagnostic groups for vestibular disorders.

11.3 Relation between various measures of inner ear function and postural balance

We have shown that hearing threshold, particularly in the best-hearing ear, is associated with postural balance when measured in static conditions on a firm surface.

A systematic review on postural balance and hearing among older adults found a positive association between hearing and postural stability in all of the 7 included studies, but patients with vestibular disorders were not included (60). It is also known that persons with hearing loss have slower gait speed (60) and it has been shown that hearing loss is a predictor of walking difficulties in the future (193).

There are several theories for explaining the relationship between reduced hearing and postural balance. Perhaps the most obvious is that postural balance depends on the vestibular apparatus, and because the cochlea and vestibular apparatus are closely related both functionally, developmentally, and anatomically, they may share common susceptibility to damage and congenital disorders(194) (194,195). For instance, children with hearing loss have reduced postural balance, and this has been suggested to be the result of concurrent damage to vestibular and cochlear structures (196). On the other hand, a Finnish study of twins did not find evidence that the association between hearing and postural control among older adults could be explained by genetic influences (197).

Even though it is well known that patients with acute vestibular loss experience increased instability (148), this improves as the loss is compensated for (152). It has also been shown that patients with bilateral vestibulopathy have good postural

stability in static conditions with eyes open with slight deterioration with eyes closed (162).

Menière's disease and vestibular schwannoma are both associated with a gradual deterioration of both hearing and vestibular function on the affected ear. However, in our study hearing in the best-hearing ear was most strongly related to postural balance, and this suggests that the association between hearing and postural balance is not mainly caused by unilateral diseases of the labyrinth. This was further supported by the findings that vestibular asymmetry was not associated with postural sway with eyes closed or eyes open or with Romberg's quotient. Former findings in our group that instability predicts growth in patients with vestibular schwannoma (168) contradicts this conclusion but can be explained by patients with growing vestibular schwannomas experiencing uncompensated alterations in vestibular function due to the growing tumor, and this is therefore analogous to acute vestibular disease. Our study consisted mainly of patients with chronic symptoms, and we conclude that chronic unilateral vestibulopathy is not very important for postural balance in static conditions on a firm surface.

Therefore, other reasons to explain the correlation between hearing and balance seen in our study should be sought. As previously mentioned, it has been shown that humans can use auditory cues to maintain postural balance (57,59,198). However, in this study testing was performed in a quiet environment and the effect of ambient noise can therefore not explain the associations between hearing and postural balance seen in this study.

It has also been suggested that people with hearing impairments use much of their cognitive capacity on hearing and therefore have less capacity for balance-related tasks (60,199). As our study also found the same association among younger patients and on a relatively simple balance test, we do not believe that the cognitive load is the most important factor for explaining the association between hearing and postural stability in our study.

More plausible explanations for this cohort are therefore the hypotheses that hearing loss causes decreased participation in social activities with consequences for cognition and physical activity, which in turn causes reduced postural stability (60) and in particular that hearing and postural balance could be affected by underlying confounding disorders that cause both hearing loss and reduced balance.

Cerebrovascular diseases and associated risk factors are possible confounding factors, and it is well known that reduced hearing is associated with both dementia, stroke, cardiovascular disease, and cardiovascular risk factors such as diabetes mellitus and smoking (47,200,201). However, the authors in a large prospective study considered cerebrovascular risk factors only to have a small and perhaps not clinically significant effect on hearing (46).

For postural balance and neurological disease, the association is shown in several studies (149,202–205) and the association between posturography and cardiovascular disease has been shown by Urban and colleagues who found that dynamic posturography was better at detecting cerebral white matter due to ischemia than electronystagmography (206). There is evidence from both animal studies and clinical studies that diabetes causes direct damage to the peripheral vestibular system (207). However, a Japanese study found no effect of diabetes without neuropathy on postural balance, and the increased sway seen among diabetics with neuropathy disappeared after adjusting for nerve-transmission velocity (208). Those findings could indicate that the effect of diabetes on proprioception is more important than the effect on the inner ear by microangiopathy and mitochondrial damage (47). Agrawal and colleagues have shown an association between reduced balance on modified Romberg and diabetes mellitus, but in adjusted analysis there was no significant association with smoking or hypertension in their study (194).

In our study we found that patients with suspected cerebrovascular disease had impaired postural balance. There was also a significant association between patient-reported individual cardiovascular risk factors, but this effect was cancelled out after adjusting for hearing level.

Overall, the present study indicates that the correlation between hearing loss and static postural balance is not primarily mediated by reduced vestibular function in the ear with hearing loss. The correlation between hearing loss and postural balance seems rather to depend on several factors working together, such as cerebrovascular disease and other underlying pathologies, even though this study's design could not determine this causality in detail.

11.4 Survival

Survival and vestibular disease

One of the main findings in this thesis is that patients with suspected vestibular disease do not have worse survival than the general population. This was a new and important finding that contradict the former evidence that patients in the general population with vestibular symptoms or impaired balance have a markedly increased mortality (2).

There may be several reasons for this discrepancy between our findings and the increased mortality among patients with vestibular symptoms in the general population.

First, it indicates an efficient screening of patients in primary care. In Norway patients require a referral from a general practitioner in order to be evaluated by a specialist in the hospital, and our findings indicate that patients with more severe causes of vestibular symptoms such as cardiovascular cause and stroke and patients who are very frail are generally not referred to the otolaryngology clinic.

Secondly, our findings indicate that patients with vestibular disorders do not have particularly increased mortality. When comparing the various diagnostic groups, we found that patients with cerebrovascular cause of dizziness had increased mortality, and we found that patients with non-episodic symptoms had increased mortality. These findings are very important because they illustrate that the most common causes of vestibular symptoms have a good prognosis and that consequences such as falls and occupational and traffic-related accidents may not be very common. We

therefore suspect that the increased mortality seen among persons with vestibular symptoms in the general population is not necessarily due to vestibular disorders but rather due to other disorders that also cause dizziness and unsteadiness. Examples of such disorders may be orthostatic hypotension, hypotension due to hypertensive medication, heart failure, reduced proprioception due to diabetes mellitus, or reduced muscular strength, and these symptoms therefore are more signs of reduced health than vestibular disorders. The formerly mentioned finding of increased mortality among persons with vestibular symptoms in the general population (2) should therefore be interpreted in light of our findings that patients with vestibular diagnoses generally have a prognosis similar to the general population while persons with a cerebrovascular cause of dizziness have increased mortality.

We also find important differences in survival within this cohort. Patients who reported episodic dizziness (periodic dizziness or short attacks) had better survival while unsteadiness between dizziness attacks and reduced balance were associated with increased mortality. Episodic dizziness is associated with better survival indicating that this is generally caused by non-fatal causes of dizziness. In ICD-11 episodic vestibular syndrome includes Menière's disease, vestibular migraine, BPPV, SCDS, disembarkment syndrome, autoimmune inner ear disease, and vestibular paroxysmia. Perhaps with the exception of autoimmune inner ear disease, these are generally considered to be benign conditions. Other causes for episodic vestibular symptoms are orthostatic hypotension, central paroxysmal positional vertigo, postural orthostatic tachycardia syndrome, vertebrobasilar TIA, and cardiac arrhythmias (87). Our study suggests that more dangerous causes of episodic vestibular symptoms are not very prevalent among patients seen in an otolaryngology clinic.

As mentioned above, we also found that patients with spinning vertigo had better survival. This shows that spinning vertigo in this cohort is most often caused by benign disorders, as also was suggested by van Vugt and colleagues (209). However, this is not a specific finding and as discussed previously the effect of spinning vertigo in our study was cancelled out when timing was introduced in the analyses.

Survival among patients with chronic symptoms and reduced balance

Patients who reported chronic unsteadiness and patients with reduced balance had increased mortality, and this supports previous studies that have found impaired balance to be associated with increased risk of falls (210) and with reduced survival in middle-aged and older persons (211,212). Another study also found that there was an increased risk of stroke among patients who were admitted with unsteadiness compared to other types of dizziness (213). We believe that there are several mechanisms that could explain the increased mortality among patients with chronic unsteadiness and reduced balance.

First, persons with vestibular symptoms are reported to have a higher risk of falls (214), and falls are the most common cause of injury-related morbidity and mortality among older adults (215). However, we did not find any association between postural balance and caloric asymmetry or between caloric asymmetry and survival, and it should be kept in mind that vestibular symptoms are not synonymous with vestibular disorders.

Second, self-experienced unsteadiness is associated with reduced physical activity (216) which has further negative consequences for health, and unsteadiness has also been associated with increased disability after two years (217). This corresponds well with our findings that patients who experienced unsteadiness between attacks had increased mortality.

Third, we found associations between unsteadiness and cardiovascular risk factors. And as mentioned previously a relationship between hearing loss and decline in mobility has been reported (40), and hearing loss has been associated with increased mortality both from trauma (42) and cardiovascular disease(43)(43,44). When relating this to the previous discussion on the association between hearing and postural balance, this provides further evidence that the increased mortality in patients with balance impairments is caused by several different mechanisms and that the direct causal effect from vestibular disorders may not be the most important.

11.5 Methodological considerations with strengths and limitations

The present study has some limitations. The symptom questionnaire (appendix, paper 2) used in this study was not validated before the study started and some aspects deserve particular discussion.

First, the questionnaire was not constructed to be a stand-alone diagnostic questionnaire, but rather a questionnaire to support the clinician to obtain the most relevant patient-reported information in a systematic fashion.

Second, the categories in this questionnaire are not completely comparable to the categorization used in ICD-11 or in ICVD (85,91). In particular, the timing categories are somewhat different in this study. The classification used in the questionnaire was designed to differentiate between patients with BPPV short attacks (measured in seconds), Menière's disease with periods of dizziness (measured in hours), and chronic dizziness (persisting symptoms). However, in our study neither reports of short attacks of dizziness nor periods of dizziness were significant predictor for the diagnosis of BPPV or Menière's disease. Therefore, it might have been better to classify the timing of symptoms in only two categories as episodic and chronic. However, because patients tended to report only one of these categories, it appears that it was a reasonable classification for patients. In addition, our findings showed that this categorization of timing was relevant for all outcomes. We therefore believe that these findings illustrate the importance of determining the time aspect of patient-reported symptoms, but further studies using the classification in ICD-11 are warranted to determine effect estimates for those categories.

Third, it is not determined if a rephrasing of the question on triggers could have made it more specific for reproducible triggers versus exacerbation of pre-existing symptoms, and also if information from a clinical interview or phone interview would differ from the reports obtained by a questionnaire. This might be an issue for generalizing the findings related to triggered dizziness/vertigo from a questionnaire to a clinical interview with a patient.

Additionally, the questionnaire in this study was administered in Norwegian and to a Norwegian-speaking patient population. Even though the various responses have been translated to English has it not been determined how language plays a role in the description of vestibular symptoms and in the use of questionnaires.

Further, because patients were tested several years ago, we do not have VEMP or v-HIT results for these patients. For caloric testing it was determined if patients had bilateral vestibulopathy with no or very weak response on both sides, but we did not have an absolute value of slow phase velocity for the two sides, and specific analyses for patients with bilateral vestibulopathy were not performed. This would be relevant for a future study.

There are also several limitations with the caloric irrigation test. First, it is stated that there are variations in the response between different individuals, between different ears, and even between individuals measured at different times (138). Additionally, as the side difference depends on a percentage difference between the two sides, a small difference in absolute value between two ears with a "weak response" (low slow phase velocity) could be considered significant, while a larger difference between two ears with a "strong response" would not be considered significant (138). Another limitation of the caloric irrigation test is that it essentially only tests the horizontal semi-circular canal and the superior vestibular nerve, while the other two semi-circular canals, the otolith organs and the inferior vestibular nerve are not assessed by this test. Further, the caloric test is a test of the lower frequency range, while most physiologic stimuli are of much higher frequencies (138). With the development of v-HIT, some authors have suggested that v-HIT should replace caloric testing in the acute setting because this is quicker and usually better tolerated test by the patients (218). However, a meta-analysis comparing v-HIT to caloric testing among patients with chronic dizziness found the sensitivity of v-HIT to be as low as 34%, but with a high specificity of 94%(131). In particular, it appears that caloric testing is more sensitive for Menière's disease (131) and vestibular schwannoma (132). It may also be the best compromise of a relatively easy and sensitive way to diagnose bilateral vestibulopathy and presbyvestibulopathy in which both diagnoses require a measure

of reduced vestibular function (13,127). Due to the higher sensitivity of caloric testing but high specificity of v-HIT, some authors suggest that caloric testing may be reserved for patients with normal v-HIT (74). In the acute setting, it appears that caloric testing could be replaced by the quicker and more portable v-HIT as this shows promising results in diagnosing acute vestibular loss among patients with acute vestibular syndrome (132,218,219). However, the caloric test still appears to remain the gold standard for assessing vestibular function in patients with chronic complaints.

The posturography performed in this study was only performed on a firm surface on a static platform, and the addition of testing with a soft surface or with a dynamic platform would have provided additional information.

As already mentioned, we aimed at performing these studies without using specific diagnoses as explanatory variables, but rather the diagnostic elements. This will also make sure that the findings are not affected by changes in diagnostic criteria over time. However, future studies should preferably include a wider array of vestibular testing, not only VEMP or v-HIT, but also positional testing with video-nystamography. However, patients were diagnosed according to the available information, but only the primary diagnosis was included in the study, and preferably the one that was related to the peripheral vestibular system. Co-existing morbidities such as migraine and secondary PPPD were therefore underreported. Whether one or several diagnoses are reported for each patient may also greatly affect the reported prevalence of vestibular disorders. How the population would be diagnosed with present day diagnostic criteria is not known.

