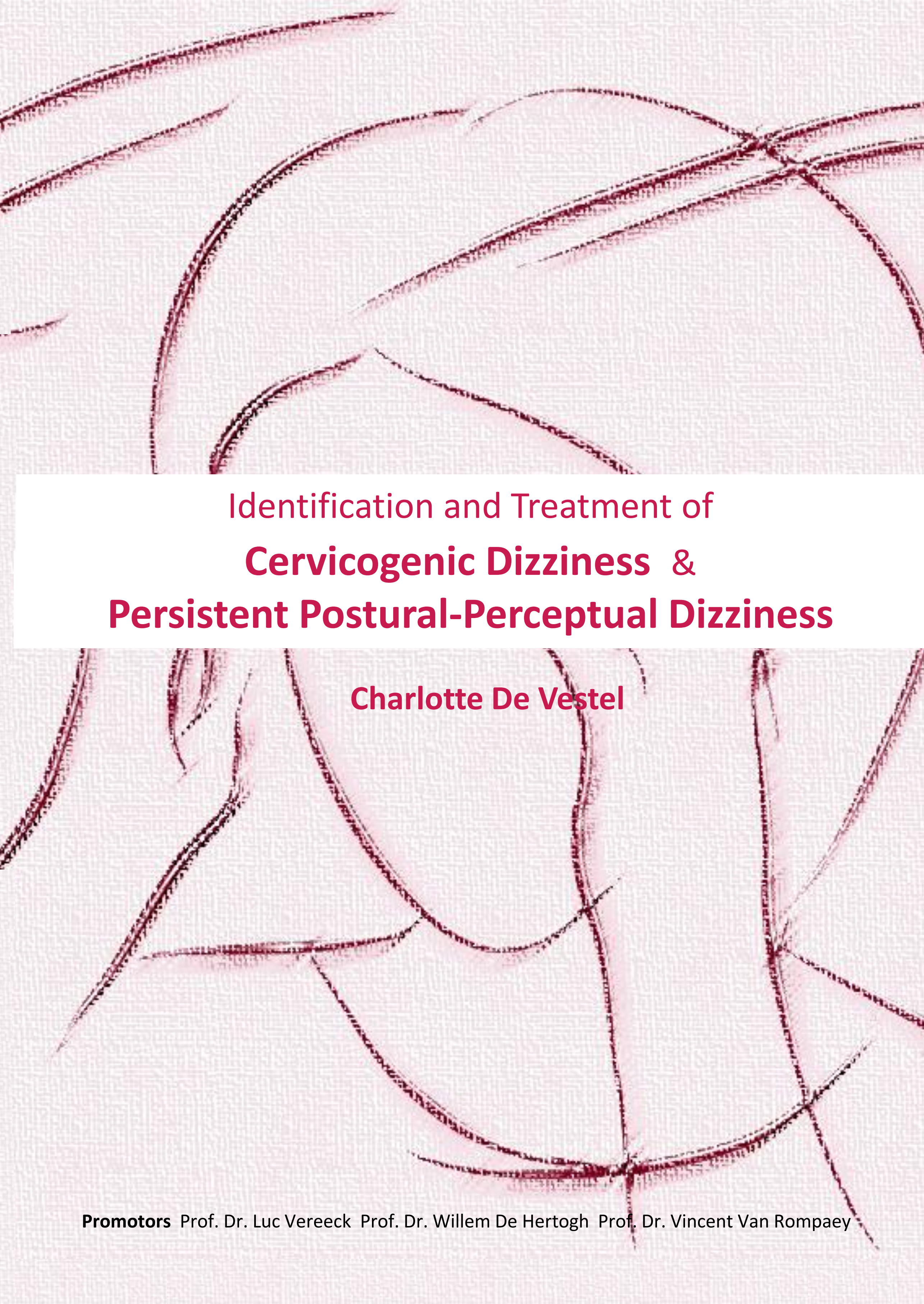


Identification and Treatment of **Cervicogenic Dizziness** & **Persistent Postural-Perceptual Dizziness**

Charlotte De Vestel

Promotors Prof. Dr. Luc Vereeck Prof. Dr. Willem De Hertogh Prof. Dr. Vincent Van Rompaey

Identification and Treatment of Cervicogenic Dizziness & Persistent Postural-Perceptual Dizziness

Identificatie en Behandeling van Cervicogene Duizeligheid &
Persisterende Positionele-Perceptie Duizeligheid

Charlotte De Vestel

Disclaimer

Cover: edited image from Shutterstock
Printed by: ALL Printing Services

University of Antwerp
Faculty of Medicine and Health Sciences
Department of Rehabilitation Sciences and Physiotherapy

Identification and Treatment of Cervicogenic Dizziness & Persistent Postural-Perceptual Dizziness

Identificatie en Behandeling van Cervicogene Duizeligheid &
Persisterende Positionele-Perceptie Duizeligheid

Charlotte De Vestel

Promotors: Prof. Dr. Luc Vereeck, Prof. Dr. Willem De Hertogh, Prof. Dr. Vincent Van Rompaey
Thesis submitted for the degree of Doctor of Medical Sciences at the University of Antwerp

Examining committee

Prof. Dr. Ann Hallemans – President of the jury
Department of Rehabilitation Sciences and Physiotherapy/Movant - *University of Antwerp*
Multidisciplinary Motor Centre Antwerp (M^2OCEAN) - *Antwerp University Hospital*

Prof. Dr. Luc Vereeck – Promotor
Department of Rehabilitation Sciences and Physiotherapy/Movant - *University of Antwerp*
Multidisciplinary Motor Centre Antwerp (M^2OCEAN) - *Antwerp University Hospital*

Prof. Dr. Willem De Hertogh – Promotor
Department of Rehabilitation Sciences and Physiotherapy/Movant - *University of Antwerp*
Multidisciplinary Motor Centre Antwerp (M^2OCEAN) - *Antwerp University Hospital*

Prof. Dr. Vincent Van Rompaey – Promotor
Department of Translational Neurosciences - *University of Antwerp*
Department of Otorhinolaryngology and Head & Neck surgery - *Antwerp University Hospital*

Prof. Dr. Tim van Den Wyngaert – Member of the jury
Departement of Molecular, Morphology and Microscopy - *University of Antwerp*
Department of Nuclear Medicine - *Antwerp University Hospital*
Integrated Personalized and Precision Oncology Network (IPPON) - *University of Antwerp*

Prof. Dr. Otto Maarsingh – Member of the jury
Department of General Practice – *Amsterdam University Medical Center*

Prof. Dr. Joke Spildooren – Member of the jury
Department of Rehabilitation Sciences and Physiotherapy - *University of Hasselt*

Contents

List of figures

List of tables

Abbreviations

CGD	Cervicogenic Dizziness
CNS	Central Nervous System
COP	Center Of Pressure
CROM	Cervical Range Of Motion
CTT	Cervical neck Torsion Test
DHI	Dizziness Handicap Inventory
FGA	Functional Gait Assessment
HADS	Hospital Anxiety and Depression Scale
HRA	Head repositioning Accuracy test
JPE	Joint Position Error
NBQ	Neck Bournemouth Questionnaire
PPPD	Persistent Postural-Perceptual Dizziness
RDT	Rod-and-Disc Test
RFT	Rod-and-Frame Test
SPNT	Smooth Pursuit Neck Torsion test
TUG	Timed-Up and Go test
VAAI	Vestibular Activities Avoidance Instrument
VRBQ	Vestibular Rehabilitation Benefits Questionnaire
VRT	Vestibular Rehabilitation Therapy
VSS-SF	Vertigo Symptom Scale – Short Form
VVAS	Visual Vertigo Analogue Scale
WAD	Whiplash-associated disorder
WEBAVER	WEb-BAsed VEstibular Rehabilitation

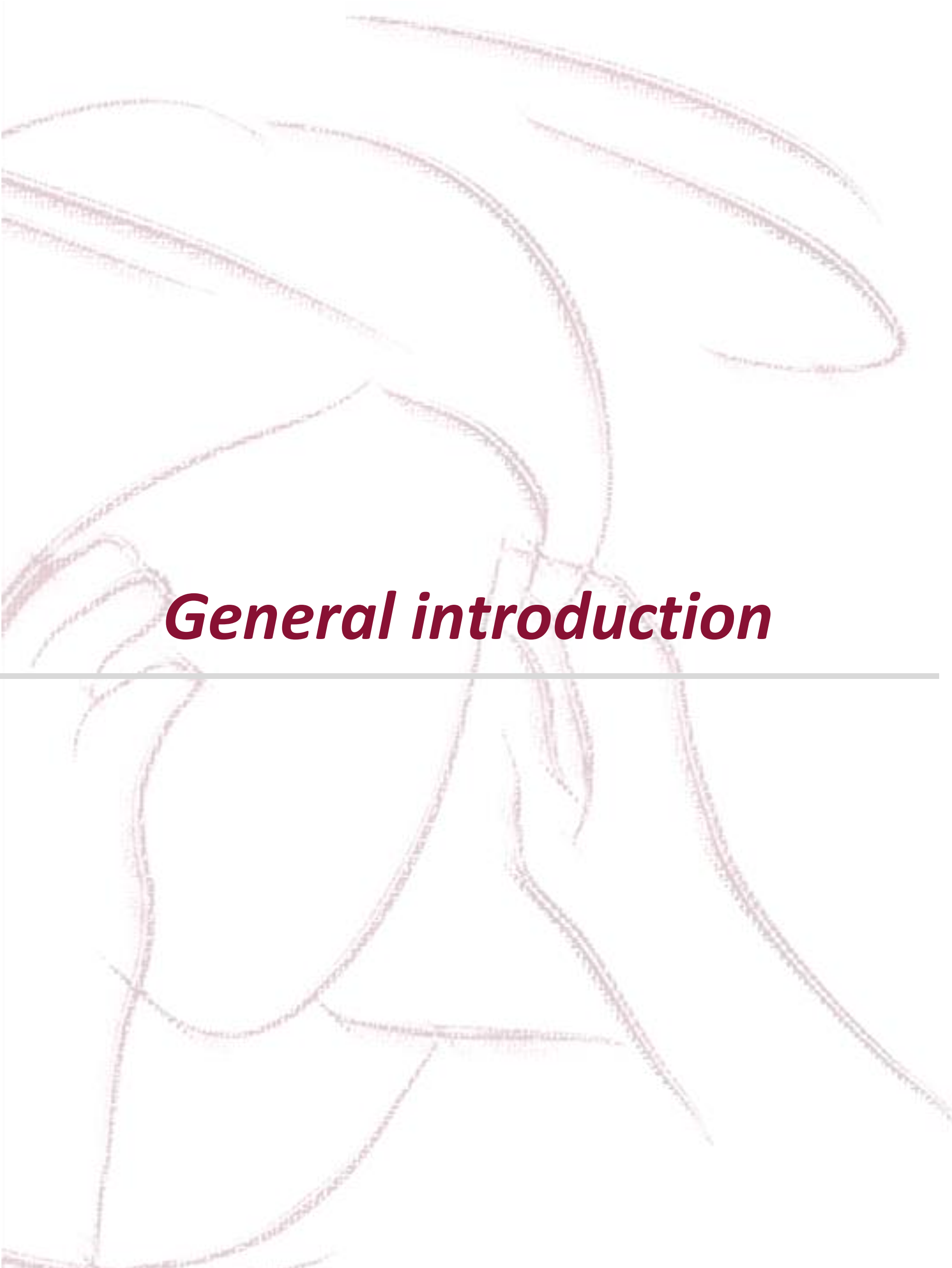
Preface

Our body is an ingenious construction, which enables us to perform complex functions in an often subconscious way. Part of these complex functions is provided by the "balance system", which - through the central integration and processing of information from the eyes, the vestibular organs and the proprioceptors – allows us to navigate in space, focus our gaze and maintain our balance.