Most patients in this study were examined in the outpatient setting with chronic symptoms. How this relates to the acute setting cannot be determined in detail, but the findings on type of dizziness correspond well with former findings on imprecision in the quality of dizziness (78)

The main strengths of the study are the long follow-up period, the large study population, and the consistent use of a questionnaire in combination with objective testing. This provided a robust foundation for the statistical analyses.

12. Future perspectives

The findings presented in this thesis may have implications for the classification and interpretation of vestibular symptoms as well as for the design of patient questionnaires to be used in the diagnosis of vestibular disorders.

History-taking should focus on the timing of symptoms when evaluating patients with vestibular symptoms, but should also remain open to the possibility of multiple coexisting conditions with different time courses. Patients describing non-episodic symptoms and chronic imbalance are at higher risk and should be considered for further evaluation probably including cardiovascular risk-factors and fall risk.

Future studies are suggested to determine how triggers of dizziness are best determined and how this is relevant in the diagnostic process.

Nausea and vomiting should be differentiated, where vomiting is a better indicator of unilateral vestibular loss as measured by the caloric test.

Several important questions are also raised by the present studies. While we have shown that postural balance in static conditions is associated with hearing, we have not found evidence that it is associated with chronic asymmetric vestibular function. Further studies exploring cause of death related to vestibular symptoms, vestibular diagnoses, hearing, and postural balance are advocated to further disentangle the complex relationship between postural balance, hearing, and mortality. While this study has focused on long-term survival, other outcomes such as quality of life, work participation, and repeated testing in a long-term follow up of dizzy patients should also be considered in future studies. Because both vestibular symptoms and hearing problems are highly prevalent, such research may lead to appropriate preventive measures in reducing the mortality associated with these common complaints in the general population.

This thesis also illustrates the challenges with diagnoses that are based on patient-reported vestibular symptoms. These challenges are not surprising when we consider the complexity of the central vestibular pathways and how the cortical connections

are so different from other sensory input. Hopefully, new vestibular function tests and biomarkers of common vestibular disorders, such as vestibular migraine, PPPD, and mal de debarquement, will be developed in the future. However, because vestibular symptoms are so common, it will be an aim that diagnostics can be performed with a minimum of special equipment and without compromising accuracy in determining the efficient therapy for the individual patient.

13. Conclusion

This thesis provides evidence that the timing of vestibular symptoms and a differentiation between nausea and vomiting are important when interviewing patients with dizziness. The type of dizziness provides additional information but does not appear useful for categorization. It also showed an association between hearing and postural balance, an association that could not be explained by unilateral vestibulopathy.

It further shows that patients with suspected vestibular disorders have a prognosis similar to the general population, but with several important subgroups where patients reporting persisting symptoms and reduced balance have increased mortality.

The thesis also illustrates potential challenges with diagnostics and epidemiological research that is based on patient reported symptoms alone. This encourages further work on developing objective diagnostic criteria for vestibular disorders and suggests that questionnaires used in epidemiologic research should be thoroughly validated.

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16. Publications

I

Evaluation of Self-Reported Symptoms in 1457 Dizzy Patients and Associations with Caloric Testing and Posturography

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(Final peer-reviewed manuscript)

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Short running head: Symptoms, caloric asymmetry and postural balance

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Abstract

Objective: To determine if symptoms regarding timing and triggers of dizziness are useful for categorizing patients with dizziness, and to evaluate how patient-reported symptoms predict vestibular asymmetry, postural sway and vestibular diagnoses.

Study design: Retrospective chart review.

Setting: Tertiary referral center.

Patients: Patients referred for suspected vestibular disease.

Interventions: Patients completed a symptom questionnaire prior to laboratory testing with static posturography and bithermal caloric tests.

Main Outcome Measure: Evaluate whether responses from a symptom questionnaire predict caloric asymmetry, postural balance and diagnoses.

Results: 1457 patients, 60.1% women, mean age 49.9 (±16.6) years were included. Vomiting was the strongest predictor for caloric asymmetry in adjusted analysis, Odds Ratio (OR): 1.60 (95% CI: 1.24-2.06), followed by chronic hearing loss OR: 1.59 (1.19-2.13). Patients who reported constant dizziness had impaired postural balance, quantified as 15% increase in postural sway in adjusted analyses (7.25%-24.6%). We found no association between caloric asymmetry and postural instability with eyes closed.

Conclusion: Most patients were able to describe the timing of their symptoms and a categorization based on timing seems feasible. There seemed to be an over-reporting of triggers and confirmatory testing of triggers is therefore advocated. Vomiting, but not nausea, is a strong indicator of vestibular disease. Caloric asymmetry and postural balance were not associated, and assessment of fall risk may be warranted in patients who reports constant dizziness, visual disturbances or dizziness triggered by light, darkness or sounds.

Introduction

Dizziness and vertigo are common complaints among patients seen in otolaryngology clinics and account for approximately 10 % of consultations[1]. Usually the diagnostic process starts with an interview that guides further clinical and laboratory testing[2,3]. Thus, it is important to establish how clinicians can use the anamnestic information to determine a diagnosis with the appropriate use of laboratory investigations.

Conventionally, the quality of dizziness symptoms was categorized into four groups considered to correspond with specific etiologies: a rotational sensation indicating vestibular, impending fainting or loss of consciousness indicating cardiovascular, disequilibrium or loss of balance indicating neurologic, and ill-defined "lightheadedness" indicating psychiatric etiology[4]. This categorization is still in widespread use [3,5], but may be misleading since dizziness quality is inconsistently reported by patients[3,6–9]. New diagnostic approaches with a focus on timing and triggers of symptoms have been advocated[7,10]. This was supported by a cross-sectional study in an emergency department where patients reported timing and triggers more consistently than type of dizziness[11]. However, further research to determine the accuracy and utility of these new diagnostic models have been recommended[3], and these models have not been adequately evaluated in the out-patient setting. In addition, most vestibular diagnoses depend on symptoms reported by the patients, and not objective findings alone. Fluctuating aural symptoms are a requisite for being diagnosed with Menières disease and recurrent attacks of positional vertigo or dizziness are a requisite for BPPV. For several diagnoses, such as vestibular migraine and persistent postural-perceptual dizziness (PPPD), the diagnosis depends entirely on reported symptoms[12–15]. Examination of associations between symptoms and corresponding diagnoses can therefore determine to what degree clinicians adhere to diagnostic criteria. However, such analyses may be insufficient to determine whether symptoms predict physical function or structural damage. We therefore aimed to evaluate whether patient-reported symptoms can predict both test results and diagnoses. This may determine the relevance of reported symptoms and would be valuable not only for the clinician in considering testing of

individual patients, but also in further developing and validating diagnostic criteria for specific vertigo syndromes.

The caloric test is one of the most common methods for measuring unilateral vestibular function[16] and has been considered the gold-standard for diagnosing chronic unilateral vestibular loss[17]. Caloric asymmetry is often present in peripheral vestibular disorders such as vestibular neuritis, Menière's disease and vestibular schwannoma[16,18]. Newer tests have been developed in recent years, such as the video head impulse test (v-HIT) and vestibular evoked myogenic potentials (VEMP), which measure vestibular asymmetry in different and complimentary ways. However, the caloric test remains one of the most commonly performed tests in vestibular laboratories. Static platform posturography is a common method for quantifying unsteadiness in the standing position and is frequently used in vestibular laboratories. Its diagnostic utility has been disputed, since postural instability is an unspecific finding in patients with vestibular as well as non-vestibular disorders[19], but some studies have reported usefulness in identifying patients at risk for falls [20,21]. For this reason, it is of interest to evaluate how postural sway relates to patient-reported symptom characteristics, in order to identify when this examination is relevant and to identify patients at risk of falls.

We hypothesized that patients' reports on timing and triggers of dizziness can be used to categorize patients. The aim of this study was thus to determine how timing and triggers are reported by patients, and further evaluate if patient-reported symptoms, provoking phenomena and symptom patterns can predict vestibular asymmetry, postural sway as well as vestibular diagnoses.

Methods

This study is a retrospective chart review of patients examined for suspected vestibular disease during a 12-year period at the Department of Otorhinolaryngology & Head and Neck Surgery, Haukeland University Hospital, Norway. All consecutive patients who had completed a self-reported symptom-questionnaire at diagnostic workup and undergone vestibular testing including bi-thermal caloric tests and

posturography were included. The study was approved by the Regional Committee for Medical and Health Research Ethics (REK 2012-1075). Patients alive at follow-up were informed of the study by mail and given the opportunity to withdraw.

Postural balance was quantified by static posturography (Cosmogamma®, A C International, Cento, Italy). Patients were instructed to stand still on the platform with arms along the side for 60 seconds. Two tests were performed, first with eyes open, then with eyes closed. The path length in millimeters refers to the distance traveled by the center of pressure (COP) during a test, and this represents postural sway. The Romberg quotient (RQ) is the ratio between path length with eyes closed (EC) and eyes open (EO) represented by the formula RQ = EC : EO[22].

Caloric testing was used to evaluate one side of the peripheral vestibular apparatus at a time[16]. The caloric response to irrigation of each ear canal with subsequently hot and cold water (44 and 30 °C) was recorded using electro- or video-nystagmography. Asymmetry between the two ears was calculated using Jongkees' equation with values ≥ 25 % considered pathologic[16]. Patients with bilaterally absent or inadequate caloric response were excluded from analysis on vestibular asymmetry. Diagnoses were determined by an otolaryngologist at time of examination and reviewed by the two of the authors (FG, SHG).

A questionnaire including time-course of symptoms, description of dizziness, triggers for dizziness, and accompanying symptoms was answered by patients, a translated version is provided in Supplementary digital content, Fig 3. In cases where the patient needed assistance with the questionnaire, this was provided by the patient's family if they were present, laboratory personnel or the examining physician.

Statistical analysis

Path lengths were positively skewed and log-transformed before regression analyses and tests for Pearson's correlation coefficient. Back transformation was performed to obtain geometric means and for the regression analysis coefficients represent ratios of geometric means. Regression analyses were performed by forward stepwise regression analysis for log-path length with eyes closed and by forward stepwise logistic regression for asymmetric caloric test and the most common

diagnoses. Variables with significance level p <0.05 were included in the forward stepwise analysis. All statistical analyses were performed using Stata (StataCorp. 2017. Stata: Release 15. Statistical Software. College Station, TX: StataCorp LLC). Two-sided p-values < 0.05 were considered significant.

Results

Study population

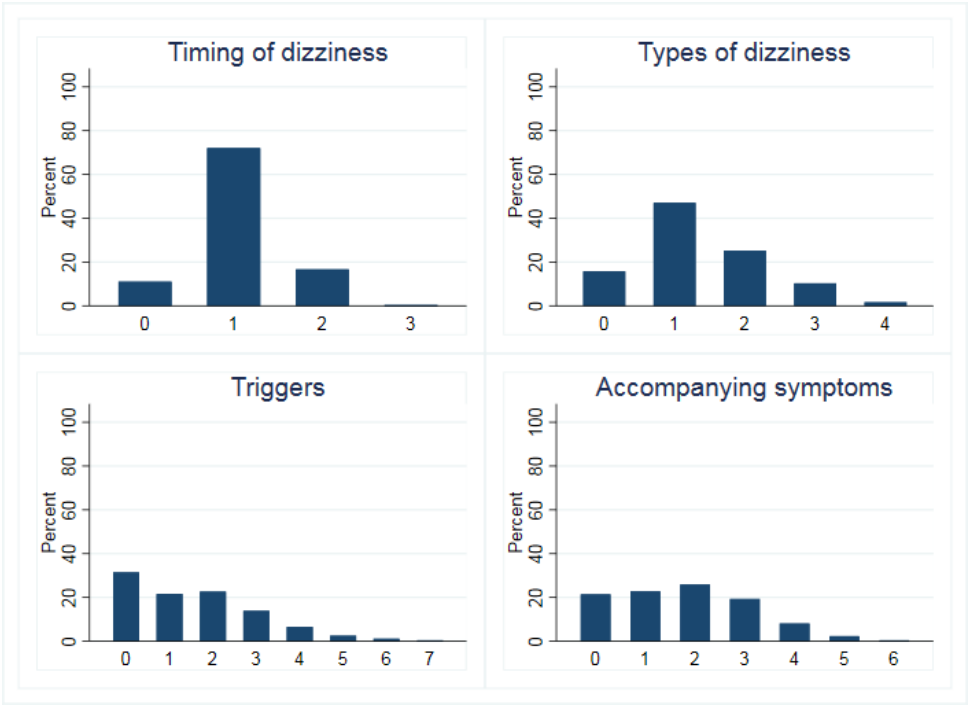
1555 patients met the inclusion criteria. Of these, 98 patients were excluded due to missing consent. Thus, 1457 patients were included, with mean age 49.9 (±16.6) years, and 875 (60.1%) were women. 595 patients (40.1%) were diagnosed with disease related to the ear or vestibular nerve, the most common being vestibular neuritis diagnosed in 198 (13.6%) patients, BPPV in 190 (13.0%) and Menières disease diagnosed in 139 (9.5%) patients. 27 (1.85%) had vestibular schwannoma, 41 (2.8%) were diagnosed with other inner- or middle-ear disease. 109 (7.5%) were considered to have cervicogenic cause of dizziness, 114 (7.8%) were diagnosed with cerebrovascular cause of dizziness and 354 (24.3%) were termed as non-vestibular cause of dizziness. 14 (1.0%) of the patients had bilateral pathologic or unmeasurable caloric response.