Disturbances in the balance system can cause dizziness, along with various other concomitant symptoms such as nausea and postural instability. It is not hard to imagine that dizziness can have a major impact on an individual's functioning, especially when it persists over a long period of time.

As there are many causes of dizziness, this doctoral thesis concentrates on two specific forms: cervicogenic dizziness (CGD) and persistent postural-perceptual dizziness (PPPD). Our goal is to provide clinicians with tools to recognise these two forms in patients with chronic dizziness on the one hand, and to treat them effectively on the other.

We hope that this doctoral thesis will broaden your interest in and understanding of the balance system and its possible pathological processes, and give you concrete tools to work with in clinical practice for patients with CGD and PPPD.



General introduction

In this first section, a general introduction to the research topic is given. Chronic dizziness, and two of its sub-forms cervicogenic dizziness (CGD) and persistent postural-perceptual dizziness (PPPD) are described through their definition, prevalence, pathophysiology, diagnosis, and relevance to research. Finally, the outline of the doctoral thesis and our main research questions are presented.

1. Chronic dizziness

1.1. Definition

Chronic dizziness is defined by the International Classification of Vestibular Diseases (ICVD) as "*the sensation of disturbed or impaired spatial orientation without a false or distorted sense of motion*" [1]. How patients experience chronic dizziness varies from person to person. They may feel lightheaded, giddy, or unsteady [2]. The dizziness may be spontaneous or triggered (e.g., visual stimuli or head movements) [3, 4]. Lastly, chronic dizziness is often accompanied by additional symptoms [e.g., postural instability, involuntary rhythmic eye movements ('nystagmus'), nausea] [5]. For this reason, the term "dizziness syndrome" is sometimes used.

The dizziness is frequent, i.e., almost daily, with fluctuations in intensity, such as good and bad days [2], or less in the morning than in the evening [6]. A recent study suggests that the symptoms must be present for at least 15 days per month [7]. There is no strict cut-off point as to how long the dizziness symptoms must have been present. The most common criterion is at least three months [3, 4, 8], but other studies work with, for example, a minimum of six months [9].

1.2. Prevalence

The prevalence of dizziness in the general population may be as high as 40% [10-12]. The prevalence is higher in women and older age [12]. Little information is available about the proportion of patients whose symptoms persist chronically. It is thought to be only a minority (1.4%) [10], but this includes multiple causes of dizziness, such as orthostatic hypotension, hormone-related and cardiorespiratory disorders. If we consider only the vestibular causes, the prevalence of chronic dizziness is significantly higher, with a risk of up to 50% in vestibular neuritis [13, 14].

1.3. Pathophysiology

Before going into detail about why some patients' dizziness symptoms persist, it is necessary to explain why we become dizzy.

1.3.1. Why do we get dizzy?

Gaze stabilisation, orientation in space and postural control are the result of the continuous central integration of multiple afferent sensory inputs. The main sensory information comes from the visual, vestibular and somatosensory (mainly the proprioceptors in muscles and joints) systems [15]. Dizziness can occur due to altered sensory flow towards the central nervous system (i.e., peripheral cause) and/or altered central processing of the sensory information (i.e., central cause) [4, 15, 16]. These peripheral and central causes of dizziness are explained in more detail below.

Peripheral causes of dizziness include disorders of the vestibular (e.g., benign paroxysmal positional vertigo, vestibular neuritis, Meniere's disease), visual (e.g., diplopia) and/or somatosensory systems (e.g., cervicogenic dizziness, see further below).

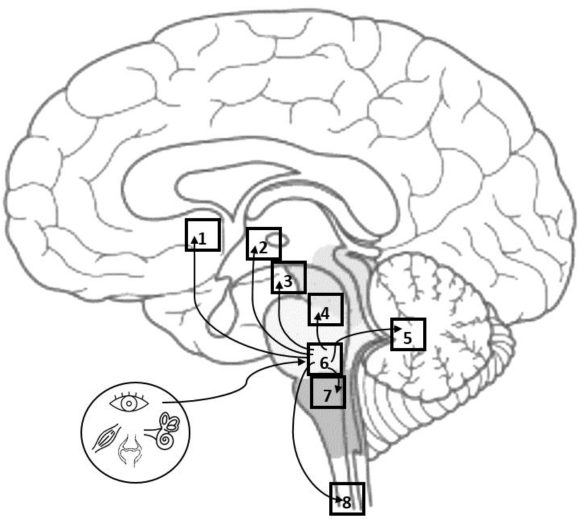
Central causes of dizziness may be a brain tumor (e.g., vestibular schwannoma), or altered functional brain connectivity (e.g., persistent postural-perceptual dizziness, see further below). The latter is a maladaptation to an initial acute event of dizziness/imbalance, where the shift to high-demanding postural and visual strategies - which is initially a normal protective response of the body - persists despite remission of the acute event [17].

The multisensory input enters the vestibular nuclei (located in the brainstem) from where the information is further transmitted to various brain areas (**FIGURE 1**). Each of these brain areas reacts in its own way to disturbances of the sensory information, giving rise to the ‘dizziness syndrome’:

- *Thalamus*: From here, information travels on to the parieto-insular vestibular cortex. This makes it possible to recognise and control the position of the head and body in space [18].
  → Disturbances can lead to spatial disorientation.

- *Oculomotor, trochlear and abducens* nuclei: From here, the eye muscles are controlled, and gaze is stabilised (via the vestibulo-ocular reflex) [19].
  → Disturbances can lead to nystagmus.
- *Vestibulocerebellum*: From here, body movements are refined and corrected, and the eye muscles are controlled [20, 21].
  → Disturbances can lead to postural instability and nystagmus.
- *Spinal cord*: From here, motor muscles in the body are controlled (e.g., vestibulospinal reflex) [22].
  → Disturbances can lead to postural instability.
- *Nucleus tractus solitarius*: From here, information goes to, among others, the nucleus ambiguus, the dorsal motor nucleus of the vagus nerve, and the parabrachial nucleus. These structures are involved in the regulation of autonomous (e.g., cardiovascular, respiratory, and gastrointestinal) functions [23].
  → Disturbances can lead to complaints of nausea, hyperventilation, and sweating.
- *Limbic system*. This includes structures such as the hippocampus, amygdala and nucleus accumbens that are involved in the regulation of emotions [24].
  → Disturbances may lead to emotional lability (e.g., anxiety and depression).

Figure 1. Multisensory central processing [a, b]



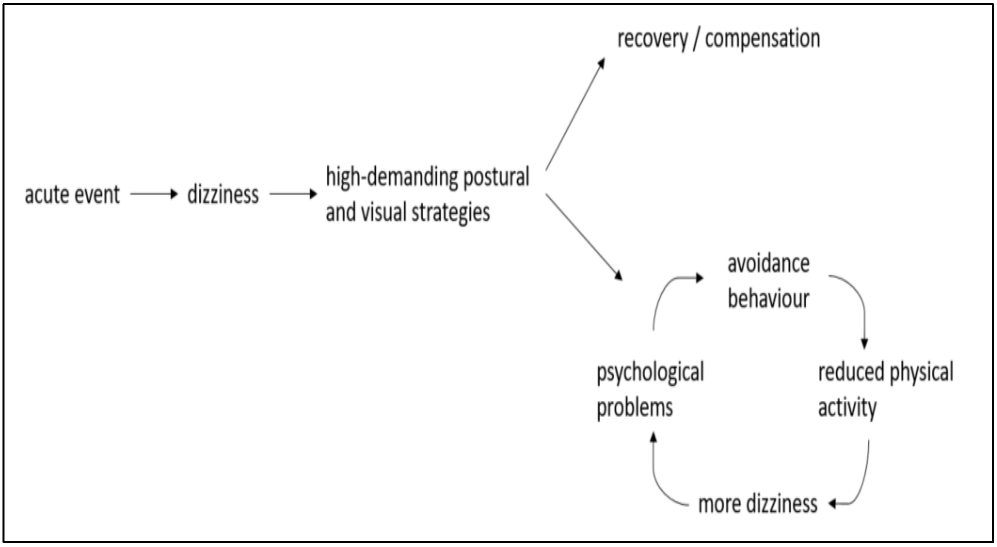
[a] Projections from the vestibular nuclei to various brain areas that enable us to maintain balance, focus our gaze, and orientate ourselves in space.

[b] Legend:
1 = accumbens nucleus;
2 = thalamus;
3 = hippocampus and amygdala;
4 = oculomotor nuclei;
5 = vestibulocerebellum;
6 = vestibular nuclei;
7 = solitary nucleus;
8 = spinal cord

1.3.2. What causes dizziness to persist?

The risk of developing chronic dizziness is largely determined by three factors: the nature of the current dizziness, the patient's baseline health status, and the patient's management of the dizziness symptoms [25]. Regarding the first factor, the risk of chronicity increases when the current dizziness is frequent or continuous and/or highly disabling [26]. The second risk factor is pre-existing health or psychological problems, and/or increased age [27, 28]. The third risk factor is poor coping strategies for the dizziness [29], such as continued adherence to high-demanding postural (i.e., avoidance of dizziness provoking movements) [30] and visual strategies (i.e., shift to favouring visual input at the expense of the vestibular and somatosensory information) [31], and the development of psychological disorders [32]. The negative psychological impact on the patient may be due to the unpredictable nature of dizziness in terms of timing and frequency, and the often-present uncertainty about its exact cause, prognosis and the effect of treatment [33]. As a result of this poor coping, a vicious cycle is created in which dizziness is perpetuated rather than recovery and/or compensation taking place (**FIGURE 2**) [34].

Figure 2. *Vicious cycle of dizziness* [a]



[a] Based on Popkirov et al. (2018) ‘Persistent postural-perceptual dizziness (PPPD): a common, characteristic and treatable cause of chronic dizziness’ [34]

1.4. Research relevance

Patients with chronic dizziness present a particular challenge to clinicians [35]. The cause is often difficult to determine [8], while the negative impact of dizziness on the patient, his/her environment, and the society can be considerable [29].

Diagnostic difficulties include the subjectivity of the symptoms, the multicausality - usually it is a combination of factors that leads to the persistence of dizziness - and the lack of abnormalities on clinical/laboratory tests [35]. Consequently (after ruling out serious pathologies which are fortunately rare), the clinician must rely on the medical history and standard clinical examination to make an estimate of the possible diagnosis. Moreover, given the frequent occurrence of psychological comorbidities, it is tempting to write off the dizziness as a psychological disorder [8]. However, psychological problems often arise only as a secondary consequence of persistent dizziness [36, 37]. Incorrect or inadequate diagnosis leads to underestimation of the treatable causes. Therefore, with this doctoral thesis we want to further explore the clinical presentation of patients with chronic dizziness.

Persistent dizziness reduces patients' health and daily activity level, and in turn their social life [29]. The high financial burden on our health care system and the reduced work productivity (e.g., reduced workload, job termination) negatively affect society [38]. Therefore, a second aim of this doctoral thesis is to contribute to insights on how to effectively treat patients with chronic dizziness.

2. Cervicogenic dizziness (CGD)

2.1. Definition

As the name suggests, cervicogenic dizziness (CGD) is the dizziness associated with the cervical spine. Cervicogenic dizziness (CGD) was first described by Ryan and Cope (1955) under the name cervical vertigo [39]. Later, the terms cervical dizziness and proprioceptive dizziness/vertigo were used. The current name is cervicogenic dizziness, although there is a forthcoming consensus document of the Bárány Society that reverts to the term cervical dizziness. The term dizziness should be preferred to vertigo because the dizziness symptoms in CGD are of non-rotational nature [40].