Dizziness symptoms

Median interval since first symptom of dizziness was 405 days, range <1 day to 45 years. Dizziness symptoms are presented in Table 1. Multiple answers were allowed, and Figure 1 illustrates how many responses each patient had within the following categories: timing of dizziness, type of dizziness, triggers, and accompanying symptoms. 1050 patients (72.1%) reported only one type of timing, while 686 patients (47.1%) reported only one type of dizziness. 179 patients (12.3%) reported both spinning and rocking dizziness.

Fig 1

Responses given by each patient within various symptom-categories. Number of answers is displayed on the x-axis and percentage of patients who reported this number is displayed on the y-axis.



Association between patient-reported symptoms and caloric response

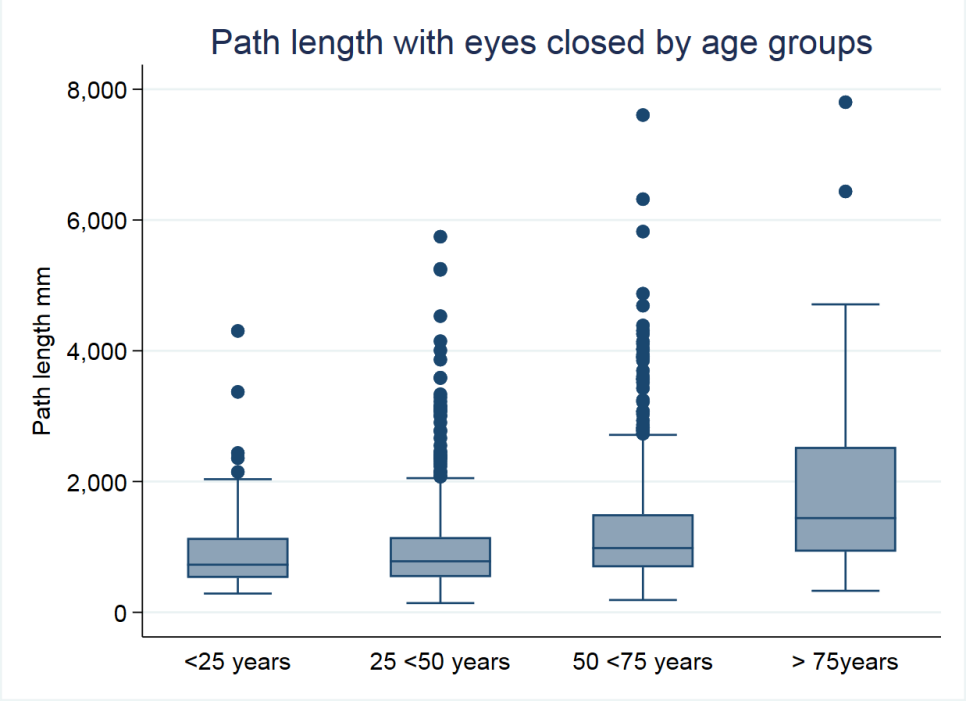
439 patients (30.4%) had caloric asymmetry. In logistic regression analyses adjusted for age, sex and self-reported symptoms (Table 2), patients who reported vomiting or chronic hearing loss (hearing loss that was unrelated to dizziness attacks) had increased risk for caloric asymmetry, OR: 1.60 ($p<0.001$) and OR: 1.59 ($p=0.002$) respectively. Patients with short attacks of dizziness OR: 0.60 ($p<0.001$), periodic dizziness OR: 0.76 ($p=0.034$), rocking dizziness OR: 0.74 ($p=0.021$) or syncope associated with dizziness attacks 0.60 ($p=0.049$) had reduced risk for caloric asymmetry. None of the triggers were associated with caloric asymmetry.

Association between patient-reported symptoms and postural balance

Constant dizziness was in adjusted analyses associated with a 15.5% (p<0001) increase in sway. Dizziness triggered by light or darkness, sound, and visual disturbances were associated with an increased postural sway of 14.0% (p=0.026), 13.9% (p=0.014) and 9.1% (p=0.013) respectively (Table 3). Female sex and attacks of dizziness were associated with a 12.8% (p<0.001) and 12.2% (p<0.001) reduction in postural sway, respectively. Postural sway by age-group is shown in Figure 2. There was no association between postural sway and the number of reported dizziness types (p=0.088).

Fig 2

Postural sway with increasing age. Boxes display median and interquartile range. The length of the whiskers are 1.5 times the interquartile range, and separate dots represent outside values.



Association between caloric response and path length

There was no correlation between caloric asymmetry and postural sway with eyes closed (p=0.244), eyes open (p=0.446) or Romberg's Quotient of path length (p=0.333). Regression analyses for postural sway adjusting for age, sex, and pathologic caloric response gave no significant differences.

Association between patient-reported symptoms and final diagnoses

Stepwise logistic regression analysis was performed to identify which patient-reported symptoms were associated with the most common diagnoses (Table 4). The following symptoms were associated with vestibular neuritis: reports of constant dizziness (OR: 2.78, p<0.001), vomiting (OR: 2.72, p<0.01) and spinning vertigo (OR: 1.69, p<0.002). The following symptoms were associated with BPPV: Dizziness triggered by positional change (OR: 3.90, p<0.001), spinning vertigo (OR 2.08, p<0.001) and dizziness triggered by neck movements (OR: 1.51, p=0.021). The following symptoms were associated with Menières disease: hearing loss accompanying dizziness attacks (OR: 13.4, p<0.001), vomiting (OR: 3.60, p<0.001), hearing loss independent of dizziness attacks (OR:13.36, p<0.001), tinnitus accompanying dizziness attacks (OR: 3.55, p<0.001), spinning vertigo (OR:1.92, p=0.003), tinnitus independent of dizziness attacks (OR: 1.91, p=0.009) and dizziness in short attacks (1.59, p=0.025). For cerebrovascular cause of dizziness an increased risk was seen among patients reporting no symptoms accompanying dizziness attacks (OR:1.98, p=0.020) or dizziness associated with a sensation of near fainting (OR: 1.72, p=0.026).

Discussion

The aim of this study was to evaluate whether a categorization of dizzy patients based on their description of timing and triggers of dizziness is feasible, and how patient-reported symptoms can predict caloric asymmetry, objective postural instability and diagnoses. We found that timing of symptoms was consistently reported. Reports of vomiting, but not nausea, were associated with vestibular asymmetry. However, patients tended to over-report triggers of dizziness, and there was considerable overlap in types of dizziness. The study identifies potential

challenges with dizziness-diagnostics based on questionnaires alone and for epidemiological studies that are exclusively based on patient-reported symptoms.

Most patients reported only one time-pattern for their dizziness, and there was association between the timing-categories and laboratory results. To differentiate between intermittent or continuous dizziness has been suggested by several authors,[7,10] and the latest classification of vestibular syndromes in ICD-11 is based on timing[23]. Our results indicate that this is a practical method to group patients with vestibular syndromes.

The International Classification of Vestibular Disorders (ICVD) defines triggered dizziness when there is a temporally appropriate relationship between stimulus and dizziness, and under most circumstances a reproducible, repetitive relationship should be present[24]. In our study we found that patients reported a surprisingly high number of triggers. We suggest that patients do not intuitively differentiate between reproducible triggers and factors that exacerbate preexisting dizziness or cause discomfort when asked as part of a questionnaire. Reported triggers such as sound-induced dizziness may therefore not necessarily represent a genuine Tullio-phenomenon indicating superior semicircular canal dehiscence syndrome or perilymphatic fistula. The same may apply to patients with suspected BPPV and suggests that the history may be insufficient to diagnose triggered dizziness and confirmatory testing of triggers is therefore advocated. Further studies are needed to evaluate if other wording of the questions can improve the accuracy of triggered dizziness in questionnaires.

Vomiting associated with dizziness was a highly significant predictor of caloric asymmetry and for being diagnosed with Menière's disease and vestibular neuritis, whereas nausea was not. Nausea and vomiting are commonly associated with peripheral vestibular disorders such as vestibular neuritis, labyrithitis and Menière's disease, but also with central disorders like vestibular migraine[25]. Previous studies have combined nausea and vomiting to indicate a vestibular diagnosis [25–28]. Our findings suggest that vomiting, more than nausea, may be helpful in distinguishing peripheral from central vestibular disorders in the out-patient setting.

Less than half of the patients reported only one type of dizziness quality in this study. This corresponds with results by Kerber et al and Newman-Toker et al[8,11], and confirms that a categorization of patients based on quality of dizziness is unreliable.

Patients with self-reported hearing loss independent of dizziness attacks had an increased risk of impaired postural balance. This is in agreement with a previous study were we found that increased hearing thresholds was an independent predictor of poor postural balance[29].

Age, constant dizziness and dizziness triggered by light or sounds were associated with impaired balance. The association between age and postural instability is well-known[30] and constant dizziness is more likely to be associated with a chronic and ongoing problem rather than an intermittent vestibular dysfunction such as BPPV. Sensitivity to light and sounds are well-known symptoms in patients with migraine, while hyperacusis and sound-induced dizziness may result from disorders of the inner ear. More detailed questions and objective tests of light and sound sensitivity are necessary in order to determine the full diagnostic potential of these symptoms. Patients with decreased balance have increased risk of falls[20] with subsequent morbidity and injury-related deaths[31]. We therefore suggest static posturography and assessment of falls risk for the dizzy patients that are older, report constant dizziness, visual disturbances or dizziness triggered by light or sounds.

There was no correlation between postural sway in static conditions and asymmetric vestibular function. This corresponds with our previous findings on patients with vestibular schwannoma[32]. While an acute unilateral vestibular loss is clearly associated with postural imbalance, a chronic and stable loss is usually compensated. The majority of patients in the present study reported a long symptom duration, and the effect of a unilateral loss was probably outweighed by the effects of other disorders, such as reduced proprioception, central nervous or orthopedic disorders on postural balance.

Strengths of this study include the large number of patients, which support even negative results. Moreover, the analyses based on objective outcomes (caloric asymmetry and postural instability) represents a strength, since the associations

between symptoms and diagnoses often are circular as most vestibular diagnoses rely on patient-reported symptoms.

Patient history was recorded by questionnaires filled in by the patients themselves, if necessary with help from health personnel or accompanying persons. The use of questionnaires is a cost-efficient way of recording the patient history, and this study represents a test of the validity of such an approach. We have previously experimented with questionnaires filled in by the referring physicians but found that the patients tended to fill in the questionnaires more completely. We also thought that the patients themselves would give the most reliable account of their own symptoms. It can be laborious to obtain a valid history from patients with dizziness complaints, in particular for those with a long symptom duration. A questionnaire may simplify this process. How the questionnaire responses corresponded with a clinical interview was not validated in this study.

The study has some limitations. First, the findings in this study relate to outpatients, most of them with long-standing dizziness, and may not necessarily be generalized to patients in an acute setting. Secondly, modern tests of vestibular asymmetry, such as the v-HIT or VEMPs, were not used throughout the study-period and were therefore not included in the present study. These tests could have provided a more nuanced picture and detected more patients with vestibular disease. However, for chronic peripheral vestibular disorders such as Menière's disease or vestibular schwannoma, a review article found the caloric test to be the most sensitive measure[33].

Patients with BPPV will generally have a symmetric caloric response[34]. We have therefore performed specific analyses to determine how symptoms predict BPPV. In addition, we performed separate analyses after patients diagnosed with BPPV were excluded. These analyses show comparable results with the main study and support our main findings (supplementary digital content). The present study did not include central oculomotor tests such as ocular smooth pursuit, saccades or optokinetic nystagmus, which are commonly performed in vestibular laboratories. Pathologies in these tests are less defined and are rarely seen in our practice. Dynamic posturography could have contributed to a more detailed analysis of

postural control[19]. However, dynamic posturography requires large and costly equipment, is more time-consuming, and static posturography is therefore more commonly available in clinical practice.

We have shown that patients often report several triggers and types of dizziness when using questionnaires, and the limited association between symptoms and laboratory results remains a fundamental diagnostic problem in dizziness diagnostics. In clinical practice, an interview and physical examination remains essential. As symptom descriptions tend to be equivocal, further developments in laboratory testing and imaging techniques are warranted in order to make the diagnosis of vestibular disorders more reliable.

In conclusion, we find that timing of dizziness was the most clearly reported symptom category and this was also associated with objective findings. Thus, we conclude that timing may be the best element to categorize patients with dizziness. We found that patients did not differentiate between triggers and exacerbating factors. We recommend caution when interpreting reports on triggers, and confirmatory testing is therefore advocated. Vomiting, but not nausea, is a predictor of peripheral vestibular disease. Postural imbalance was associated with increasing age, reports of constant dizziness, visual disturbances or dizziness triggered by light, darkness or sounds. These factors indicate that posturography and assessment of falls risk should be considered.

Table 1

Dizziness questionnaire and frequency of reported symptoms in 1457 dizzy patients. Multiple answers were allowed.

Timing of dizziness:		
	Short attacks	675 (46 %)
	Periods	565 (39 %)
	Constant	298 (21 %)
	Other, free text	7 (0.5 %)
Types of dizziness:		

	Spinning	705 (48 %)
	Rocking	457 (31 %)
	Other, free text	343 (24 %)
	Walking on pillows or floating	297 (20 %)
	Drop-attacks / vestibular falls	164 (11 %)
Accompanying symptoms:		
	Syncope	101 (7 %)
	Headache	428 (29 %)
	Nausea	813 (56 %)
	Vomiting	388 (27 %)
	Visual disturbances	438 (30 %)
	Near-fainting	228 (16 %)
	Other, free text	193 (13 %)
	None	129 (9 %)
Tinnitus:		
	During dizziness attacks	100 (7 %)
	Independent of dizziness attacks	419 (29 %)
Hearing loss:		
	During dizziness attacks	57 (4 %)
	Independent of dizziness attacks	254 (17 %)
Triggers of dizziness:		
	Positional change	536 (37 %)
	Sleep deprivation	210 (14 %)
	Neck movements	445 (31 %)
	Light or darkness	119 (8 %)
	Sound	152 (10 %)
	Psychological factors	408 (28 %)
	Medication	22 (2 %)
	Infection / fever	52 (3 %)
	Other, free text	258 (18 %)
	None	284 (20 %)

Table 2

Patient-reported symptoms from a dizziness questionnaire associated with caloric asymmetry in 1443 dizzy patients

	Univariate		**Adjusted**		Stepwise analysis[a]
	Odds Ratio (95% CI)	p-value	Odds Ratio (95% CI)	p-value	
Sex (female)	0.76 (0.60-0.95)	**0.017**	0.79 (0.63-1.00)	**0.046**	**6**
Timing of dizziness					
Short attacks	0.68 (0.54-0.85)	**0.001**	0.60 (0.47-0.76)	**<0.001**	**2**
Periods	0.90 (0.71-1.13)	0.368	0.76 (0.59-0.98)	**0.034**	**5**
Constant	1.35 (1.03-1.77)	**0.027**			
Types of dizziness					
Rocking	0.75 (0.58-0.96)	**0.023**	0.74 (0.58-0.96)	**0.021**	**4**
Accompanying symptoms					
Syncope	0.60 (0.36-0.98)	**0.041**	0.60 (0.36-1.00)	**0.049**	**7**
Vomiting	1.51 (1.18-1.94)	**0.001**	1.60 (1.24-2.06)	**<0.001**	**3**
Near-fainting	0.66 (0.47-0.92)	**0.014**			
Hearing loss					
Independent of dizziness attack	1.63 (1.23-2.17)	**0.001**	1.59 (1.19-2.13)	**<0.002**	**1**

Patients with bilateral weak or absent response on caloric testing were excluded from this analysis (n=14). Significant categories from univariate logistic regression and adjusted model from stepwise logistic regression. Odds Ratio from logistic regression analysis for vestibular asymmetry. Vestibular asymmetry defined as ≥ 25% asymmetry on caloric response according to Jongkees' formula [26]. CI: Confidence interval.

[a] Indicating inclusion sequence in forward stepwise regression analysis.

Table 3

Patient-reported symptoms from a dizziness questionnaire associated with postural instability in 1457 dizzy patients

	Univariate		Adjusted		Stepwise analysis[b]
	Coeff[a] (95% CI)	p-value	Coeff[a] (95% CI)	p-value	
Sex (female)	-0.12 (-0.19; -0.06)	**<0.001**	-0.14 (-0.20; -0.07)	**<0.001**	**3**
Age	0.01 (0.01; 0.01)	**<0.001**	0.01 (0.01; 0.01)	**<0.001**	**1**
Timing of dizziness					
Short attacks	-0.17 (-0.23;-0.11)	**<0.001**	-0.13 (-0.19;-0.07)	**<0.001**	**2**
Constant	0.22 (0.14; 0.30)	**<0.001**	0.14 (0.07; 0.22)	**<0.001**	**4**
Types of dizziness					
Drop-attacks / vestibular falls	0.11 (0.01; 0.21)	**0.034**			
Other type of dizziness	0.07 (-0.01; 0.14)	0.076			
Triggers of dizziness					
Light or darkness	0.15 (0.04; 0.27)	**0.011**	0.13 (0.02; 0.25)	**0.026**	**7**
Sound	0.13 (0.02; 0.24)	**0.016**	0.13 (0.03; 0.23)	**0.014**	**5**
Medication	0.26 (-0.01; 0.52)	0.055			
Accompanying symptoms					
Headache	0.08 (0.00; 0.15)	**0.037**			
Visual disturbances	0.08 (0.01; 0.15)	**0.022**	0.09 (0.02;0.16)	**0.013**	**6**
Hearing loss					
Independent of dizziness attacks	0.13 (0.05; 0.22)	**0.002**			
Tinnitus, independent of dizziness attacks	0.08 (0.01;0.16)	**0.021**			

Significant and trending categories from univariate regression analysis and full model from stepwise regression analysis. Postural instability quantified as path length of center of pressure in millimeters during 60 seconds of quiet standing with eyes closed on a static force platform. CI: confidence interval. [a]Coeff. represents regression coefficients from regression analysis for the natural logarithm of the path length. [b] Indicating inclusion sequence in forward stepwise regression analysis.

Table 4

Logistic regression analyses for patient-reported symptoms as predictors for diagnoses in 1457 patients with dizziness

Vestibular neuritis	**Odds Ratio**	**p**	**95% CI**		**Stepwise inclusion[a]**
Constant dizziness	2.782	**<0.001**	1.965	3.938	1
Vomiting accompanying dizziness	2.722	**<0.001**	1.629	3.167	2
Spinning vertigo	1.688	**0.002**	1.212	2.351	3
Short attacks of dizziness	0.613	**0.005**	0.434	0.866	4
Drop-attacks / vestibular falls	0.0443	**0.009**	0.240	0.818	5
BPPV					
Dizziness triggered by positional change	3.970	**<0.001**	2.717	5.800	1
Spinning vertigo	2.077	**<0.001**	1.480	2.913	2
Dizziness triggered by sound	0.403	**0.007**	0.207	0.784	3
Dizziness triggered by neck movements	1.509	**0.021**	1.065	2.139	4
Dizziness triggered by light or darkness	0.416	**0.026**	0.192	0.900	5
No triggers of dizziness	0.456	**0.031**	0.223	0.932	6
Dizziness triggered by infection / fever	0.629	**0.041**	0.403	0.980	7
Menières disease					
Hearing loss accompanying dizziness attacks	13.357	**<0.001**	6.110	29.200	1
Vomiting accompanying dizziness attacks	3.601	**<0.001**	2.383	5.058	2
Hearing loss independent of dizziness attacks	3.101	**<0.001**	1.901	5.058	3
Dizziness triggered by positional change	0.381	**<0.001**	0.235	0.619	4
Tinnitus accompanying dizziness attacks	3.548	**<0.001**	1.832	6.869	5
Spinning vertigo	1.916	**0.003**	1.246	2.945	6
Headache accompanying dizziness attacks	0.552	**0.014**	0.344	0.886	7
Tinnitus independent of dizziness attacks	1.912	**0.009**	1.175	3.110	8
Dizziness in short attacks	1.593	**0.025**	1.059	2.395	9

Near fainting	0.482	**0.030**	0.249	0.932	10
Cerebrovascular disease					
No accompanying symptoms with dizziness	1.978	**0.020**	1.115	3.510	1
Near fainting	1.723	**0.026**	1.069	2.777	2

Logistic regression analyses with stepwise inclusion of significant factors ($p<0.05$) is performed for each diagnosis, the final model for each diagnosis is shown. CI: Confidence interval. [a] Indicating inclusion sequence in forward stepwise regression analysis.

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Supplementary Digital Content:

Table 5. Supplementary analysis of patient-reported symptoms from a dizziness questionnaire associated with caloric asymmetry in 1254 dizzy patients. Patients with BPPV excluded from the analysis.

	Adjusted		Stepwise analysis
	Odds Ratio (95% CI)	p-value	
Timing of dizziness			
Short attacks	0.66 (0.51;0.84)	**0.001**	**2**
Types of dizziness			
Rocking	0.67 (0.51;0.87)	**0.003**	**4**
Associated symptoms			
Vomiting	1.72 (1.32; 2.25)	**<0.001**	**1**
Near-fainting	0.68 (0.47; 0.97)	**0.035**	**5**
Hearing loss			
Independent of dizziness attack	1.64 (1.21;2.22)	**0.001**	**3**

Significant categories from adjusted model from stepwise logistic regression. Odds Ratio from logistic regression analysis for vestibular asymmetry. Vestibular asymmetry defined as ≥ 25% asymmetry on caloric response according to Jongkees' formula [26]. CI: Confidence interval. Patients with bilateral weak or absent caloric response are excluded from the analysis.

[a] Indicating inclusion sequence in forward stepwise regression analysis.

Fig 3. Symptom questionnaire administered to patients evaluated with vestibular testing for dizziness or balance problems*

Does the dizziness occur in

□ Short attacks □ Periods □ Constant □ Other, please specify_____

Does it feel like the room/floor is moving when you are dizzy?

□ Yes, the floor rocks like a boat
□ Yes, the room spins like a merry-go-round
□ Other type of dizziness, please specify_____

Do you feel like you are walking on pillows/floating when you are dizzy?

□ No □ Yes

Does it occur that you fall down because you loose all your strengths?

□ No □ Yes

Have you had any other symptoms when you are dizzy?

□ No □ Nausea □ Vomiting □ Headache
□ Visual disturbanc □ Near-fainting □ Syncope □ Other_____

Are you bothered by...:

Tinnitus?	□ No	□ Yes	□ During attacks	□ Independent of attacks
Hearing loss?	□ No	□ Yes	□ During attacks	□ Independent of attacks

Are there certain things/events that you know can trigger attacks of dizziness?

□ None	□ Positional change	□ Sleep deprivation
□ Psychological stress	□ Neck movements	□ Light or darkness
□ Sounds	□ Psychological factors	□ Medications
□ Infections/ fever	□ Other _____	

* Original questionnaire was administered in Norwegian.

II

III

The Laryngoscope

Long-Term Survival in 1,931 Patients With Dizziness: Disease- and Symptom-Specific Mortality

Jan Erik Berge, MD; Stein Helge Glad Nordahl, MD, PhD; Hans Jørgen Aarstad, MD, PhD; Frederik Kragerud Goplen, MD, PhD

Objective: To evaluate mortality among patients referred for suspected vestibular disorder and to examine whether specific symptoms or disorders predict long-term survival among patients with dizziness or vertigo.

Study Design: Retrospective cohort study.

Methods: This retrospective cohort study analyzed long-term survival data. Consecutive patients examined for suspected vestibular disease at an otolaryngology clinic completed a detailed questionnaire regarding symptoms and comorbidities.

Results: The study included 1,931 patients. Their mean age (standard deviation) was 50.5 (16.5) years, and 60% were women. The mean follow-up period was 20.6 years (range, 15.3–27.5 years). The standardized mortality ratio for the entire cohort compared with the Norwegian age- and sex-matched population was 1.03 (95% confidence interval [CI]: 0.94–1.12), illustrating no difference in overall survival. Patients with a cerebrovascular cause of dizziness had higher mortality in adjusted Cox regression analyses (hazard ratio [HR] 1.56, 95% CI: 1.11–2.19), whereas patients reporting periodic or short attacks of dizziness had lower mortality (HR 0.62 [0.50–0.77] and 0.76 [0.63–0.93], respectively). Reported unsteadiness between dizziness attacks was associated with higher mortality with an HR of 1.30 (95% CI: 1.08–1.57).

Conclusion: This long-term study found comparable mortality rates between patients evaluated for suspected vestibular disorder and that of the general population. However, subgroup analyses showed reduced mortality in patients with periodic or short attacks of dizziness and increased mortality in patients with unsteadiness between attacks or cerebrovascular causes of dizziness. The time course of vestibular symptoms should be determined, and thorough evaluation including fall risk and comorbidities must be considered in patients with nonepisodic symptoms.

Key Words: Dizziness, vertigo, unsteadiness, vestibular symptoms, mortality.

Level of Evidence: 3

***Laryngoscope*, 131:E2031–E2037, 2021**

INTRODUCTION

Vestibular symptoms include dizziness, vertigo, vestibulovisual symptoms, and unsteadiness.[1] The US National Health Interview Survey (NHIS) indicated that 23.8 million adult Americans (11.1%) had reported dizziness or balance problems during the last 12 months.[2] Those experiencing these symptoms had a twofold higher mortality rate (relative risk, 2.2; 95% confidence interval [CI], 1.8–2.8), a risk comparable to that of other leading causes of death such as diabetes mellitus, cardiovascular disease, and cancer.[2] It is less likely that the patient will be referred to clinics specializing in vestibular disorders if the referring physician finds other serious underlying disease to be the most likely cause of the patient's symptoms. However, the predictors of long-term survival have not been examined in patients with dizziness seen in otolaryngology or neurotology clinics. To what extent vestibular disorders such as Ménière's disease and benign paroxysmal positional vertigo (BPPV) are associated with survival is unknown; furthermore, whether specific vestibular symptoms such as unsteadiness or spinning vertigo are relevant for survival has also not been elucidated.