Furman and Cass (1996) defined CGD as '*a non-specific sensation of altered orientation in space and dysequilibrium originating from abnormal afferent* *activity from the neck*' [41]. This refers to the most common theory that CGD arises as a result of a change in cervical proprioceptive afferent activity (see further below - *Pathophysiology*) [15, 42]. Other symptoms associated with CGD are postural imbalance, decreased neck mobility, headache, neck pain, referred pain to the shoulder region, and visual disturbances [41, 43-45].

CGD was not included in the 11th edition of the International Classification of Diseases (https://icd.who.int/en). The existence of CGD is often disputed due to the lack of tests that can demonstrate the neck's contribution to dizziness (see further below – *Diagnosis*) [46].

2.2. Prevalence

No information is available on the prevalence of CGD itself, which may be partly explained by the diagnostic difficulties of the condition (see further below - *Diagnosis*). An estimate can be made based on the prevalence of the causes. The most common cause of CGD is after a whiplash injury [44]. The lifetime prevalence of whiplash injury is about 10% in the general population [47]. Of these patients, up to 58% develop a whiplash-associated disorder (WAD) in which dizziness is part of the reported symptoms [48, 49]. However, it should be noted that this can also include vestibular causes of dizziness (e.g., benign paroxysmal positional vertigo, perilymphatic fistulae). Other less frequent causes of CGD are cervical spondylosis (general population prevalence of 14% [50]) and cervical myofascial pain syndrome (general population prevalence of 46% [51]).

2.3. Pathophysiology

There are several theories on the pathophysiological mechanism of cervicogenic dizziness. The most discussed are the (neuro)vascular and proprioceptive hypotheses [40, 52].

2.3.1. The (neuro)vascular hypotheses

The neurovascular hypothesis (i.e., Barré-Lieou syndrome) relies on a transient intracerebral ischaemia caused by irritation of the sympathetic fibres around the vertebral arteries, leading to vasoconstriction of these arteries. The existence of the Barré-Lieou syndrome is confirmed by some studies [53-55], refuted by others [56, 57]. On the other hand, the vascular hypothesis (i.e., vertebrobasilar insufficiency or Bow hunter's syndrome) also assumes reduced cerebral blood flow as a cause of dizziness, but in this case due to mechanical compression of the vertebral artery during heterolateral cervical rotation [58]. Bow hunter's syndrome is said to be not very common because it only occurs in the presence of multiple arterial abnormalities.

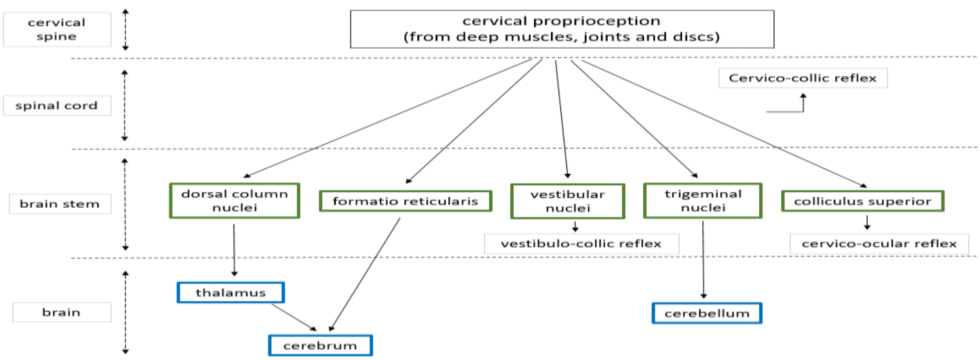
Both the neurovascular and vascular hypotheses would rather cause vertigo, and additional symptoms such as syncope, paraesthesia and motor weakness [59].

2.3.2. The proprioceptive hypothesis

The most common theory for CGD, and the one adhered to in this doctoral thesis, is dizziness due to altered cervical proprioceptive afferent input. The dizziness is the result of the central mismatch between the vestibular, visual and the altered proprioceptive information [15].

The cervical spine, with its high spindle density in the deep neck muscles, and mechanoreceptors in the cervical intervertebral discs and the zygapophyseal joints, has a very well-equipped proprioceptive system [60-62]. These structures transmit proprioceptive information (i.e., about the position and movements of the head in relation to the trunk) to the central nervous system (CNS). Besides the input to the CNS, there are also reflex arcs that control the eyes (i.e., cervico-ocular reflex) and head position (i.e., cervico-collic and vestibulo-collic reflexes). Since the vestibular system only registers positions and movements of the head in space, cervical proprioceptive afferents are necessary. It is the combination of the vestibular and cervical information that allows us to have a true perception in space and maintain postural balance [45]. An overview of the proprioceptive projections to the CNS is shown in **FIGURE 3**.

Figure 3. Overview of the proprioceptive projections to the central nervous system[a]



[a] Based on Roijezon et al. (2015) 'Proprioception in musculoskeletal rehabilitation. Part 1: Basic science and principles of assessment and clinical interventions' [45]

Studies confirm the important role the cervical spine plays in spatial orientation and postural control. Experimental alteration of cervical proprioceptive afferent input (e.g., via unilateral or bilateral electrical stimulation or vibration) in healthy adults causes reduced visual perception of verticality [63], postural deviation [64] and reduced walking speed [65].

What is less clear is what exactly causes the change in cervical proprioception in patients with CGD. Studies show that pain, inflammation, muscle fatigue and muscle atrophy can negatively influence proprioception [45, 66]. This may be due to a degenerative (e.g., cervical spondylosis), traumatic (e.g., whiplash injury) or ideopathic (e.g., ideopathic neck pain) disorder [44]. Although research on this subject is still in its early stages, it is assumed that alteration of proprioceptive information is more pronounced after trauma than in non-traumatic conditions [67].

2.4. Diagnosis

The uncertainty about the cause of CGD is also reflected in its diagnostic difficulties. No specific diagnostic test for CGD is available, so the probability of CGD is determined by the exclusion of other causes, and the presence of following criteria:

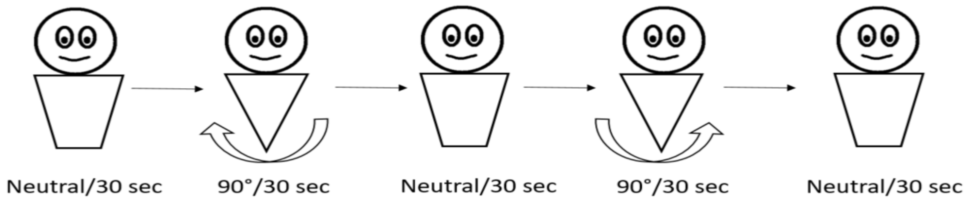
- neck dysfunction and/or neck pain [4],
- a clear positive correlation over time between the neck pain and dizziness [44],
- dizziness complaints triggered by changes in head position or head movements (mainly to rotation and extension) [68].

However, the extent to which neck pain and dizziness must be present and how they relate to each other varies greatly from study to study [4]. For example, some studies set criteria on the duration of dizziness and neck pain [69-71], while others do not [42, 72, 73]. Moreover, the use of neck pain as a diagnostic marker is subject to debate. Some prefer positive findings during the clinical neck examination indicating the presence of neck dysfunction, rather than the presence of neck pain [4, 46].

In addition, there are clinical tests that, after ruling out other causes for the dizziness, can be performed to further increase the likelihood of CGD. These are the cervical neck torsion test (CTT), the smooth pursuit neck torsion test (SPNT), and the head repositioning accuracy test (HRA). **TABLE 1** lists these tests and their diagnostic accuracy.

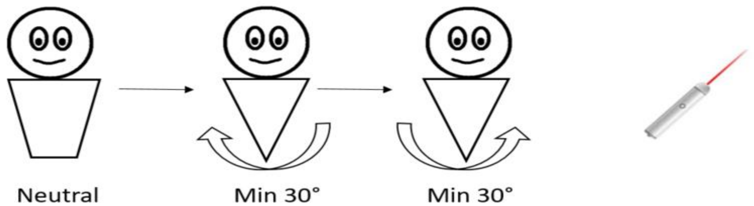
Table 1. *Clinical tests for cervicogenic dizziness (CGD) [a]*

a) Cervical neck torsion test (CTT)



Description: The patient sits on a swivel chair. While the head is fixated by the examiner, the trunk is successively turned to the right, back to neutral, to the left and back to neutral. As the head continues to look forward, cervical torsion occurs. Each of the four positions is held for 30 seconds. The CTT is positive when nystagmus (> 2 degrees per second, but no spontaneous nystagmus) occurs in one or more of the four positions (trunk rotation right, neutral position, trunk rotation left, or neutral position).
Diagnostic accuracy: sensitivity 72% and specificity 92% (CGD versus BPPV) [74].

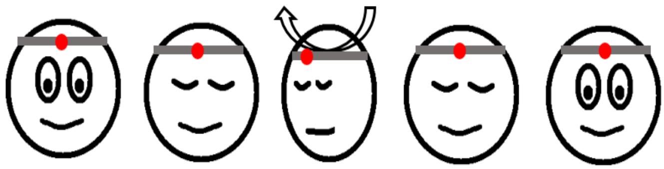
b) Smooth pursuit neck torsion test (SPNT)



Description: The patient sits on a swivel chair. The head is fixated by the examiner. The examiner first performs the "smooth pursuit" test with the patient in a neutral position. The patient has to follow a laser pointer with the eyes (arc of 40°, at 2 Hz, and peak velocity of 20 degrees per second). The test result is the average gain, i.e., the ratio between the eye velocity and the target velocity. Then, the trunk is rotated successively minimum 30 degrees to the right and left, repeating the smooth pursuit test each time. The larger the difference in smooth pursuit average gain between the normal position and the neck torsion positions, the larger the likelihood of whiplash-induced CGD.

Diagnostic accuracy:
sensitivity 90% and specificity 91% (CGD with WAD and dizziness) [74]
sensitivity 27% and specificity 55% (CGD with WAD and dizziness) [75]
sensitivity 56% and specificity 88% (CGD with WAD and dizziness) [76]

c) Head Repositioning Accuracy Test (HRA)