Although patient history is essential when diagnosing patients with dizziness, the diagnostic yield and prognostic value of various patient-reported symptoms remain uncertain. Differentiation based on the type of dizziness was previously advocated, and spinning vertigo was considered a typical feature of benign, peripheral vestibular disorders.[3,4] Van Vugt et al. reported lower mortality among older patients in primary care settings with vertigo compared with the mortality in those with presyncope, disequilibrium, or other types of dizziness.[5] However, patients are inconsistent when describing the types of dizziness they have experienced,[6] and differentiation based on the reported type of dizziness has been criticized.[4] An alternative differentiation is based on the time course and triggers of dizziness,[7,8] and categorization of acute, episodic, and chronic vestibular syndromes is included in the World

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Health Organization International Classification of Diseases (ICD-11).[9] The risk of falls increases with increasing numbers of patient-reported vestibular symptoms, and self-reported unsteadiness has been shown to predict falls and disability after 2 years.[10,11] These findings correspond well with several studies reporting that impaired balance in physical testing was associated with reduced survival in middle-aged and older persons.[12–14] Thus, as dizziness and balance problems are associated with a dramatic increase in mortality in the general population, it is also important to investigate this association in the otolaryngology setting. Furthermore, the identification of specific findings in the history or specific diagnoses that predict increased death risk is also important as such information could lead to individualized follow-up.

The present study aimed to evaluate overall survival among patients examined for dizziness in a tertiary otolaryngology clinic and to determine the survival prediction of dizziness diagnoses and the details of patient history such as dizziness type, symptom timing, and associated symptoms.

MATERIALS AND METHODS

This cohort study included consecutive patients examined between 1992 and 2004 at the vestibular and balance laboratory at the Department of Otorhinolaryngology and Head and Neck Surgery at Haukeland University Hospital, Norway. The clinic serves as a tertiary care clinic for vestibular disorders and also receives referrals from primary care physicians for patients with suspected vestibular disease.

Before examination, the patients completed a questionnaire containing questions on the symptom time course, dizziness description, dizziness triggers, accompanying symptoms, and how they felt between attacks of dizziness (not troubled, unsteady, or other [free text]). The questionnaire also included questions on previous and concurrent diseases, including diabetes mellitus and cardiovascular disease. The categories were not mutually exclusive, but for timing patients usually reported only one category. A more detailed description of the questionnaire and responses in various categories has been described in detail previously.[15]

The patients underwent laboratory testing including videonystagmography or electronystagmography, bithermal caloric testing, and audiometry.

The causes of dizziness were determined by an otolaryngologist after clinical examination. The inclusion of patients was performed over 12 years, and there were some changes in the diagnostic criteria over this period. To verify the accuracy of diagnoses, all diagnoses were reviewed by two of the coauthors (F.K.G. and S.H.G.N.) and categorized for the purpose of this study.

The study was approved by the Regional Committee for Medical and Health Research Ethics (REK 2012-1075) with requirement that patients still alive were informed of the study by mail and provided an opportunity to withdraw. All patients alive in 2016 were thus informed, and patients with unknown address were excluded from the study.

Date of examination in the clinic was regarded as start of observation time. Data on vital status and date of death if they had died were retrieved from the Norwegian National Registry on June 28, 2019; this represents the end of the observation period. Patients where it could not be determined whether they had died or were alive at this time were regarded as lost to follow-up and were excluded from the study. Person-years at risk were calculated from start of observation time until whichever occurred first June 28, 2019, or death.

Kaplan-Meier curves were used to illustrate survival in patients grouped by diagnoses and selected symptoms. Statistical differences between survival curves were tested by log-rank tests.

The standardized mortality ratio (SMR) was calculated by indirect standardization to compare mortality in the cohort with the mortality of the general Norwegian population. The SMR represents the relative mortality of the study population compared with the expected mortality in a reference population. The expected number of deaths was calculated as the total number of person-years at risk for each sex-specific age group with 5-year intervals multiplied by the corresponding death rate in the Norwegian population for the same groups. The sex-specific age group mortality was retrieved from Statistics Norway,[16] and mortality rates from 1999 were used as the reference mortality rate as this was the middle year of inclusion in the study.

Cox proportional hazards regression models were used to calculate crude and adjusted hazard ratios (HRs) for patient-reported symptoms and known comorbidities (diabetes mellitus and cardiovascular disease). HRs represent the ratio of probability of death depending on predictor variables. In this study, we report the HR between patients reporting specific symptoms compared with patients not reporting that specific symptom. Forward Cox-regression analysis adjusted for age, sex, former cardiovascular disease, and diabetes mellitus was performed to create a final model with a significance level set at $P < .05$. The assumptions of proportional hazards and specifications were checked using graphical methods, link tests, and tests based on Schonfeld residuals.

All statistical analyses were performed using Stata (StataCorp. 2017. Stata: Release 15. Statistical Software; StataCorp LLC, College Station, TX). Two-sided P-values < .05 were considered statistically significant.

RESULTS

Of the 2,058 patients with patient-reported symptoms of dizziness at baseline, 40 were lost to follow-up and 87 were missing consent; thus, this study included 1,931 patients. Of these, 1,154 (59.8%) were women and the mean age at examination was 50.5 years (standard deviation 16.5 years). The mean time interval from examination in the clinic until the end of observation was 20.6 years (range, 15.3–27.5 years). The most common vestibular diagnosis was vestibular neuritis (252 patients, 13.1%) followed by BPPV (235 patients, 12.2%), Ménière's disease (204 patients, 10.6%), and vestibular schwannoma (76 patients, 3.9%). A total of 151 patients (7.8%) were diagnosed with a cerebrovascular cause of dizziness without concurrent vestibular disease, whereas 715 patients (37.0%) were diagnosed with unspecified nonvestibular causes of dizziness.

Mortality Compared With The General Population

The 5- and 10-year mortality rates in the entire cohort were 4.3% and 10.1%, respectively. The SMR was 1.03 (95% confidence interval [CI] 0.94–1.12) for the entire cohort, illustrating no difference in mortality compared with the expected mortality in the general Norwegian population matched for age and sex. Patients who reported periodic dizziness had a 17% lower mortality

rate with an SMR of 0.83 (0.70–0.98) compared with the age- and sex-matched general Norwegian population, whereas patients reporting constant dizziness had borderline significantly increased mortality with an SMR of 1.20 (1.00–1.43) compared with the age- and sex-matched Norwegian population.

Predictive Values of Selected Symptoms of Dizziness

Figure 1 shows the unadjusted Kaplan-Meier plots of survival based on selected symptoms. Survival analysis adjusted for age and sex (Table 1) showed the risk of mortality to be 27% lower in patients reporting periods of dizziness (HR 0.73, 95% CI: 0.60–0.89) compared with patients who did not report this symptom. In contrast, patients reporting constant dizziness had a 30% higher risk of mortality (HR 1.30 [1.05–1.60]) compared with patients who did not report constant dizziness. Patients who reported spinning vertigo or dizziness triggered by sound had a lower risk of mortality (HR 0.83 [0.69–0.99] and 0.61 [0.40–0.93], respectively), whereas dizziness triggered by medication was associated with a nearly twofold increase in risk of mortality (HR 1.85 [1.08–3.14]).

Cox regression analysis performed for each symptom adjusted for age, sex, diabetes mellitus, and cardiovascular disease showed that periodic dizziness was associated with a 30% lower risk of mortality (HR 0.70 [0.58–0.86]), whereas constant dizziness was associated with a 25% increased risk of mortality (HR 1.26 [1.01–1.55]). Spinning vertigo and dizziness triggered by sound were associated with a reduced risk of mortality in analyses adjusted for age, sex, and comorbidities (HR 0.80 [0.67–0.96] and 0.61 [0.39–0.93], respectively).

The results of stepwise Cox regression analysis of patient-reported symptoms adjusted for age, sex, cardiovascular disease, and diabetes mellitus are presented in Table 2. Among patient-reported symptoms, periodic or short attacks of dizziness were associated with reduced risk of mortality (HR 0.62 [0.50–0.77] and 0.76 [0.63–0.93], respectively). Unsteadiness between dizziness attacks was associated with increased risk of mortality (HR 1.30 [1.08–1.57]). Dizziness triggered by sound was associated with decreased risk of mortality (HR 0.59 [0.38–0.91]). Analysis without adjustment for cardiovascular disease and diabetes mellitus identified the same significant predictors (data not shown).

Survival According to Diagnosis

Unadjusted Kaplan-Meier plots of survival according to cause of dizziness are shown in Figure 2. Cox regression analysis adjusted for age, sex, and cause of dizziness showed increased risk of mortality among patients with cerebrovascular causes of dizziness 1.56 (1.11–2.19) compared with that in patients with BPPV (Table 3).

Survival According to Symptom Categories

Patient reports of one or more triggers of dizziness were associated with reduced risk of mortality in the unadjusted analysis (HR 0.71 [0.60–0.86]) compared with patients who did not report any triggers of dizziness. This was, however, no longer significant after adjusting for age, sex, and comorbidities (HR 0.83 [0.69–1.00]). After adding the numbers of responses by the patients in the categories of dizziness timing, dizziness type, associated symptoms, and dizziness triggers, the total number of responses was associated with reduced risk of mortality (HR 0.92 [0.89–0.95] in unadjusted analysis and 0.95 [0.92–0.99] in analyses adjusted for age, sex, and comorbidities).

DISCUSSION

The main finding in this study was that patients examined in an otorhinolaryngological clinic for suspected

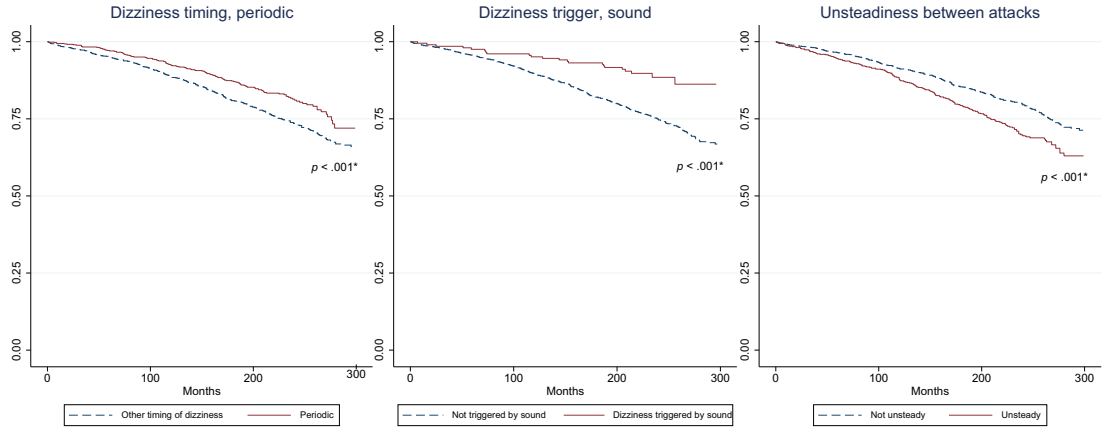

Fig. 1. Kaplan-Meier unadjusted survival estimates by patient-reported symptoms in 1,931 patients with dizziness. *P-value from log-rank test.

TABLE I.
Cox Regression Analysis with Hazard Ratios of Survival for Various Patient-Reported Symptoms and Comorbidities among 1,931 Patients with Dizziness.

			Adjusted for Age and Sex		Adjusted for Age, Sex, Diabetes Mellitus, and Cardiovascular Disease	
		Number of Patients Reporting the Condition or Symptom (%)	Hazard Ratio† (95% CI‡)	*P*-Value*	Hazard ratio† (95% CI‡)	*P*-Value*
Other diseases	Diabetes mellitus	49 (2.5%)	2.40 (1.80–3.38)	**<.001**	2.37 (1.68–3.33)	**<.001**
	Cardiovascular disease	156 (8.1%)	1.60 (1.27–2.00)	**<.001**	1.58 (1.26–1.98)	**<.001**
Dizziness timing	Short attacks	874 (45.3)	0.85 (0.71–1.02)	.081	0.87 (0.72–1.04)	.131
	Periods	706 (36.6)	0.73 (0.60–0.89)	**.002**	0.70 (0.58–0.86)	**.001**
	Constant	399 (20.7)	1.30 (1.05–1.60)	**.014**	1.26 (1.01–1.55)	**.033**
	Other, free text	7 (0.4)	2.65 (0.85–0.26)	.093	2.30 (0.73–7.20)	.154
Dizziness type	Spinning	933 (48)	0.83 (0.69–0.99)	**.038**	0.80 (0.67–0.96)	**.017**
	Rocking	596 (30.9)	1.08 (0.88–1.22)	.453	1.06 (0.86–1.30)	.577
	Other, free text	401 (20.8)	1.07 (0.86–1.33)	.529	1.03 (0.83–1.28)	.799
	Walking on pillows or floating	375 (19.4)	0.80 (0.61–1.05)	.113	0.82 (0.63–1.08)	.165
	Drop attacks/ vestibular falls	213 (11.0)	1.18 (0.89–1.56)	.240	1.15 (0.87–1.51)	.335
Accompanying symptoms	Syncope	132 (6.8)	1.05 (0.74–1.49)	.772	1.11 (0.78–1.58)	.547
	Headache	550 (28.5)	0.91 (0.74–1.12)	.053	0.90 (0.73–1.11)	.333
	Nausea	1,049 (54.3)	0.89 (0.75–1.07)	.205	0.86 (0.72–1.03)	.109
	Vomiting	507 (26.3)	0.96 (0.78–1.17)	.676	0.95 (0.78–1.16)	.633
	Visual disturbances	560 (29.0)	0.96 (0.77–1.18)	.673	0.92 (0.74–1.14)	.452
	Near-fainting	289 (15.0)	0.99 (0.76–1.28)	.921	0.91 (0.70–1.19)	.491
	Other, free text	241 (12.5)	0.84 (0.61–1.15)	.271	0.83 (0.61–1.14)	.262
	None	473 (24.5)	1.10 (0.91–1.35)	.324	1.19 (0.97–1.45)	.099
Tinnitus	During dizziness attacks	153 (7.9)	1.07 (0.77–1.50)	.670	0.97 (0.69–1.36)	.866
	Independent of dizziness attacks	543 (17.5)	0.89 (0.72–1.10)	.276	0.90 (0.73–1.11)	.329
Hearing loss	During dizziness attacks	93 (4.8)	1.14 (0.77–1.70)	.512	1.18 (0.79–1.76)	.411
	Independent of dizziness attacks	338 (17.5)	0.96 (0.77–1.20)	.715	0.96 (0.76–1.20)	.696
Dizziness triggers	Positional change	678 (35.1)	1.03 (0.85–1.24)	.789	1.00 (0.83–1.20)	.964
	Sleep deprivation	278 (14.4)	0.87 (0.61–1.24)	.440	0.86 (0.60–1.23)	.408
	Neck movements	555 (28.7)	0.93 (0.76–1.14)	.474	0.39 (0.75–1.12)	.392
	Light or darkness	138 (7.1)	0.94 (0.60–1.45)	.764	0.88 (0.57–1.38)	.579
	Sound	204 (10.6)	0.61 (0.40–0.93)	**.022**	0.61 (0.39–0.93)	**.022**
	Psychological factors	115 (6.0)	1.03 (0.67–1.57)	.909	0.93 (0.60–1.43)	.728
	Medication	35 (1.8)	1.85 (1.08–3.14)	**.024**	1.64 (0.96–2.81)	.071
	Infection/fever	66 (3.4)	1.04 (0.54–2.02)	.900	1.05 (0.54–2.05)	.878
	Other, free text	344 (17.8)	0.82 (0.63–1.08)	.162	0.84 (0.64–1.11)	.220
Unsteadiness between attacks		687 (35.6)	1.20 (1.00–1.44)	.050	1.19 (0.99–1.43)	.060

†Hazard ratio represents the ratio of risk of mortality between patients reporting a specific symptom or disease compared with patients not reporting the specific symptom or disease.
‡CI = confidence interval.
*$P < .05$ (bold text).

vestibular disorder had a long-term overall mortality rate similar to that of the general population after adjusting for age and sex. However, we observed major differences within the group, with reduced mortality among patients with short attacks or periodically fluctuating dizziness and increased mortality in patients with constant symptoms or unsteadiness between attacks.

Our main findings are consistent with those of a Swedish population-based study that observed no increased mortality in patients on sick leave or disability

TABLE II.
Cox Regression Analysis Adjusted for Age and Sex Including All Significant Variables for Survival with Hazard Ratios for Patient-Reported Symptoms among 1,931 Patients with Dizziness.

		Hazard Ratio[†] (95% CI[‡])	*P*-Value	Stepwise Analysis[§]
Other diseases	Diabetes mellitus	2.31 (1.64–3.26)	<.001	1
	Cardiovascular disease	1.66 (1.32–2.08)	<.001	2
Timing of dizziness	Periodic	0.62 (0.50–0.77)	<.001	3
	short attacks	0.76 (0.63–0.93)	.006	4
Between attacks of dizziness	Unsteady	1.30 (1.08–1.57)	.005	5
Dizziness trigger	Sound	0.59 (0.38–0.91)	.017	6

The model for survival from forward Cox regression with a significance level of $P < .05$, adjusted for age, sex, self-reported symptoms, and comorbidities.
[†]Hazard ratio represents the ratio of risk of mortality between patients reporting a specific symptom or disease compared with patients not reporting the specific symptom or disease.
[‡]CI, confidence interval.
[§]Indicating inclusion sequence in forward stepwise regression analysis, with age and sex included in the model *a priori*.

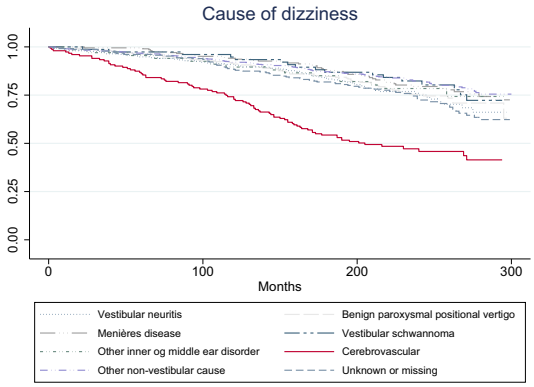

Fig. 2. Kaplan-Meier unadjusted survival estimates according to the cause of dizziness in 1,931 patients.

pensions due to vestibular disorders[17] but are not in line with those in the NHIS study in which patients with dizziness or balance problems had twofold increased mortality.[2] Other studies have reported increased risks of stroke and vascular events among emergency department patients with dizziness[18–20] and hypertensive patients with recurrent vertigo.[21] However, our present cohort comprised mainly outpatients referred to an ENT clinic due to suspected vestibular disorder. We, therefore, infer that our patients had been screened by the referring physicians for major nonvestibular causes, such as evident cardiovascular or cerebrovascular disorder, and were usually not referred in cases of severe comorbidity or an obvious nonvestibular cause of their vestibular symptoms.

The findings in the present study should not be directly generalized to patients with dizziness in acute or subacute setting. We found that patients with cerebrovascular causes of dizziness had a higher risk of mortality compared with patients with BPPV. This may not be surprising as cerebrovascular causes includes ischemic and hemorrhagic strokes known to be among the leading causes of death globally.[22] We expect that patients with cerebrovascular cause of dizziness are overrepresented in emergency departments compared with the otolaryngological outpatient clinic. In addition, the increased mortality among patients with dizziness in emergency departments is most pronounced during the

TABLE III.
Cox Regression Analysis with Hazard Ratios of Survival for Various Causes for Dizziness among 1,931 Patients, Adjusted for Age, Sex, and Cause of Dizziness.

	Number of Patients (%)	Hazard Ratio[†] (95% CI)	*P*-Value[*]
Cause of dizziness			
BPPV	235 (12)	Reference	
Vestibular neuritis	252 (12)	1.10 (0.77–1.57)	.599
Ménière's disease	204 (11)	0.89 (0.60–1.32)	.566
Vestibular schwannoma	76 (4)	0.87 (0.51–1.48)	.595
Other inner- or middle-ear disorder	67 (3)	1.29 (0.74–2.25)	.365
Cerebrovascular	151 (8)	1.56 (1.11–2.19)	**.011**
Other nonvestibular cause	715 (37)	1.05 (0.77–1.43)	.744
Unknown or missing	231 (12)	1.18 (0.83–1.68)	.352

[†]Hazard ratio represents the ratio of risk of mortality between patients with a specific diagnosis compared with patients with BPPV.
[*]$P < .05$ (bold text).
BPPV = benign paroxysmal positional vertigo; CI = confidence interval.

first few months after discharge.[18–20] The population in our study comprised mainly patients with long-lasting symptoms.

Patients who reported chronic dizziness and unsteadiness showed increased risk of mortality. These patients may be less socially and physically active due to vestibular symptoms, with further negative consequences for their health. Falls are also among the leading causes of injury and death among older US citizens.[23] Therefore, a causal influence may exist between chronic vestibular symptoms and mortality. In addition, chronic dizziness and unsteadiness are associated with numerous medical, neurologic, and cardiovascular disorders, many of which are linked to increased mortality.

Reports of dizziness attacks or periodic fluctuations were associated with better survival. This can be explained by this time course being typical for benign vestibular disorders such as BPPV, Ménière's disease, and vestibular migraine. These disorders were prevalent in our study population. However, episodic dizziness can also be associated with orthostatic hypotension, mass lesions in the posterior fossa, and transient ischemic attack.[7] These findings indicate that the more serious causes of episodic dizziness were outnumbered by benign disorders in this cohort and that the episodic disorders have better survival compared with patients reporting chronic dizziness. Therefore, a differentiation between episodic and chronic symptoms is clinically important as this may represent two groups of patients with different mortality.

Our findings strongly support the new categorization of vestibular syndromes based on the time aspect of symptoms, as suggested in the ICD-11 and the International Classification of Vestibular Disorders (ICVD).[9,24] Most population-based studies combine dizziness and unsteadiness. We recommend that future studies on vestibular symptoms and mortality distinguish unsteadiness from dizziness and vertigo.

Our analyses showed that triggered dizziness, particularly that triggered by sound, was associated with a reduced risk of mortality compared with those patients who did not report this symptom. Vertigo and dizziness triggered by sound, that is, the Tullio phenomenon,[25] are distinct symptoms in the ICVD[1] and are reportedly associated with defects in the labyrinth, such as superior semicircular dehiscence syndrome.[26] However, in our study, 10% of patients reported dizziness triggered by sound, indicating this to be a less-specific finding that should be confirmed by clinical examination and further imaging and laboratory testing, as needed. Nevertheless, patient-reported dizziness triggered by sound generally represents benign conditions. The present study supports former findings that patient-reported triggers of dizziness should be confirmed by clinical testing.[15]

Although spinning vertigo was associated with reduced risk of mortality after adjusting for age, sex, and comorbidities, it failed to reach significance in the final model (stepwise inclusion) when other symptom characteristics, including timing, were included. Van Vugt and colleagues found vertigo to be associated with a more favorable outcome than other types of dizziness among elderly patients in primary care,[5] whereas Newman-Toker and colleagues found that the type of dizziness was inconsistently reported by patients in an emergency department.[6] Our findings indicated that the time course of symptoms such as short attacks or episodic dizziness was more relevant to survival than the quality of symptoms, such as spinning vertigo.

The main strength of this study was the very long follow-up of a large cohort with well-documented vestibular diagnoses and patient-reported baseline data. The results are especially relevant to clinics receiving referrals due to chronic or episodic vestibular disorders, and this study provides valuable clinical indicators of more serious underlying disorders. We found that patients in this cohort did not have a higher mortality rate than the general population, but patients with episodic symptoms had better survival compared with the other patients in the cohort. A limitation of the study is that we did not have data on cause of death or on falls. Such information could have provided additional information on what causes the increased mortality among certain groups and may determine if chronic dizziness were associated with falls or if the increased mortality were associated with other disorders such as cardiovascular disease. In addition, several commonly assigned diagnoses were not included in the analyses as these were not defined by diagnostic criteria when the study was designed, including vestibular migraine and persistent postural-perceptual dizziness.

CONCLUSION

In this long-term follow-up of patients with vestibular symptoms evaluated in an otolaryngology clinic, overall mortality was comparable with that in the general population. However, periodic or short attacks of dizziness were associated with better survival, whereas chronic dizziness and unsteadiness between attacks were associated with increased mortality. These results underscore the importance of classifying patients based on the timing of symptoms. Patients reporting chronic symptoms should be examined for specific risk factors and fall risk.

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The Romberg sign, unilateral vestibulopathy, cerebrovascular risk factors, and long-term mortality in dizzy patients

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Objectives: Describe the relationship between unsteadiness, canal paresis, cerebrovascular risk factors, and long-term mortality in patients examined for dizziness of suspected vestibular origin.

Study design: Observational cohort with prospective collection of survival data.

Setting: University clinic neurotological unit.

Patients: Consecutive patients aged 18–75 years examined in the period 1992–2004 for dizziness of suspected vestibular origin.

Outcome measures: Overall survival. Standardized mortality ratio (SMR). Factors: Unsteadiness, canal paresis, age, sex, patient-reported diabetes, hypertension, heart disease, stroke, or TIA/minor stroke. Patients were classified as steady or unsteady based on static posturography at baseline compared to normative values.

Results: The study included 1,561 patients with mean age 48 years and 60 % females. Mean follow-up was 22 years. Unsteadiness was associated with higher age, heart disease, diabetes, hypertension, and cerebrovascular dizziness. There were 336 deaths over 31,335 person-years (SMR 0.96; 95 % confidence interval: 0.86–1.07). Canal paresis was not related to unsteadiness (chi square: $p = 0.46$) or to mortality (unadjusted Cox hazard ratio: 1.04, 95% CI: 0.80–1.34). Unsteadiness was an independent predictor of mortality (adjusted Cox hazard ratio: 1.44, 95% CI: 1.14–1.82).

Conclusions: Unsteadiness measured by static posturography is associated with higher age, known cerebrovascular risk factors, and with increased long-term mortality, but not with canal paresis in patients evaluated for dizziness. The study highlights the importance of evaluating patients with conspicuous postural instability for non-vestibular causes.

KEYWORDS

survival, posturography, dizziness, vertigo, vestibular disorders, caloric response, balance

Introduction

The Romberg sign (Moritz Romberg 1795–1873) is present when a patient tends to sway or fall while standing with feet together and eyes closed. It was first described in the 19th century as a useful indicator of proprioceptive loss due to neurosyphilis (tabes dorsalis) (1). Romberg himself was probably unaware that a similar disruption of balance may be caused by vestibular loss (2). This ambiguity complicates the interpretation of the Romberg sign in clinical practice.

In patients with acute vestibular symptoms, commonly seen in emergency departments, oculomotor signs denoted by the acronym "HINTS" are more suitable than the Romberg test to single out patients with a central lesion–for example due to a posterior circulation stroke–as opposed to more common benign peripheral vestibular disorders (3). Marked postural sway may be present in both central and peripheral lesions. However, in patients with severe truncal ataxia who are unable to sit or stand without support, a central lesion is usually suspected (4).