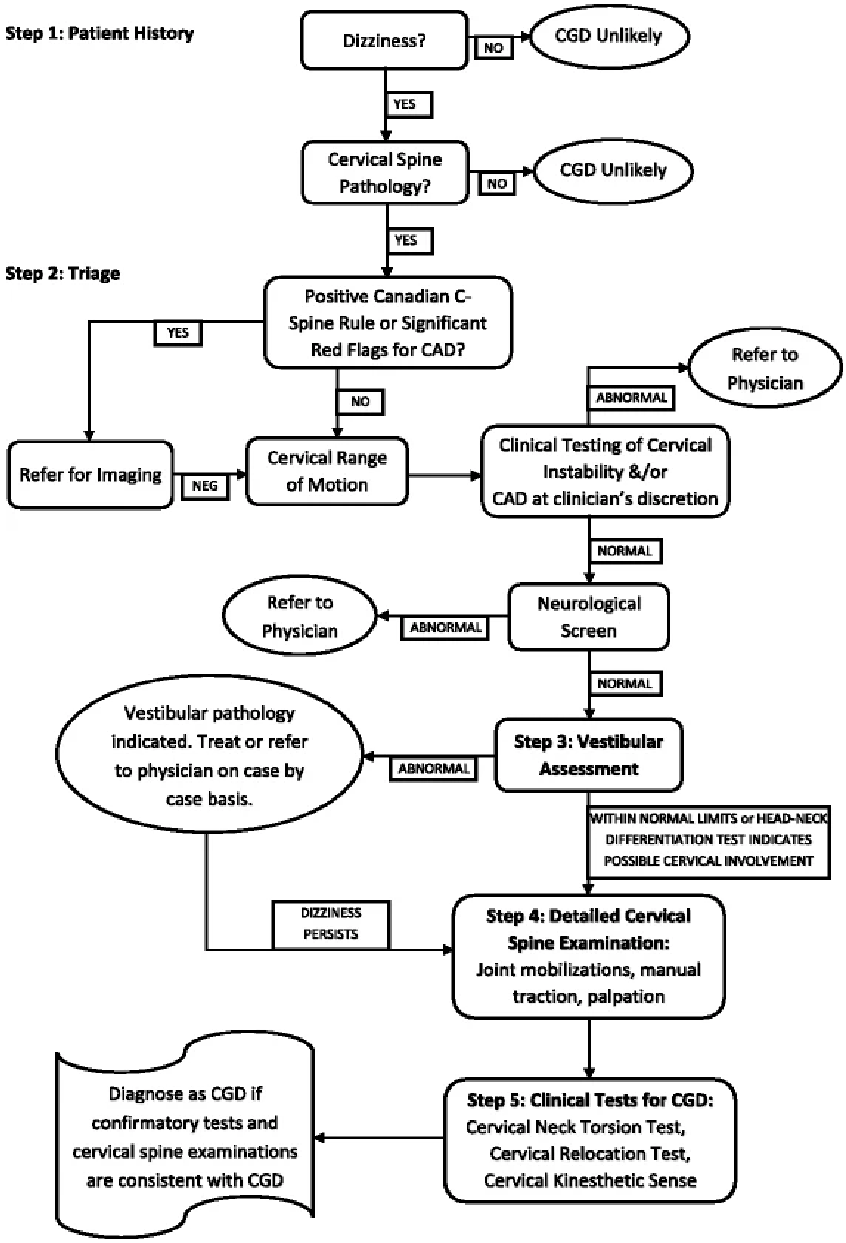
Description: The patient sits on a chair and wears a laser light on the head that projects onto a target on the wall in front of him/her. The patient closes the eyes, slowly turns the head to the right, slowly turns the head back and then verbally indicates to the examiner when (s)he thinks (s)he has returned to the original head position. The patient then opens the eyes again and receives feedback on how the task was performed by seeing to what extent the laser light is still projecting on the target on the wall. If the laser light no longer projects on the target, the head position is corrected before starting the next exercise. The exercise is performed with head rotation to the right, head rotation to the left, flexion and extension, repeating the direction of movement 3 times each. The test is positive if the average deviation between the actual and the subjectively correct position is > 4.5° in one or more of the movement directions.

Diagnostic accuracy: sensitivity 72% and specificity 75% (CGD versus BPPV) [74]

[a] Abbreviations: BPPV = benign paroxysmal positional vertigo; CGD = cervicogenic dizziness; WAD = whiplash associated disorder

For a concrete method of establishing the possible diagnosis of CGD, the flow chart by Reiley et al. (2017) can be used [46]. This involves a step-by-step exclusion of other causes for the dizziness, including prior neurological and vestibular examination. The flow chart is shown in **FIGURE 4**.

Figure 4. *Flowchart for the diagnosis of CGD* [a]



[a] From: Reiley et al. (2017) 'How to diagnose cervicogenic dizziness' [46]. For all details related to the interpretation of this flow chart, please consult their article.

2.5. Research relevance

Neck complaints are frequent in patients with chronic dizziness [77]. Given the hypothesis that the cervical spine may contribute to the onset or persistence of dizziness, this doctoral thesis aims to further investigate the relation between neck complaints and CGD.

CGD is a diagnosis of exclusion. CGD can only be suspected on the basis of medical history and positive findings on additional specific clinical tests (i.e., CTT, SPNT, and HRA) [46]. The medical history is, however, a subjective evaluation method and therefore less reliable. The clinical tests, in turn, require specific equipment (e.g., laser light, electronystagmography) that is often not available in clinical practice. Furthermore, the CTT and SPNT are only performed in the horizontal plane (i.e., rotational movements), so CGD provoked by movements other than head rotation may remain unnoticed [46]. Finally, diagnostic accuracy of the clinical tests has only been assessed in specific groups (e.g., BPPV, WAD) using strict study inclusion criteria (e.g., only BPPV patients without neck complaints), and thus the diagnostic value of these tests remains unknown in a general population of patients with chronic dizziness [74-76]. As a consequence of the above, we wanted to further investigate the clinical characteristics of CGD and the diagnostic value of simple clinical tests for CGD in patients with chronic dizziness.

Finally, effective treatments for CGD are described in the literature. However, a systematic review of these treatment possibilities in function of the chosen diagnostic criteria for CGD is lacking.

3. Persistent postural-perceptual dizziness (PPPD)

3.1. Definition

Persistent postural-perceptual dizziness (PPPD), which has been recently defined by the consensus committee for the classification of vestibular disorders of the Bárány Society [3], is the collective term for chronic functional vestibular disorders. It refers to conditions that cause vestibular symptoms due to altered functional brain connectivity following an acute (vestibular) cause of dizziness or unsteadiness (see further below - *Pathophysiology*). These conditions include phobic postural vertigo (PPV) [78], space and motion discomfort (SMD) [79], visual vertigo (VV) [80], and chronic subjective vertigo (CSD) [8]. Each of these conditions has its own type, course, triggering symptoms, precipitants, and findings on clinical/laboratory examination [3]. Their common feature is that no structural cause can be attributed to the symptoms. PPPD is recognised by the World Health Organisation (WHO) and is included in the 11th edition of the International Classification of Diseases (https://icd.who.int/en).

3.2. Prevalence

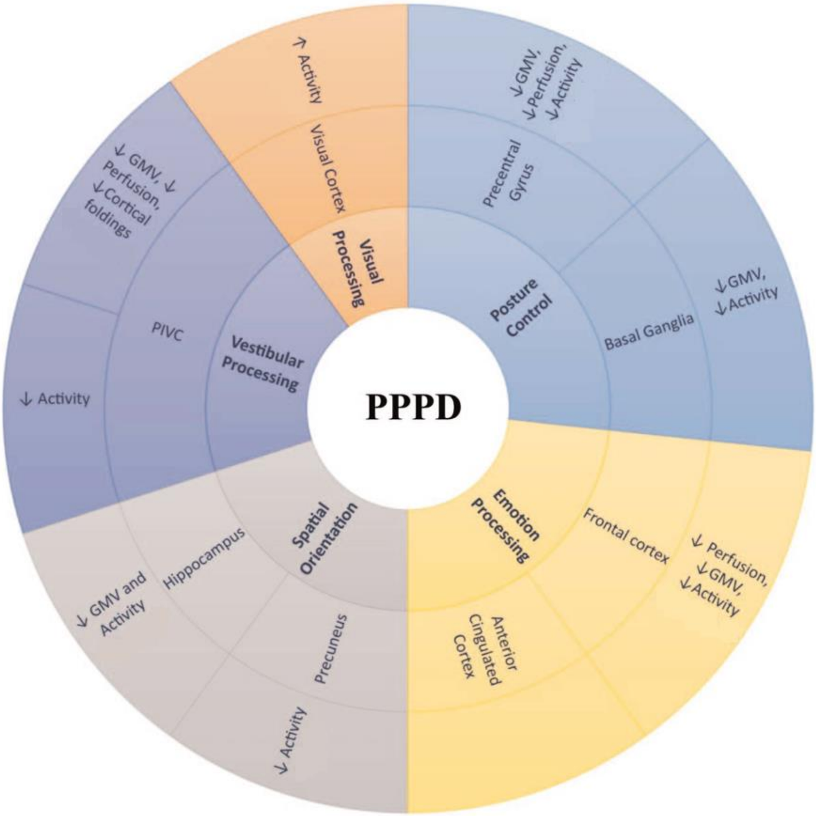
Studies on the prevalence of PPPD are scarce. Studies looking more closely at the PPV [81] and CSD [8] subtypes suggest that PPPD occurs in up to 20% of patients reporting vestibular complaints. Another study states that PPPD (with 14% of cases) is the second most common cause of chronic dizziness, preceded only by depression [82]. Finally, it is noted that PPPD is most frequently present in middle-aged and female patients [82-85].

3.3. Pathophysiology

PPPD is thought to result from the continuation of the physiological and behavioural adaptations intended to cope with the original (acute) disorder that caused the dizziness or imbalance [86]. These include the continuation of postural strategies (e.g., vigilance over head and body movements), and increased visual dependence to compensate for the reduced vestibular input [17]. Although this is a normal protective response of the body in the acute phase, the persistence of these adaptations is detrimental to the recovery process to regain normal balance control. Factors that may cause these adaptations to persist are a pre-existing higher neuroticism and/or lower extraversion level, or developed psychological comorbidity due to the impact of the acute event on the individual (e.g., anxiety, depression) [87].

Imaging studies have been able to portray these maladaptive strategies through demonstrable changes in the structure, function and connectivity of brain regions responsible for vestibular, visual, postural control, spatial orientation and emotional processing (**FIGURE 5**) [88, 89]. For example, increased visual dependence is reflected in increased activity in the visual brain region (i.e., the occipital lobe) and decreased activity in the brain region for processing vestibular information (i.e., the parieto-insular vestibular complex (PIVC)) [88].

Figure 5. *Overview of alterations in brain function in PPPD* [a, b]



[a] From: Teh et al. (2022) 'Neuroimaging Systematic Review in Persistent Postural-Perceptual Dizziness: The Elaborate Alterations in the Delicate Network to Remain Balanced' [88]

[b] Abbreviations: GMV = grey matter volume; PIVC = parieto-insular vestibular cortex; PPPD = persistent postural-perceptual dizziness

3.4. Diagnosis

There are no specific diagnostic tests for PPPD. Functional brain imaging would offer the possibility of detecting patients with PPPD with some accuracy, but this is obviously cumbersome and rarely available in the clinical setting. Therefore, five criteria have been formulated, all of which must be present in the patient and which can be verbally tested for during the medical history to determine the likelihood of PPPD (**TABLE 2**) [3].

***Table 2.** Diagnostic criteria for Persistent Postural-Perceptual dizziness (PPPD)* [a]

All five (A→E) criteria must be fulfilled to make the diagnosis of PPPD.
A. One or more symptoms of dizziness, unsteadiness, or non-spinning vertigo are present on most days for 3 months or more. – Symptoms last for prolonged (hours-long) periods of time, but may wax and wane in severity. – Symptoms need not be present continuously throughout the entire day.
B. Persistent symptoms occur without specific provocation, but are exacerbated by three factors: – Upright posture, – Active or passive motion without regard to direction or position, and – Exposure to moving visual stimuli or complex visual patterns.
C. The disorder is precipitated by conditions that cause vertigo, unsteadiness, dizziness, or problems with balance including acute, episodic, or chronic vestibular syndromes, other neurologic or medical illnesses, or psychological distress. – When the precipitant is an acute or episodic condition, symptoms settle into the pattern of criterion A as the precipitant resolves, but they may occur intermittently at first, and then consolidate into a persistent course. – When the precipitant is a chronic syndrome, symptoms may develop slowly at first and worsen gradually.
D. Symptoms cause significant distress or functional impairment.
E. Symptoms are not better accounted for by another disease or disorder.

[a] From: Staab et al. (2017) 'Diagnostic criteria for persistent postural-perceptual dizziness (PPPD): Consensus document of the committee for the Classification of Vestibular Disorders of the Bárány Society' [3]

3.5. Research relevance

PPPD is the second most important cause of persistent dizziness [82]. Its diagnosis is based solely on medical history [3]. However, given the vague, hard-to-describe feeling that dizziness is, it can be difficult for the patient to confirm/deny the criteria for PPPD. Objective clinical tests are not available, and neuroimaging of the brain is cumbersome for use in clinical practice. Therefore, this doctoral thesis aims to further investigate the clinical characteristics of PPPD and the diagnostic value of simple clinical tests for PPPD in patients with chronic dizziness.