In patients with episodic or chronic vestibular symptoms, commonly seen in outpatient clinics, the spectrum of possible causes is even wider, and even advanced posturographic systems, have been found to have limited diagnostic value (5). If the simple Romberg test is to be used at all in this setting, the clinician would be right to ask whether marked postural instability with eyes closed should be interpreted as a sign of a peripheral vestibular problem, or rather of a proprioceptive or central nervous disease and whether this finding has implications for the prognosis of the patient, for example with respect to long-term survival.

Patients suffering from dizziness or vertigo are often found to have benign disorders of the peripheral vestibular system (6), and severe underlying conditions have, to some extent, been ruled out by referring physicians (7). Nevertheless, a considerable proportion suffers from disorders of unclear or complex etiology, and some may have more serious underlying disorders including cerebrovascular disease. Dizziness and unsteadiness are sometimes indicators of serious disease. In a large population-based study, Corrales et al. (8) found a near doubling of mortality (OR 1.7, 95% CI 1.4–2.2) in adult Americans reporting dizziness or balance problems after adjusting for age, sex, education, ethnicity, race, diabetes, cardiovascular or cerebrovascular disease, and cancer. This study did not differentiate between dizziness and unsteadiness. Other studies have shown that postural instability, quantified by different clinical scoring systems, is associated with increased mortality in elderly (9) and middle-aged persons (10).

In a previous study, we found that standardized mortality ratio in patients examined for dizziness of suspected vestibular origin was the same as in the general population (11). This implies that vestibular symptoms *per se* are not necessarily a sign of serious underlying disease. On the contrary, such symptoms are often caused by benign vestibular disorders, the most common being benign paroxysmal positional vertigo, vestibular migraine, and persistent postural-perceptual dizziness. However, increased mortality was found in a subgroup of patients reporting unsteadiness between dizziness attacks. This suggests that it is of importance to differentiate the symptoms of dizziness/vertigo from that of unsteadiness.

The purpose of this study was to examine the value of an objective measure of standing balance, a version of the Romberg test–static posturography with eyes closed–with respect to its ability to discriminate patients with unilateral vestibulopathy–as measured by the caloric test–from patients with more serious underlying disorders–as measured by comorbidity and long-term mortality.

Materials and methods

Patients and setting

This is a study of survival data gathered prospectively from a cohort of consecutive patients aged 18–75 years examined between 1992 and 2004 in a neurotological laboratory at the Department of Otorhinolaryngology and Head and Neck Surgery at Haukeland University Hospital in Bergen. The subjects were mostly outpatients referred for suspected vestibular disorder. For patients seen more than once during the study period, only data from the first examination was included in the study.

Ethics

The study was approved by the Regional Committee for Medical and Health Research Ethics of Western Norway (2012/1075/REK vest).

Survival data

Survival data were obtained from the Norwegian National Population Register and updated as per 31 January 2021. Standardized mortality ratios (SMR) were calculated based on life tables by sex and age published by Statistics Norway (12).

Static posturography

All patients underwent static posturography as described previously (13). Briefly, the patient was asked to stand quietly on a static force platform (Cosmogamma®, AC International, Cento, Italy) for 60 s with eyes open and then for 60 s with eyes closed. The visual surroundings were kept constant and the room quiet. The platform contained three strain gauge transducers connected to a computer that calculated the

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TABLE 1 Descriptive data of participants ($n = 1,561$).

Parameter	Values
Age (years); *mean, SD*	48.4, 14.0
18–39 years; *n*	444
40–49 years; *n*	369
50–59 years; *n*	391
60–75 years; *n*	357
Female; *n, %*	934, 59.8
Posturography	
Unsteady patients; *n, %*	357, 22.9
Path length (mm)*; *quartiles (25%, 50%, 75%)*	521, 724, 1,069
Caloric test; *n*	1,326
Canal paresis; *n, %*	378, 28.5
Patient-reported comorbidities	
Diabetes; *n, %*	30, 1.9
Hypertension; *n, %*	213, 13.6
Heart disease; *n, %*	84, 5.4
Stroke or TIA; *n, %*	26, 1.7
10-year survival (percent)	
Observed, lower CI, upper CI	93.9, 92.7, 95.0

TIA, transitory ischemic attack; n, count; SD, standard deviation; mm, millimeters; CI, 95 % confidence interval.
*Arithmetic mean of path length with eyes open and eyes closed.

TABLE 2 Clinical diagnoses in 1,561 patients examined in a university clinic for suspected vestibular disorder.

Diagnosis	Count	Percent
Peripheral vestibular		
Benign paroxysmal positional vertigo	209	13.4 %
Vestibular neuritis	184	11.8 %
Labyrinthitis	26	1.7 %
Menière's disease	175	11.2 %
Vestibular schwannoma	63	4.0 %
Other ear and hearing disorders		
Otosclerosis	8	0.5 %
Sudden deafness	8	0.5 %
Chronic otitis media	1	0.1 %
Other middle ear disease	11	0.7 %
Hearing loss NOS	15	1.0 %
Trauma		
Perilymphatic fistula	7	0.4 %
Skull fracture	13	0.8 %
Head injury without fracture	24	1.5 %
Whiplash	11	0.7 %
Decompression sickness	6	0.4 %
Barotrauma	4	0.3 %
Neurological disorders		
Cerebrovascular	106	6.8 %
Central vestibular NOS*	148	9.5 %
Multiple sclerosis	6	0.4 %
Borreliosis	1	0.1 %
Epilepsy	3	0.2 %
Other		
Drug induced	4	0.3 %
ME	1	0.1 %
Postinfectious	29	1.9 %
Cervicogenic	136	8.7 %
Congenital	2	0.1 %
Psychogenic	15	1.0 %
Non-otogenic NOS	274	17.6 %

NOS, not otherwise specified; ME, myalgic encephalopathy; CNS, central nervous system.
*Including vestibular migraine.

center of pressure (COP) exerted by the patient's feet on the platform while maintaining balance. The length of the curve in millimeters (path length) described by the COP during each examination was used as the main parameter indicating postural instability. The path length may vary from zero–the theoretical result of an immovable object being placed on the platform–to several thousands, indicating severe postural instability. Normative values were taken from a previous study (13). Path lengths >895 millimeters with eyes open or 1,665 millimeters with eyes closed were considered abnormal.

Caloric testing

All patients underwent bithermal (44 and 30 degrees centigrade) caloric testing after static posturography, and caloric asymmetry was calculated according to Jongkees' formula. Caloric asymmetry >25 % was considered abnormal and defined as a canal paresis.

Clinical data and covariates

The clinical diagnoses were reviewed retrospectively by two of the co-authors (FG, SHGN). Patients were divided into four age groups (18–39, 40–49, 50–59, and 60–75 years). Cardio-vascular comorbidities were evaluated clinically based on information given by the patient and examining physicians. Included covariates were canal paresis, patient-reported hypertension, diabetes, history of stroke, TIA/minor stroke (TIA, transitory ischemic attack), or heart disease. In addition, some of the patients received a diagnosis of dizziness of suspected cerebrovascular origin. This was a clinical diagnosis made by an otorhinolaryngologist and not based on explicit criteria or imaging. It was rarely indicative of an acute stroke since most patients were seen in an elective, outpatient setting. However, since dizziness of cerebrovascular origin may

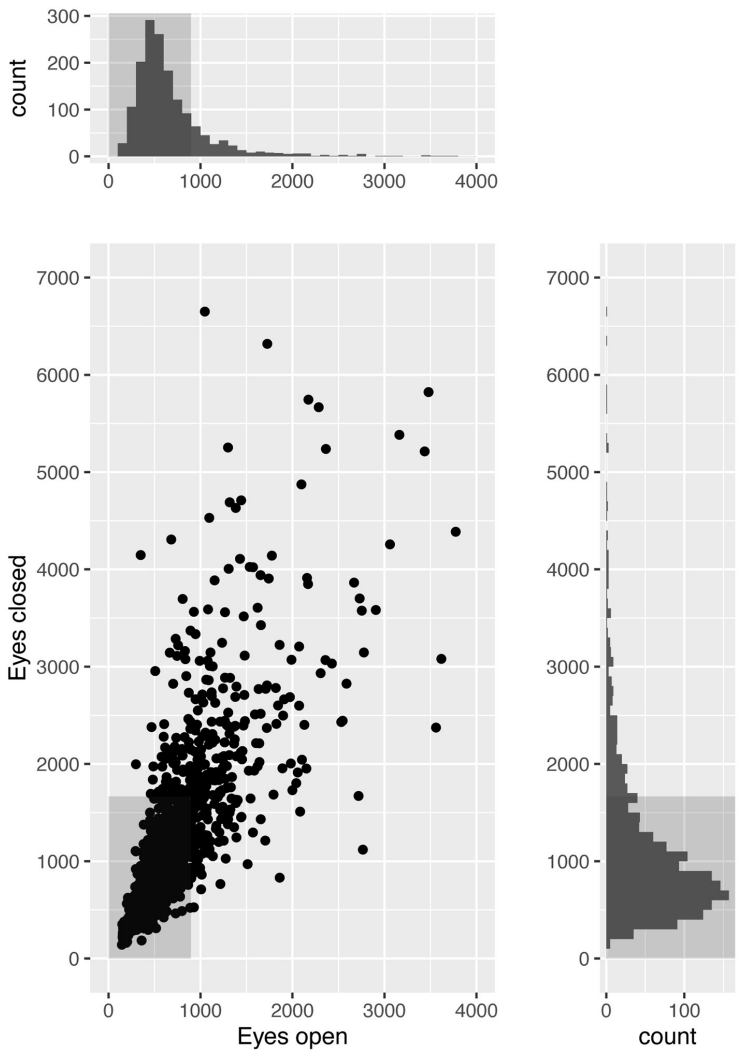

FIGURE 1
Static posturography results in 1,561 patients examined for dizziness of suspected vestibular origin. Scatterplot with marginal histograms showing postural sway while standing quietly on a static force platform for 60 s with eyes open and closed. Plotted values are the length in millimeters of the path described by the center of pressure under the patient's feet. Gray boxes indicate normal limits.

influence survival, this diagnosis was included among the risk factors in the study.

Statistical analysis

For statistical analysis and data interpretation, two variables of postural sway were used. First, a continuous variable was made by averaging path length with eyes open and eyes closed. This variable was then stratified by quartiles to four levels indicating low, low-median, median-high, or high postural instability. Second, a dichotomized variable was created using previously published normative data (13). If the path length was outside normal limits either with eyes open or closed, the patient was characterized as "unsteady." Otherwise, the patient was considered "steady."

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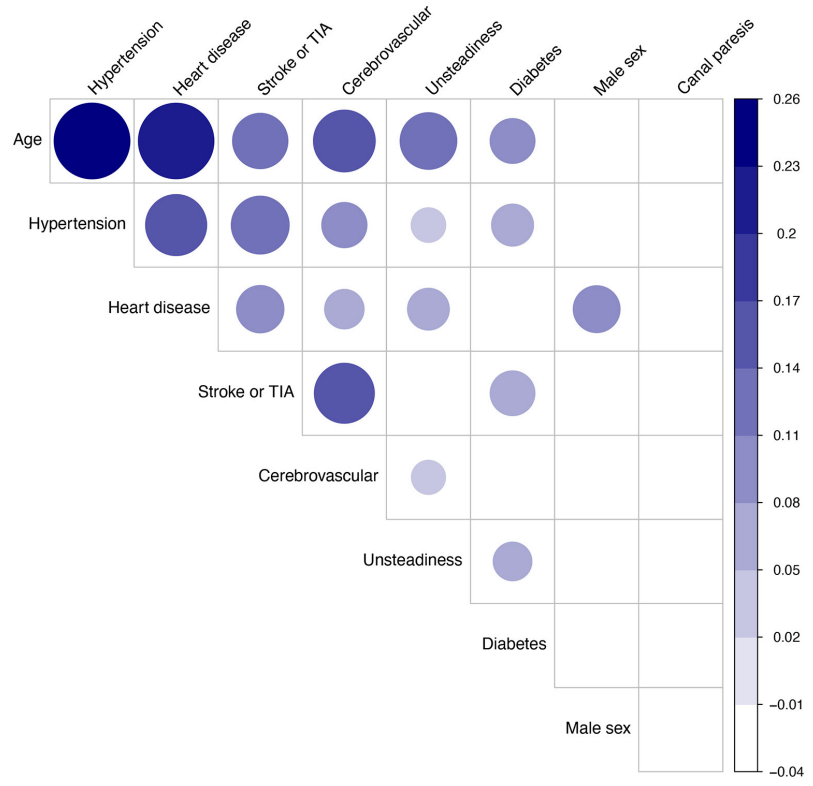

FIGURE 2
Correlation matrix analysis of nine candidate factors, prior to survival analysis, in 1,561 patients examined for dizziness of suspected vestibular origin. Dots indicate significant correlations ($p < 0.05$). Dot size and darkness indicate strength of correlation (Pearson's R). Factor ordering: first principal component order.

Cox proportional hazards regressions models were used to calculate crude and adjusted hazard ratios for survival predicted by age, sex, postural instability, diabetes, hypertension, heart disease, stroke, TIA/minor stroke, and dizziness of cerebrovascular origin. Adjusted hazard ratios were reported after backward stepwise elimination of non-significant factors. Follow-up time was defined as the time interval between the first examination and the last update of survival data (31 January 2021).

Statistical analysis was performed using R 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria), the Epi (14) and popEpi packages (15). Two-sided p-values < 0.05 were considered significant.