A review of possible treatments for PPPD is available in the literature [90]. These include cognitive behavioural therapy, serotonergic medication, and vestibular rehabilitation therapy (VRT) supplemented by visual desensitisation therapy [90, 91]. However, there is currently a lack of knowledge on how to integrate visual desensitisation into a home-based VRT in a customisable, budget and user-friendly way.

4. Thesis outline

Part 1 of this doctoral thesis - consisting of two chapters - addresses the first objective, which was to investigate how CGD and PPPD can be identified in a population of patients with chronic dizziness. The main research questions were:

- "To what extent do patients with CGD differ from patients with other forms of chronic dizziness on clinical cervical and balance tests, and what is the diagnostic value of these tests for CGD?" (Chapter 1)
- "To what extent do patients with PPPD differ from patients with other forms of chronic dizziness on clinical visual dependence and balance tests, and what is the diagnostic value of these tests for PPPD?" (Chapter 2)

Part 2 of this doctoral thesis - consisting of two chapters - addresses the second objective: how to effectively treat CGD and PPPD. The main research questions were:

- “What is the evidence-based recommendation for the treatment of CGD, according to its diagnostic criteria used?” (Chapter 1)
- "What is the user experience of WeBaVeR, our self-developed customised web-based home vestibular rehabilitation therapy (VRT) programme containing visual desensitisation exercises, for the treatment of patients with PPPD?" (Chapter 2)

As is often the case with research projects, this doctoral thesis only touches a small part of the large and complex problem that chronic dizziness is. Nevertheless, we are sure that the new insights gained from our research have contributed to a better knowledge and treatment of patients with chronic dizziness.

5. References

1. Bisdorff, A., et al., *Classification of vestibular symptoms: towards an international classification of vestibular disorders.* J Vestib Res, 2009. **19**(1-2): p. 1-13.
2. Bronstein, A.M. and T. Lempert, *Management of the patient with chronic dizziness.* Restorative Neurology and Neuroscience, 2010. **28**(1): p. 83-90.
3. Staab, J.P., et al., *Diagnostic criteria for persistent postural-perceptual dizziness (PPPD): Consensus document of the committee for the Classification of Vestibular Disorders of the Barany Society.* J Vestib Res, 2017. **27**(4): p. 191-208.
4. Knapstad, M.K., *Clinical characteristics in patients with cervicogenic dizziness: A systematic review.* Health science reports, 2019. **2**(9): p. e134.
5. Dieterich, M., *Dizziness.* Neurologist, 2004. **10**(3): p. 154-164.
6. Feuerecker, R., et al., *Chronic subjective dizziness: Fewer symptoms in the early morning - a comparison with bilateral vestibulopathy and downbeat nystagmus syndrome.* Journal of Vestibular Research-Equilibrium & Orientation, 2015. **25**(2): p. 67-72.
7. Formeister, E.J., et al., *Episodic versus Chronic Dizziness: An Analysis of Predictive Factors.* Ann Otol Rhinol Laryngol, 2021: p. 34894211025416.
8. Staab, J.P. and M.J. Ruckenstein, *Expanding the differential diagnosis of chronic dizziness.* Arch Otolaryngol Head Neck Surg, 2007. **133**(2): p. 170-6.
9. Kruschinski, C., et al., *A three-group comparison of acute-onset dizzy, long-term dizzy and non-dizzy older patients in primary care.* Aging Clin Exp Res, 2011. **23**(4): p. 288-95.
10. Neuhauser, H.K., et al., *Burden of dizziness and vertigo in the community.* Arch Intern Med, 2008. **168**(19): p. 2118-24.
11. Poulsen, H., *Patrick DL, Peach H, eds.: Disablement in the community. Oxford University Press, Oxford, England 1989, 230 pages. Price not stated.* Scandinavian Journal of Social Medicine, 2016. **19**(1): p. 80-80.
12. Teggi, R., et al., *Point prevalence of vertigo and dizziness in a sample of 2672 subjects and correlation with headaches.* Acta Otorhinolaryngol Ital, 2016. **36**(3): p. 215-9.
13. Okinaka, Y., et al., *Progress of caloric response of vestibular neuronitis.* Acta Otolaryngol Suppl, 1993. **503**: p. 18-22.
14. Carlson, M.L., et al., *Long-term dizziness handicap in patients with vestibular schwannoma: a multicenter cross-sectional study.* Otolaryngol Head Neck Surg, 2014. **151**(6): p. 1028-37.
15. Kristjansson, E. and J. Treleaven, *Sensorimotor function and dizziness in neck pain: implications for assessment and management.* J Orthop Sports Phys Ther, 2009. **39**(5): p. 364-77.

16. Van Ombergen, A., et al., *Altered functional brain connectivity in patients with visually induced dizziness.* Neuroimage Clin, 2017. **14**: p. 538-545.
17. Dieterich, M. and J.P. Staab, *Functional dizziness: From phobic postural vertigo and chronic subjective dizziness to persistent postural-perceptual dizziness.* Current Opinion in Neurology, 2017. **30**(1): p. 107-113.
18. Grusser, O.J., M. Pause, and U. Schreiter, *Vestibular neurones in the parieto-insular cortex of monkeys (Macaca fascicularis): visual and neck receptor responses.* J Physiol, 1990. **430**: p. 559-83.
19. Dieterich, M. and T. Brandt, *The parietal lobe and the vestibular system.* Handb Clin Neurol, 2018. **151**: p. 119-140.
20. Coffman, K.A., R.P. Dum, and P.L. Strick, *Cerebellar vermis is a target of projections from the motor areas in the cerebral cortex.* Proc Natl Acad Sci U S A, 2011. **108**(38): p. 16068-73.
21. Miall, R.C. and E.W. Jenkinson, *Functional imaging of changes in cerebellar activity related to learning during a novel eye-hand tracking task.* Exp Brain Res, 2005. **166**(2): p. 170-83.
22. Kato, I., T. Miyoshi, and C.R. Pfaltz, *Studies on habituation of vestibulospinal reflexes. Effects of repetitive optokinetic and vestibular stimuli upon the stepping test.* ORL J Otorhinolaryngol Relat Spec, 1977. **39**(4): p. 195-202.
23. Singh, P., S.S. Yoon, and B. Kuo, *Nausea: a review of pathophysiology and therapeutics.* Therap Adv Gastroenterol, 2016. **9**(1): p. 98-112.
24. Rajagopalan, A., et al., *Understanding the links between vestibular and limbic systems regulating emotions.* J Nat Sci Biol Med, 2017. **8**(1): p. 11-15.
25. Bailey, K.E., et al., *Which primary care patients with dizziness will develop persistent impairment?* Arch Fam Med, 1993. **2**(8): p. 847-52.
26. Obermann, M., et al., *Long-term outcome of vertigo and dizziness associated disorders following treatment in specialized tertiary care: the Dizziness and Vertigo Registry (DiVeR) Study.* J Neurol, 2015. **262**(9): p. 2083-91.
27. Sloane, P., D. Blazer, and L.K. George, *Dizziness in a community elderly population.* J Am Geriatr Soc, 1989. **37**(2): p. 101-8.
28. Boult, C., et al., *The relation of dizziness to functional decline.* J Am Geriatr Soc, 1991. **39**(9): p. 858-61.
29. Yardley, L., et al., *Prevalence and presentation of dizziness in a general practice community sample of working age people.* British Journal of General Practice, 1998. **48**(429): p. 1131-1135.
30. Yardley, L., *Overview of psychologic effects of chronic dizziness and balance disorders.* Otolaryngol Clin North Am, 2000. **33**(3): p. 603-16.

31. Pavlou, M., R.A. Davies, and A.M. Bronstein, *The assessment of increased sensitivity to visual stimuli in patients with chronic dizziness.* J Vestib Res, 2006. **16**(4-5): p. 223-31.
32. Roh, K.J., et al., *Role of Emotional Distress in Prolongation of Dizziness: A Cross-Sectional Study.* Journal of Audiology and Otology, 2018. **22**(1): p. 6-12.
33. House, J.W., W.G. Crary, and M. Wexler, *The inter-relationship of vertigo and stress.* Otolaryngol Clin North Am, 1980. **13**(4): p. 625-9.
34. Popkirov, S., J.P. Staab, and J. Stone, *Persistent postural-perceptual dizziness (PPPD): a common, characteristic and treatable cause of chronic dizziness.* Pract Neurol, 2018. **18**(1): p. 5-13.
35. Bronstein, A.M., T. Lempert, and B.M. Seemungal, *Chronic dizziness: a practical approach.* Pract Neurol, 2010. **10**(3): p. 129-39.
36. Kroenke, K., et al., *Causes of persistent dizziness. A prospective study of 100 patients in ambulatory care.* Ann Intern Med, 1992. **117**(11): p. 898-904.
37. Staab, J.P. and M.J. Ruckenstein, *Which comes first? Psychogenic dizziness versus otogenic anxiety.* Laryngoscope, 2003. **113**(10): p. 1714-8.
38. Ruthberg, J.S., et al., *The economic burden of vertigo and dizziness in the United States.* J Vestib Res, 2021. **31**(2): p. 81-90.
39. Ryan, G.M. and S. Cope, *Cervical vertigo.* Lancet, 1955. **269**(6905): p. 1355-8.
40. Devaraja, K., *Approach to cervicogenic dizziness: a comprehensive review of its aetiopathology and management.* European Archives of Oto-Rhino-Laryngology, 2018. **275**(10): p. 2421-2433.
41. JM Furman, S.C., *Balance disorders: A case-study approach*. Philadelphia.
42. Karlberg, M., et al., *Postural and symptomatic improvement after physiotherapy in patients with dizziness of suspected cervical origin.* Arch Phys Med Rehabil, 1996. **77**(9): p. 874-82.
43. Brown, J.J., *Cervical Contribution to Balance: Cervical Vertigo.*
44. Wrisley, D.M., et al., *Cervicogenic dizziness: A review of diagnosis and treament.* Journal of Orthopaedic and Sports Physical Therapy, 2000. **30**(12): p. 755-766.
45. Roijezon, U., N.C. Clark, and J. Treleaven, *Proprioception in musculoskeletal rehabilitation. Part 1: Basic science and principles of assessment and clinical interventions.* Man Ther, 2015. **20**(3): p. 368-77.
46. Reiley, A.S., et al., *How to diagnose cervicogenic dizziness.* Arch Physiother, 2017. **7**: p. 12.
47. Kumagai, G., et al., *Prevalence of whiplash injury and its association with quality of life in local residents in Japan: A cross sectional study.* J Orthop Sci, 2022. **27**(1): p. 108-114.