Results

Out of 1,796 patients with complete data on posturography and clinical covariates, 84 patients were excluded due to missing consent or unknown vital status, and further 151 due to being outside the age-range 18–75 years at baseline. Descriptive data for the remaining 1,561 participants are presented in Table 1 with clinical diagnoses in Table 2. Results from the caloric test were available for 1,326 patients of which 28.5% had a canal paresis. Dizziness of suspected cerebrovascular origin was noted in 106 (6.8%) of the patients. Posturography results are shown in Figure 1 and the correlation matrix between risk factors is shown in Figure 2.

Follow-up time ranged from 17 to 29 years (mean 22, SD 2.9 years). The observed number of deaths in the study population was 336 over a total of 31,335 person-years, which did not differ significantly from the expected number of 350 deaths in the Norwegian general population matched for age, sex, and calendar years (standardized mortality ratio: 0.96, 95 % confidence interval: 0.86–1.07).

Results of the Cox regression analysis are shown in Table 3. Unsteadiness on static posturography was a significant predictor of mortality independent on age, sex, self-reported

TABLE 3 Cox regression analysis of long-term survival in 1,561 patients examined for dizziness of suspected vestibular origin.

	Univariate 95% CI				Adjusted 95% CI			
Factor	HR	lower	upper	*p*	HR	lower	upper	*p*
Age								
18–39 yr	reference				reference			
40–49 yr	5.878	2.605	13.26	<0.0001	5.685	2.519	12.828	<0.0001
50–59 yr	12.548	5.769	27.29	<0.0001	11.416	5.244	24.854	<0.0001
60–75 yr	65.342	30.765	138.78	<0.0001	59.857	28.141	127.322	<0.0001
Sex								
Male	1.384	1.117	1.714	0.00298	1.379	1.111	1.711	0.00350
Self-reported comorbidity								
Diabetes	4.162	2.618	6.618	<0.0001	2.089	1.307	3.340	0.00207
Hypertension	2.630	2.059	3.358	<0.0001				
Heart disease	4.339	3.210	5.865	<0.0001				
Stroke or TIA/minor stroke	4.615	2.869	7.424	<0.0001	2.034	1.256	3.295	0.00392
Clinical diagnosis								
Dizziness of cerebrovascular origin	2.179	1.566	3.032	<0.0001				
Static posturography								
Unsteady*	1.831	1.453	2.306	<0.0001	1.438	1.138	1.815	0.00229

Univariate and adjusted hazard ratios after backward stepwise elimination of non-significant factors.
CI, confidence interval; HR, hazard ratio.
*Path length outside normative values with eyes open or closed.

comorbidities, and clinical diagnosis of dizziness of suspected cerebrovascular origin with an adjusted hazard ratio of 1.438 (95% CI: 1.138–1.815). Self-reported diabetes and stroke or TIA/minor stroke were also significant predictors in the adjusted analysis.

Kaplan-Meier analysis of survival related to four increasing levels of postural instability is shown in Figure 3. The two groups with median-high or high postural sway had decreased survival compared to the group with low postural sway (Cox regression, $p < 0.005$).

The presence of a canal paresis (caloric asymmetry >25 %) was not associated with postural instability (chi square: $p = 0.44$), nor with mortality (HR 1.036, 95% CI: 0.8002–1.34).

Discussion

In this cohort of patients examined for dizziness of suspected vestibular origin, postural instability was not associated with unilateral vestibulopathy, but rather with increasing age, cerebrovascular risk factors and increased long-term mortality. Unsurprisingly, a canal paresis was not associated with mortality. To the best of our knowledge, this is the first study to show the relationship between an objective measure of postural sway and long-term survival in dizzy patients. Combined with the patient-reported comorbidities, a relatively simple measure of postural instability may provide prognostic information in patients undergoing evaluation for dizziness. This finding underscores the importance of evaluating unsteadiness, and of differentiating this from dizziness and vertigo, in patients with vestibular symptoms.

Cerebrovascular risk factors contributed significantly to mortality, which was expected since stroke is one of the leading causes of death in Europe (16). In the acute setting, dizziness and vertigo are sometimes caused by a posterior circulation stroke (17), and even when this has been excluded, a study has indicated increased risk of a cerebrovascular event after hospital discharge (18). Moreover, a recent study provides evidence that transient isolated vertigo or dizziness may sometimes be symptoms of TIA (19). However, the present study was performed in an elective setting, and patients with suspected cerebrovascular cause of their symptoms had presumably been screened out, to some extent, by referring physicians. The diagnosis of dizziness of suspected cerebrovascular origin did not contribute to the prognosis after adjustment for patient-reported comorbidities. The reason for this may be that the major risk factors of stroke–i.e., age and patient-reported diabetes, hypertension, atrial fibrillation, and previous stroke or TIA/minor stroke–were accounted for in the adjusted analysis. Hence, the clinical diagnosis of cerebrovascular dizziness without additional objective information, such as biochemical markers, MRI or Doppler imaging findings, did not provide additional prognostic value. It is nevertheless interesting that

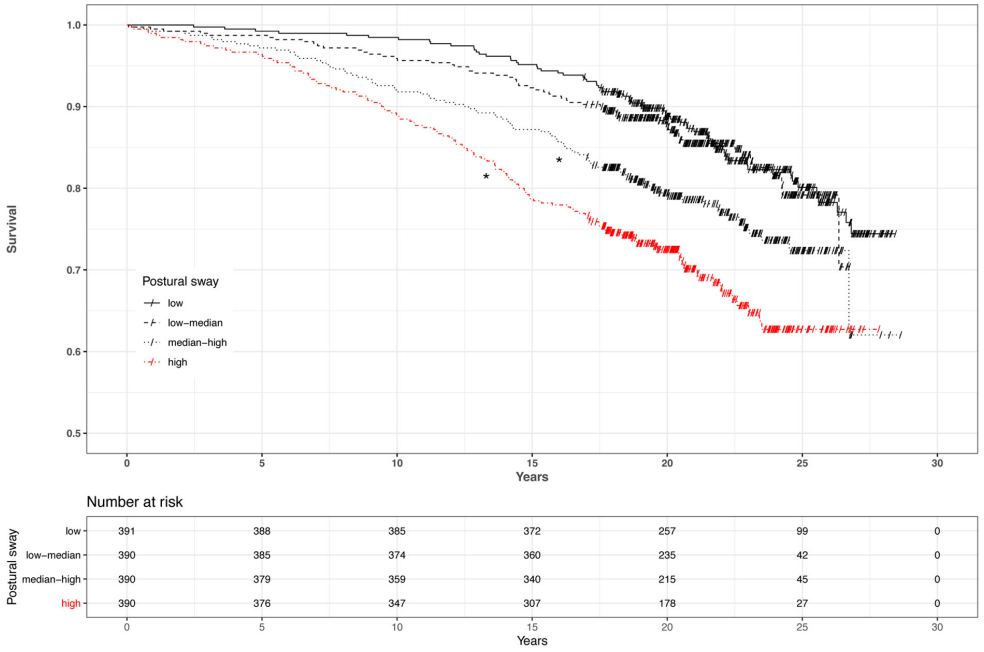

FIGURE 3
Kaplan-Meier survival in 1,561 dizzy patients and postural instability stratified by quartiles. Postural sway measured while standing quietly on a force platform for 60 s with eyes open and closed. Movement of the center of pressure was measured in millimeters, and results with eyes open and closed were averaged. Censoring events are marked with a slash (/). *Significant (Cox regression, $p < 0.005$).

posturography remained a significant predictor even after correction for these factors.

Previous studies have documented mortality in patients suffering from vestibular symptoms (8, 9, 20). In a large population-based study, Corrales et al. (8) found a near doubling of mortality (OR 1.7, 95% CI 1.4–2.2) in adult Americans reporting dizziness or balance problems after adjusting for age, sex, education, ethnicity, race, diabetes, cardiovascular or cerebrovascular disease, and cancer. In our study of dizzy patients, the standardized mortality rate was the same as in the general population. This may be explained by patient selection and screening by referring physicians, since the main purpose of the examination was to uncover vestibular disorders. The benign nature of these disorders is supported by our finding that caloric asymmetry was not associated with increased mortality. Van Vugt et al. (20) found a 40.5% 10-year mortality in a group of elderly patients with dizziness in primary care. This was not compared to standardized mortality rates. Moreover, the patients had a mean age of 79 years at inclusion, which is considerably higher than in our study. The finding by van Vugt et al. (20) that patients with vertigo had lower mortality than those with dizziness of other types is interesting, and agrees with a previous study from our group (7). In the latter study, patient-reported unsteadiness between dizziness episodes was associated with higher mortality.

Other studies have found that gait and balance problems can be used to predict mortality. Blain et al. (21) studied a population of community-dwelling women aged ≥75 years and found that 8-year survival was related to balance and walking speed after adjusting for a wide range of covariates. Cooper et al. (10) found that all-cause mortality in a group of 2,766 53-year-olds was related to measures of physical capability, specifically grip strength, chair rise speed and standing balance time. The authors found some evidence that the timed one-leg stance test with eyes closed was the factor most strongly associated with survival. A linear relationship between this test and path length from posturography has been reported in a previous study (22) indicating a partial overlap between these two methods.

A similar-sized study from Finland reported no association between posturographic unsteadiness and long-term mortality in a population-based cohort of 1,568 women (23). A positive association was found in the crude analysis between mortality

and anteroposterior, mediolateral and total maximum amplitude of the COP. However, the association was lost after adjustment for age, parents' hip fracture, smoking and leg-extension strength. The study also found postural sway to be associated with osteoporotic fractures. Possible explanations for the difference in outcomes may include different sway parameters (maximum sway amplitude vs. total path length), test conditions (eyes open vs. average between eyes open and closed) and patient selection (population sample of women vs. dizzy patients of both sexes). However, since the crude analysis revealed similar results in the two studies, the difference may also be explained by the difference in covariates. The authors of the Finnish study suggested that the association between postural sway and mortality is indirect, and that "sway is more of an indicator for general health status." This is in line with our study, finding sway to be mostly correlated with age and other cerebrovascular risk factors.

The lack of association between postural sway and caloric asymmetry is not surprising (11). Most of the patients were seen in an elective setting due to chronic or episodic symptoms. While a vestibular lesion leading to canal paresis typically causes marked unsteadiness in the acute phase, the symptoms tend to improve due to central vestibular compensation. Thus, a disease leading to asymmetric caloric function, for example a sequela to vestibular neuritis or vestibular schwannoma, may sometimes lead to less postural unsteadiness than an episodic disorder with symmetric caloric response, like BPPV or Menière's disease, or a chronic neurological or orthopedic problem.

Apart from underlying cardio- and cerebrovascular disorders, possible causal relationships between unsteadiness and mortality could involve general frailty and risk of falling. In a study of relatively active home-dwelling elderly persons with mean age 70 years, Tuunainen et al. (24) concluded that vertigo and poor postural stability constituted the major reasons for falling. Falls are a major cause of morbidity in the elderly population (25, 26), and even though vertigo of peripheral vestibular origin may not be associated with increased all-cause mortality–as our study indicates–falls rank among the leading causes of death (26). Part of the excess mortality in patients with postural instability might therefore be explained by falls.

Strengths of the present study include the objective measuring of postural balance and caloric asymmetry, the long follow-up (mean 22 years) and wide age range (18–75 years) in a large population of dizzy patients examined for suspected vestibular disorder. The long follow-up and inclusion of relatively young patients compared to previous studies, means that the study has potential for early detection and preventive measures related to long-term survival. The risk of attrition bias was considered by the authors and found to be low since <5 % of the cohort was lost to follow-up due to missing consent or unknown vital status at follow-up. The addition of standardized mortality ratios gives valuable information about the study sample in comparison to the general population.

Limitations include the fact that the patients were seen in a specialized clinic in an elective outpatient setting. The results are not necessarily applicable to patients seen for acute vestibular syndrome. Other studies indicate that people suffering from dizziness in the general population has a higher overall mortality (8). However, this does not invalidate the association between mortality and postural instability found in the present study, which agrees with other studies of less selected populations (10, 21). Since the causes of death were unknown, the direct causal link between postural instability and mortality cannot be ascertained. Future studies on disease specific mortality in patients with postural instability are needed. Until further research is available, dizzy patients with conspicuous unsteadiness should be evaluated for cerebrovascular risk factors. Preventive measures should focus on minimizing the risk of stroke and falls.

In conclusion, this study found that the Romberg sign in patients undergoing elective evaluation for vestibular symptoms was related to age and cerebrovascular risk factors including hypertension and diabetes as well as being an early predictor of mortality. It was not related to unilateral vestibulopathy as measured by the caloric test. This finding underscores the importance of differentiating objective unsteadiness from the subjective feeling of vertigo or dizziness. Patients with conspicuous unsteadiness with eyes closed require diagnostic evaluation for non-vestibular etiology and fall-risk.

Data availability statement

The original datasets presented in this article are not readily available due to Norwegian data protection legislation. Requests to access aggregated data should be directed to Frederik Kragerud Goplen (frederik.kragerud.goplen@helse-bergen.no).

Ethics statement

The study was approved in advance by the Regional Committee for Medical and Health Research Ethics of Western Norway (2012/1075/REK vest). Active consent was not required according to Norwegian legislation. Living participants were informed in writing about the study and given the opportunity to withdraw by phone, e-mail or by returning a prepaid envelope.

Author contributions

JB, FG, and TS: data collection. JB and FG: data analysis and drafting the manuscript. All authors contributed in concept

and design of the study, revision of the article for important intellectual content, and approval of the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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