48. Rubin, W., *Whiplash with vestibular involvement.* Arch Otolaryngol, 1973. **97**(1): p. 85-7.
49. Toglia, J.U., *Acute flexion-extension injury of the neck. Electronystagmographic study of 309 patients.* Neurology, 1976. **26**(9): p. 808-14.
50. Lv, Y., et al., *The prevalence and associated factors of symptomatic cervical Spondylosis in Chinese adults: a community-based cross-sectional study.* BMC Musculoskelet Disord, 2018. **19**(1): p. 325.
51. Fleckenstein, J., et al., *Discrepancy between prevalence and perceived effectiveness of treatment methods in myofascial pain syndrome: Results of a cross-sectional, nationwide survey.* Bmc Musculoskeletal Disorders, 2010. **11**.
52. Yacovino, D.A. and T.C. Hain, *Clinical characteristics of cervicogenic-related dizziness and vertigo.* Seminars in Neurology, 2013. **33**(3): p. 244-255.
53. Li, J., et al., *Sympathetic nerve innervation in cervical posterior longitudinal ligament as a potential causative factor in cervical spondylosis with sympathetic symptoms and preliminary evidence.* Medical Hypotheses, 2014. **82**(5): p. 631-635.
54. Hong, L. and Y. Kawaguchi, *Anterior Cervical Discectomy and Fusion to Treat Cervical Spondylosis With Sympathetic Symptoms.* Journal of Spinal Disorders & Techniques, 2011. **24**(1): p. 11-14.
55. Li, J., et al., *Mid-term Outcomes of Anterior Cervical Fusion for Cervical Spondylosis With Sympathetic Symptoms.* Clinical Spine Surgery, 2016. **29**(6): p. 255-260.
56. *Regional cerebral blood flow during hypotension in normotensive and stroke-prone spontaneously hypertensive rats: effect of sympathetic denervation.*
57. Mueller, S.M., D.D. Heistad, and M.L. Marcus, *Total and regional cerebral blood flow during hypotension, hypertension, and hypocapnia. Effect of sympathetic denervation in dogs.* Circ Res, 1977. **41**(3): p. 350-6.
58. Toole, J.F. and S.H. Tucker, *Influence of Head Position Upon Cerebral Circulation - Studies on Blood Flow in Cadavers.* Archives of Neurology, 1960. **2**(Jun): p. 616-623.
59. Pireau L., L.F., *Vertebrobasilar Insufficiency*. 2022: StatPearls.
60. Richmond Fj Fau - Abrahams, V.C. and V.C. Abrahams, *What are the proprioceptors of the neck?* (0079-6123 (Print)).
61. Liu, J.X., L.E. Thornell, and F. Pedrosa-Domellof, *Muscle spindles in the deep muscles of the human neck: a morphological and immunocytochemical study.* J Histochem Cytochem, 2003. **51**(2): p. 175-86.

62. Mclain, R.F., *Mechanoreceptor Endings in Human Cervical Facet Joints.* Spine, 1994. **19**(5): p. 495-501.
63. Wapner, S., H. Werner, and K.A. Chandler, *Experiments on sensory-tonic field theory of perception. I. Effect of extraneous stimulation on the visual perception of verticality.* J Exp Psychol, 1951. **42**(5): p. 341-4.
64. Lekhel, H., et al., *Postural responses to vibration of neck muscles in patients with uni- and bilateral vestibular loss.* Gait Posture, 1998. **7**(3): p. 228-236.
65. Wannaprom, N., et al., *Neck muscle vibration produces diverse responses in balance and gait speed between individuals with and without neck pain.* Musculoskeletal Science and Practice, 2018. **35**: p. 25-29.
66. Schaible, H.G. and B.D. Grubb, *Afferent and spinal mechanisms of joint pain.* Pain, 1993. **55**(1): p. 5-54.
67. Palmgren, P.J., et al., *Cervicocephalic kinesthetic sensibility and postural balance in patients with nontraumatic chronic neck pain--a pilot study.* Chiropr Osteopat, 2009. **17**: p. 6.
68. Reid, S.A., et al., *Utility of a brief assessment tool developed from the Dizziness Handicap Inventory to screen for Cervicogenic dizziness: A case control study.* Musculoskeletal Science and Practice, 2017. **30**: p. 42-48.
69. Alund, M., et al., *Dynamic posturography among patients with common neck disorders. A study of 15 cases with suspected cervical vertigo.* J Vestib Res, 1993. **3**(4): p. 383-9.
70. Grande-Alonso, M., et al., *Biobehavioural analysis of the vestibular system and posture control in patients with cervicogenic dizziness. A cross-sectional study.* Neurologia, 2018. **33**(2): p. 121-128.
71. Yahia, A., et al., *Chronic neck pain and vertigo: Is a true balance disorder present?* Ann Phys Rehabil Med, 2009. **52**(7-8): p. 556-67.
72. Yao, M., et al., *Shi-Style Cervical Mobilizations Versus Massage for Cervical Vertigo: A Multicenter, Randomized, Controlled Clinical Trial.* J Altern Complement Med, 2019.
73. Ekvall Hansson, E., et al., *Dizziness among patients with whiplash-associated disorder: a randomized controlled trial.* J Rehabil Med, 2006. **38**(6): p. 387-90.
74. L'Heureux-Lebeau, B., et al., *Evaluation of paraclinical tests in the diagnosis of cervicogenic dizziness.* Otology & neurotology : official publication of the American Otological Society, American Neurotology Society [and] European Academy of Otology and Neurotology, 2014. **35**(10): p. 1858-1865.
75. Tjell, C. and U. Rosenhall, *Smooth pursuit neck torsion test: a specific test for cervical dizziness.* Am J Otol, 1998. **19**(1): p. 76-81.

76. Kongsted, A., et al., *Are altered smooth pursuit eye movements related to chronic pain and disability following whiplash injuries? A prospective trial with one-year follow-up.* Clin Rehabil, 2008. **22**(5): p. 469-79.
77. Knapstad, M.K., et al., *Neck pain associated with clinical symptoms in dizzy patients-A cross-sectional study.* Physiother Res Int, 2020. **25**(2): p. e1815.
78. Brandt, T., *Phobic postural vertigo.* Neurology, 1996. **46**(6): p. 1515-9.
79. Jacob, R.G., et al., *Discomfort with space and motion: A possible marker of vestibular dysfunction assessed by the situational characteristics questionnaire.* Journal of Psychopathology and Behavioral Assessment, 1993. **15**(4): p. 299-324.
80. Bronstein, A.M., *VISUAL VERTIGO SYNDROME - CLINICAL AND POSTUROGRAPHY FINDINGS.* Journal of Neurology Neurosurgery and Psychiatry, 1995. **59**(5): p. 472-476.
81. Brandt, T. and M. Dieterich, *Phobischer attacken-schwankschwindel, ein neues syndrom.* Münch Med Wochenschr, 1986. **128**: p. 247-250.
82. Ishizuka, K., et al., *The Clinical Key Features of Persistent Postural Perceptual Dizziness in the General Medicine Outpatient Setting: A Case Series Study of 33 Patients.* Intern Med, 2020. **59**(22): p. 2857-2862.
83. Strupp, M., et al., *[The most common form of dizziness in middle age: phobic postural vertigo].* Nervenarzt, 2003. **74**(10): p. 911-4.
84. Yagi, C., et al., *Subtypes of Persistent Postural-Perceptual Dizziness.* Front Neurol, 2021. **12**: p. 652366.
85. Teh, C.S. and N. Prepageran, *The impact of disease duration in persistent postural-perceptual dizziness (PPPD) on the quality of life, dizziness handicap and mental health.* J Vestib Res, 2022. **32**(4): p. 373-380.
86. Holle, D., et al., *Persistent Postural-Perceptual Dizziness: A Matter of Higher, Central Dysfunction?* PLoS One, 2015. **10**(11): p. e0142468.
87. Staab, J.P., et al., *Anxious, introverted personality traits in patients with chronic subjective dizziness.* J Psychosom Res, 2014. **76**(1): p. 80-3.
88. Teh, C.S., et al., *Neuroimaging Systematic Review in Persistent Postural-Perceptual Dizziness: The Elaborate Alterations in the Delicate Network to Remain Balanced.* Otol Neurotol, 2022. **43**(1): p. 12-22.
89. Im, J.J., et al., *A Review of Neuroimaging Studies in Persistent Postural-Perceptual Dizziness (PPPD).* Nucl Med Mol Imaging, 2021. **55**(2): p. 53-60.
90. Popkirov, S., J. Stone, and D. Holle-Lee, *Treatment of Persistent Postural-Perceptual Dizziness (PPPD) and Related Disorders.* Curr Treat Options Neurol, 2018. **20**(12): p. 50.
91. Axer, H., et al., *Multimodal treatment of persistent postural-perceptual dizziness.* Brain Behav, 2020. **10**(12): p. e01864.

Part 1

Identification of patients with CGD and PPPD

Chapter 1

Clinical characteristics and diagnostic aspects of cervicogenic dizziness in patients with chronic dizziness: A cross-sectional study

Published as: De Vestel C, Vereeck L, Van Rompaey V, Reid SA, De Hertogh W. Clinical characteristics and diagnostic aspects of cervicogenic dizziness in patients with chronic dizziness: A cross-sectional study. Musculoskelet Sci Pract. 2022 Aug;60:102559. doi: 10.1016/j.msksp.2022.102559. Epub 2022 Mar 26. PMID: 35364427.

Appendix: Available at the end of this manuscript.

Highlights:

- Increased scores on the Neck Bournemouth Questionnaire (NBQ), Joint Position Error after extension ($JPE_{after\ extension}$), and Tandem Gait tests were individually associated with higher odds of having CGD.
- The NBQ, $JPE_{after\ extension}$, and Tandem Gait had high sensitivity but low specificity for CGD.
- The combination of the NBQ and Tandem Gait tests had the highest discriminative ability to detect CGD.

1. Abstract

Background and objectives: Chronic dizziness can significantly affect quality of life, but identifying the underlying cause remains challenging. This study focuses on proprioceptive cervicogenic dizziness (CGD) and aims: (1) to compare clinical test results between patients with CGD, dizzy patients without CGD, and healthy controls; and (2) to evaluate the diagnostic value of the clinical tests for CGD in patients with chronic dizziness.

Methods: Sixty patients with chronic dizziness (18 with CGD and 42 without CGD), and 43 healthy controls underwent clinical tests evaluating neck function (mobility, proprioception, muscle function and disability), balance control, and the presence of visually induced dizziness. Data were analysed through one-way ANOVA, chi-square, independent samples t-test, and logistic regression analyses.

Results: Patients with CGD had significantly more neck pain-related disability (Neck Bournemouth questionnaire (NBQ), p=0.006), but better static (Static Balance, p=0.001) and dynamic balance (Tandem Gait, p=0.049), compared to dizzy patients without CGD. Univariable analyses revealed that increased NBQ (OR 1.05 [1.01; 1.09], p=0.017), Joint Position Error (JPE) after extension (OR 1.52 [1.00; 2.32], p=0.050), and Tandem Gait scores (OR 1.09 [1.01; 1.18], p=0.046) were individually associated with higher odds of having CGD. Their optimal cut-off level (based on the maximum Youden index) had high sensitivity but low specificity for CGD. The multivariable model, including NBQ and Tandem Gait, had fair discriminative ability (AUC = 0.74, 95% CI [0.61; 0.87]).

Conclusion: The combined use of the NBQ and Tandem Gait tests had the highest discriminative ability to detect CGD in patients with chronic dizziness.
Keywords: cervical spine; dizziness; balance; diagnosis

2. Introduction

Approximately 18.2% to 48.3% of the general population suffers from dizziness at least once a year [1-3]. In 11% of these patients [4], the dizziness is chronic in nature and can cause both physical (e.g., reduced balance) and psychological issues (e.g., fear of falling, anxiety, or depression) which have a significant negative impact on the quality of life [5, 6].

Proprioceptive cervicogenic dizziness (CGD) is one of the types of chronic dizziness [7-9]. The pathophysiological mechanism behind CGD is still uncertain. It is believed to be caused by disruption of the normal cervical proprioceptive afferent input due to cervical dysfunction (e.g., mechanical, degenerative, or inflammatory disorder). As a result of aberrant proprioceptive signals, patients with CGD have dizziness (due to central mismatch with the visual and vestibular systems) [8, 10], postural imbalance (due to abnormal cervico-collic and vestibulo-collic reflex activity) [11, 12], and are more visually dependent (due to increased reliance on visual information) [13, 14].

CGD is non-rotatory in nature, lasts for several minutes to hours, and is triggered by head movements [9]. Furthermore, research shows that patients with CGD have reduced neck and balance function compared to both non-dizzy individuals with neck pain [15, 16] and without neck pain [15-23]. Patients with CGD are also more visually dependent compared to non-dizzy individuals without neck pain [24].

Studies comparing clinical characteristics in CGD with other causes of (chronic) dizziness remain scarce [22, 25-27]. Given the lack of valid diagnostic bedside/laboratory/imaging tests for CGD [8, 10], and the overall difficulty in finding the cause of chronic dizziness [28], this information would be useful in identifying CGD in patients with chronic dizziness.

The aim of this study is to compare neck function, balance control and the presence of visually induced dizziness between patients with CGD, dizzy patients without CGD, and healthy controls using corresponding clinical tests, and to investigate whether these clinical tests have diagnostic value to detect CGD in patients with chronic dizziness.

3. Methods

3.1. Design and setting

A cross-sectional study was conducted in the M^{2}OCEAN laboratory of the Antwerp University Hospital, from March 2019 to July 2020. Ethical approval was obtained from the Medical Ethics Committees of the Antwerp University Hospital (reference number 18/586).

The STROBE Statement checklist for cross-sectional studies was used for reporting the study.

3.2. Participants

Consecutive patients attending the Department of Otorhinolaryngology at the Antwerp University Hospital and two general hospitals (AZ Klina, Brasschaat and AZ Sint-Jozef, Malle) were assessed for study eligibility by an Ear-Nose-Throat (ENT) specialist. Patients provided medical history, using the 'SO STONED method' [29], and underwent a micro-otoscopic, vestibular (including video head impulse, sinusoidal harmonic acceleration, and binaural bithermal caloric testing), and audiometric assessment. Inclusion criteria were: (1) Dutch speaking; (2) minimum 18 years old; and (3) suffering from chronic non-rotatory dizziness (≥3 months). Patients were excluded in the presence of: (1) an acute vestibular disorder (e.g., BPPV, or vestibular neuritis); (2) balance problems which were not dizziness-related (e.g., lower extremity musculoskeletal disorder); (3) dizziness that was likely attributed to untreated / non-medically stabilised heart or metabolic disorders, hormonal changes, vasovagal syncope, hyperventilation, substance misuse, or acute mental disorders; or (4) a severe visual impairment which could not be corrected, e.g., by wearing glasses.

Healthy controls (being non-dizzy) were recruited by the MOVANT research team in the direct (employees) or indirect (family and friends) environment of the University of Antwerp. Two additional exclusion criteria were imposed for the controls: (1) history or current presence of rotatory dizziness; and (2) frequent episodes of non-rotatory dizziness (more than one episode in three months).

3.3. Diagnosis of proprioceptive cervicogenic dizziness (CGD)

If the eligible patient met the criteria of CGD, the (additional) diagnosis of CGD was made by the ENT specialist: (1) dizziness provoked by head positions; and (2) temporal relationship between intensity of dizziness and neck pain [8, 10].

3.4. Variables

Detailed information on the content, application and clinimetric properties of the measurement tools used in this study can be found in **APPENDIX**.

3.4.1. Descriptive variables

Age, gender, dizziness duration, presence of chronic neck pain (> 3 months) (yes/no), and *ENT diagnosis* were collected from patient's medical record.

The *Dizziness Handicap Inventory scale (DHI)* evaluates dizziness related emotional (9 items), physical (7 items), and functional disability (9 items). All 25 items were rated on an ordinal 3-level scale (‘no’ = 0; ‘sometimes’ = 2; ‘yes’ = 4 points). The total score was calculated (0 = no disability; 100 = maximal disability) [30].

The *Hospital Anxiety and Depression Scale (HADS)* consists of seven anxiety-related (HADS-A) and seven depression-related questions (HADS-D). For each question, the participant had to indicate on an ordinal 4-level scale (0-3) which statement was the closest to how he/she had been feeling the past week. The HADS-A en HADS-D total scores were calculated separately (0 = not present; 21 = maximally present) [31].

3.4.2. Clinical variables on neck function

The *Neck Bournemouth Questionnaire (NBQ)* evaluates the impact of neck pain on physical, functional, and emotional domain. A total of seven items had to be rated on a 0 to 10 numeric rating scale. The total score was calculated (0 = no disability; 70 = maximal disability) [32].

Cervical range of motion (CROM) (in degrees) was assessed using a remote sensor attached to a headband worn by the participant. The participant was asked to sit in a chair and maximally flex, extend, and rotate the head left and right six times in each direction (without exceeding pain limits). Data were wirelessly sent to the computer software programme (NeckSmart®). The mean CROM scores of six repetitions in each of the four movement directions were calculated.

Joint position error (JPE) (in degrees) is a measure of the accuracy of the cervical proprioceptive afferents. JPE was evaluated with the head-to-neutral head position repositioning test (HRA-to-NHP) using the same test materials as for the CROM evaluation. The participant was blindfolded with opaque goggles, and instructed to reposition the head to his/her neutral head position from maximal flexion, extension, and rotation left and right, six times in each direction (without exceeding pain limits). The mean JPE scores (i.e., mean deviations in degrees from the neutral position), based on six repetitions in each of the four movement directions, were calculated.

The *craniocervical flexion test (CCF)* assesses the activation and isometric endurance of the deep cervical flexors. A pressure biofeedback unit (PBU; Stabilizer™; Chattanooga Group Inc., Hixson, TN, USA) is placed behind the patient's neck and inflated to a baseline of 20mmHg. From this baseline, the patient had to perform and maintain five consecutive stages of increasing craniocervical flexion (i.e., 22-24-26-28-30 mmHg). Progression to the next stage was done when the current stage could be performed at least 3 times for 10 seconds without substitution strategies and with minimal activity of the superficial neck muscles, which were both evaluated by observation and palpation. The CCF was performed as described in the literature [33], using the same criteria for disturbed activation and/or endurance of the deep cervical flexors [33]. The highest stage that could be correctly performed and maintained (in mmHg) was retained and dichotomised for analysis (≥ 26 mmHg = normal; ≤ 24 mmHg = abnormal).

3.4.3. Clinical variables on balance control

Static balance was assessed during four poses (i.e., feet side-by-side with Jendrassik maneuver, standing on foam with Jendrassik maneuver, heel-to-toe tandem stance, and standing on one leg). Each pose was held non-stop for 30 seconds and was performed both with eyes open and eyes closed. A maximum of three attempts was allowed for each pose, but only the best score was retained for data analysis. The total static balance score is the sum of the best scores on the eight balance tests, with a maximum score of 240 seconds (120 seconds for eyes open and 120 for eyes closed) indicating normal balance function [34].

Dynamic balance was assessed through the *Timed-Up and Go test (TUG), Tandem Gait* and *Functional Gait Assessment (FGA)*. For the TUG, the time (in seconds) needed to perform the test was considered, and for the Tandem Gait, the number of correctly performed steps (with a maximum of 20 steps) [34]. High total score for FGA mirrors good dynamic balance control (0 = impaired balance; 30 = normal balance) [35].

3.4.4. Clinical variable on visually induced dizziness

Visually induced dizziness was assessed using the *Visual Vertigo Analogue Scale (VVAS) questionnaire*. Patients had to indicate how dizzy they felt in nine recognisable visually provoking situations by marking off a ten centimetre anchored line. The total VVAS score was converted to a percentage (0% = no visually induced dizziness; 100% = maximal visually induced dizziness) [36].

3.5. Data sources and measurement

An accredited physiotherapist (CDV), master in rehabilitation sciences, who had been trained in advance for the study protocol, collected the variables during a 2.5-hour examination (per participant).

The variables were tested in strict order, starting with the questionnaires, followed by the clinical balance, neck and visually induced dizziness tests. Fixed rest breaks between and during the tests were provided, as well as additional breaks if a clinical test caused or increased dizziness. The next test was not started until the participants' symptoms had returned to baseline level.

3.6. Blinding

The patient's diagnosis was only communicated to the physiotherapist after all patients had completed the study tests. The physiotherapist could not be blinded to the healthy controls.

3.7. Data management

A management plan for newly collected data was composed before the start of the study. The pseudonymised data were collected in an SPSS file, stored on a secure server property of the University of Antwerp and only accessible to the research team.

3.8. Statistical analyses

Quantitative variables were described by means and standard deviations, whereas categorical variables were presented as frequencies and percentages. Normality of the data was evaluated using Kolmogorov-Smirnov tests.

Clinical variables were compared between the three groups. For continuous variables, one-way ANOVA tests were used followed by a post-hoc analysis and Tukey correction for multiple testing when p value was lower than the Bonferroni cut-off (i.e., $p < 0.003$, calculated through 0.05 / 15 comparisons). To compare dizziness-related variables between dizzy patients with and without CGD, independent samples t-tests were used. Categorical variables were compared using chi-square ($\chi 2$) tests. For all analyses, with the exception of the multiple testing-adjusted ANOVA tests mentioned above, a significance level was set at $p < 0.05$.

The diagnostic value of the clinical tests for CGD was evaluated between patients with and without CGD. A univariable logistic regression was performed first. The optimal cut-offs (through maximisation of the Youden index, i.e., sensitivity+specificity-1) with corresponding sensitivity and specificity were calculated. Subsequently, a multivariable logistic model was fitted, starting from the main predictors of CGD emerging from the univariable analysis ($p<0.10$), using a stepwise forward model building strategy. Receiver operating characteristic (ROC) curves were plotted for the variables of the final multivariable logistic model. The area under the receiver operating curve (AUC) was obtained, and interpreted as follows: AUC of 90-100 = excellent, 80-90 = good, 70-80 fair, 60-70 poor, and 50-60 fail [37].

Analyses were performed using the software package of IBM SPSS statistics Version 27.0. (Armonk, NY: IBM Corp. Released 2020) [38] and R version 4.0.2 (R Core Team 2020).

4. Results

4.1. Participants

Seventy-four patients with chronic dizziness were referred for participation. Nine refused to participate for the following reasons: (complete) reduction of dizziness complaints with medication and/or physical therapy (2 patients), personal reasons (3 patients), and COVID outbreak (4 patients). One patient did participate in the study but had to be excluded afterwards because of unreliable test results due to disturbing background noise near the laboratory during the testing.

Of the remaining 60 patients (mean age 57.25 ± 12.9), 18 received the diagnosis of CGD. In dizzy patients without CGD, the following primary diagnoses were determined: persistent postural-perceptual dizziness (25 patients), vestibular hypofunction (4 patients), multiple sensory deficits (3 patients), vestibular migraine (3 patients), Meniere's disease (1 patient), bilateral vestibulopathy (1 patient), and mal de débarquement syndrome (1 patient). In four patients the dizziness cause was unknown.

For the control group, data from 43 participants (mean age 57.63 ± 16.9) were analysed.

4.2. Sample characteristics

Patients had significantly more *chronic neck pain* than controls. Chronic neck pain was present in all patients with CGD (as chronic neck pain was a diagnostic criterion for CGD), and in 52.4% of dizzy patients without CGD. In controls, this percentage was much lower (20,9%).

Anxiety and depression levels were also significantly higher for patients compared to healthy controls. There were, however, no differences in anxiety and depression levels between dizzy patients with and without CGD.

The *dizziness-related variables* were not significantly different between dizzy patients with and without CGD.

Age and *gender* were not significantly different between the three groups.

TABLE 1 shows the descriptive data results for all participants.

Table 1. *Description of the three study groups, and comparison between them* [a, b]

	Mean ± SD or number (%)			Statistical analyses (p-values)			
Variables (measurement tool, unit)	**With CGD (n = 18)**	**Without CGD (n = 42)**	**Healthy (n = 43)**	**3-group comparison**	**With CGD vs without CGD**	**With CGD vs healthy**	**Without CGD vs healthy**
Age (years)†	57.4 ± 11.4	57.2 ± 13.6	57.6 ± 16.9	0.990 †			
Female	9 (50.0)	25 (59.5)	21 (48.8)	0.584 §			
Presence of chronic neck pain (> 3 months)	18 (100)	22 (52.4)	9 (20.9)	**<0.001** § ***	**<0.001** § ***	**<0.001** § ***	**0.003** § *
Dizziness duration (years)†	6.5 ± 6.9	6.4 ± 5.4			0.949 ‡		
Dizziness-related disability (DHI, 0-100)†	46.8 ± 19.8	41.9 ± 18.4			0.356 ‡		
Anxiety (HADS $_{anxiety}$, 0-21)†	5.6 ± 2.8	7.3 ± 4.3	3.3 ± 2.2	**<0.001** † ***	0.144 ¶	**0.042** ¶ *	**<0.001** ¶ ***
Depression (HADS $_{depression}$, 0-21)†	5.1 ± 3.8	6.0 ± 3.3	1.9 ± 2.4	**<0.001** † ***	0.503 ¶	**0.001** ¶ *	**<0.001** ¶ ***

[a] ANOVA test (†), Independent samples t-test (‡), Chi-squared test (§), post-hoc analysis with Tukey correction (¶)

[b] p<0.05 (*) and p<0.001 (***)

Abbreviations: CGD = cervicogenic dizziness; DHI = Dizziness Handicap Inventory; HADS = Hospital Anxiety and Depression Scale; SD = standard deviation

4.3. Comparison of the clinical cervical, balance and visually induced dizziness test results between patients with CGD, dizzy patients without CGD and healthy controls

4.3.1. Comparison of the clinical cervical test results between the three study groups

Overall, cervical spine function was reduced in patients compared to healthy controls. For *neck pain-related disability* and *deep neck flexor endurance*, the scores were significantly lower in patients compared to healthy controls.

Between the patient groups, *neck pain-related disability* was significantly higher in patients with CGD compared to dizzy patients without CGD. For *deep neck flexor endurance*, there were no significant differences between dizzy patients with and without CGD.

The *CROM* and *JPE scores* were not significantly different between the three groups.

For two dizzy patients without CGD and one healthy control, data on joint position error could not be captured due to technical problems with the measuring device.

Results on the cervical tests for all participants are shown in **TABLE 2**.

Table 2. *Comparison of the clinical cervical test results between the three study groups* [a, b]

	Mean ± SD or number (%)			Statistical analyses (p-values)			
Variables (measurement tool, unit)	**With CGD (n = 18)**	**Without CGD (n = 42)**	**Healthy (n = 43)**	**3-group comparison**	**With CGD vs without CGD**	**With CGD vs healthy**	**Without CGD vs healthy**
Neck pain-related disability (NBQ, 0-70)	24.8 ± 14.0	14.0 ± 15.2	6.6 ± 6.8	**<0.001** † **	**0.006** ¶ *	**<0.001** ¶ ***	**0.016** ¶ *
CROM flexion (°)	49.9 ± 12.3	49.5 ± 11.1	52.5 ± 10.4	0.410 †			
CROM extension (°)	49.1 ± 10.6	50.1 ± 12.3	57.5 ± 13.2	0.009 †			
CROM rotation left (°)	64.0 ± 11.1	64.4 ± 13.5	67.4 ± 12.3	0.466 †			
CROM rotation right (°)	60.9 ± 12.9	63.0 ± 14.2	64.5 ± 11.7	0.601 †			
JPE after flexion (°)	2.8 ± 1.5	3.6 ± 2.2	2.4 ± 1.4	0.011 †			

JPE after extension (°)	3.4 ± 1.2	2.6 ± 1.4	3.2 ± 1.4	0.063 †			
JPE after rotation left (°)	2.3 ± 1.0	2.7 ± 2.4	2.4 ± 1.2	0.663 †			
JPE after rotation right (°)	3.4 ± 3.0	3.7 ± 3.1	3.0 ± 1.8	0.468 †			
Normal deep neck flexor endurance, ≥ 26 (CCF, mmHg)	7 (38.9)	19 (45.2)	31 (72.1)	**0.014** § *	0.649 §	**0.015** § *	**0.012** § *

[a] ANOVA test (†), Independent samples t-test (‡), Chi-squared test (§), post-hoc analysis with Tukey correction (¶)
[b] ANOVA Bonferroni cutoff: p<0.003 (**); other tests: p<0.05 (*) and p<0.001 (***)
Abbreviations: # = number; CROM = cervical range of motion; JPE = joint position error; TRPs = trigger points; CCF = craniocervical flexion test; CGD = cervicogenic dizziness; NBQ = neck Bournemouth questionnaire; SD = standard deviation; VRS = verbal rating scale

4.3.2. Comparison of the clinical balance test results between the three study groups

Overall, *static* and *dynamic balance* were reduced in patients compared to healthy controls.

Static balance was significantly more reduced in dizzy patients without CGD compared to patients with CGD and healthy controls. For *dynamic balance*, results depend on the measuring method.

Results on the balance tests for all participants are shown in **TABLE 3**.

Table 3. *Comparison of the clinical balance test results between the three study groups* [a, b, c]

	Mean ± SD			Statistical analyses (p-values)			
Variables (measurement tool, unit)	**With CGD (n = 18)**	**Without CGD (n = 42)**	**Healthy (n = 43)**	**3-group comparison**	**With CGD vs without CGD**	**With CGD vs healthy**	**Without CGD vs healthy**
Static balance (four poses, 0-240 sec)	173.7 ± 52.3	164.0 ± 57.6	201.7 ± 30.6	**0.001** † **	**0.001** ¶ *	0.092 ¶	**0.001** ¶ *
Dynamic balance (TUG, sec)	7.6 ± 2.1	8.2 ± 2.9	6.7 ± 1.4	0.012 †			
Dynamic balance (Tandem gait, # steps)	16.7 ± 6.4	12.1 ± 8.3	17.1 ± 5.5	**0.002** † **	**0.049** ¶ *	0.975 ¶	**0.003** ¶ *

Dynamic balance (FGA, 0-30)	23.6 ± 3.4	23.1 ± 5.4	28.1 ± 2.2	**<0.001** † **	0.919 ¶	**<0.001** ¶ ***	**<0.001** ¶ ***

[a] ANOVA test (†), post-hoc analysis with Tukey correction (¶)
[b] ANOVA Bonferroni cutoff: p<0.003 (**); other tests: p<0.05 (*) and p<0.001 (***)
[c] Static balance = sum of Romberg Jendrassik maneuver, standing on foam with Jendrassik maneuver, heel-to-toe tandem stance and standing on one leg, with eyes open and eyes closed
Abbreviations: BMI = body mass index; CGD = cervicogenic dizziness; DHI = Dizziness Handicap Inventory; HADS = Hospital Anxiety and Depression Scale; NP = neck pain; SD = standard deviation; TUG = Timed-Up and Go test

4.3.3. Comparison of the clinical visually induced dizziness test results between the three study groups

Patients had significantly more *visually induced dizziness* compared to healthy controls. However, no significant differences between dizzy patients with and without CGD were found.

Results on the visually induced dizziness test for all participants are shown in **TABLE 4**.

Table 4. *Comparison of the clinical visually induced dizziness test results between the three study groups* [a, b]

	Mean ± SD			Statistical analyses (p-values)			
Variables (measurement tool, unit)	**With CGD (n = 18)**	**Without CGD (n = 42)**	**Healthy (n = 43)**	**3-group comparison**	**With CGD vs without CGD**	**With CGD vs healthy**	**Without CGD vs healthy**
Visually induced dizziness (VVAS 0-100 %)	30.9 ± 17.0	27.4 ± 23.3	1.6 ± 3.9	**<0.001** † **	0.741	**<0.001** ¶ ***	**<0.001** ¶ ***

[a] ANOVA test (†), post-hoc analysis with Tukey correction (¶)
[b] ANOVA Bonferroni cutoff: p<0.003 (**); other tests: p<0.05 (*) and p<0.001 (***)
Abbreviations: VVAS = Visual Vertigo Analogue Scale; SD = standard deviation

4.4. Diagnostic value of the clinical neck, balance and visually induced dizziness tests to detect CGD in patients with chronic dizziness

For a one-unit increase in the NBQ, JPE after extension, or Tandem Gait scores, the odds of having CGD in patients with chronic dizziness were expected to increase by a factor of respectively 1.05 (95% CI [1.01; 1.09], p=0.017), 1.52 (95%

CI [1.00; 2.32], p=0.050) and 1.09 (95% CI [1.00; 1.18], p=0.046). **TABLE 5** presents the results of the univariable logistic regression.

Table 5. *Univariable logistic regression of the cervical, balance and visually induced dizziness tests for the prediction of CGD* [a]

Measurement tools	estimate	standard error	OR (95% CI)	p-value
Neck pain-related disability (NBQ, 0-70)	0.047	0.020	1.05 [1.01; 1.09]	**0.017 ***
CROM flexion (°)	0.004	0.025	1.00 [0.96; 1.05]	0.882
CROM extension (°)	-0.008	0.024	0.99 [0.95; 1.04]	0.751
CROM rotation left (°)	-0.003	0.022	1.0 [0.96; 1.04]	0.908
CROM rotation right (°)	-0.011	0.020	0.99 [0.95; 1.03]	0.586
JPE after flexion (°)	-0.227	0.166	0.80 [0.58; 1.10]	0.172
JPE after extension (°)	0.421	0.215	1.52 [1.00; 2.32]	**0.050 ***
JPE after rotation left (°)	-0.118	0.176	0.89 [0.63; 1.26]	0.502
JPE after rotation right (°)	-0.032	0.099	0.97 [0.80; 1.18]	0.749
Deep neck flexor endurance (CCF, 20-30 mmHg)	-0.096	0.181	0.91 [0.64; 1.30]	0.533
Static balance (four poses, 0-240 sec)	0.003	0.005	1.00 [0.99; 1.01]	0.535
Dynamic balance (TUG, sec)	-0.091	0.121	0.91 [0.72; 1.16]	0.451
Dynamic balance (Tandem gait, # steps)	0.084	0.042	1.09 [1.01; 1.18]	**0.046 ***

Dynamic balance (FGA, 0-30)	0.019	0.060	1.019 [0.91; 1.15]	0.747
Visually induced dizziness (VVAS 0-100 %)	0.008	0.013	1,008 [0.98; 1.03]	0,564

[a] p<0.10 (*)
Abbreviations: CCF = craniocervical flexion test; CI = confidence interval; CROM = cervical range of motion; JPE = joint position error; NBQ = Neck Bournemouth Questionnaire; OR = odds ratio; TRPs = trigger points; TUG = Timed-Up and Go test; VVAS = Visual Vertigo Analogue Scale

The NBQ (AUC = 0.72, 95% CI [0.58; 0.88]) and JPE after extension (AUC = 0.70, 95% CI [0.57;0.83]) had fair discriminative value, and the Tandem Gait (AUC = 0.65, 95% CI [0.50; 0.79]) poor discriminative value. The optimal cut-off levels of the NBQ, JPE after extension, and Tandem Gait resulted in very accurate detection of CGD (sensitivity ranged between 0.83 – 0.94), but the false positive rates were high as well (specificity ranged between 0.44 - 0.48). The optimal cut-offs of these clinical tests with corresponding sensitivity and specificity are presented in **TABLE 6**.

Table 6. *Optimal cut-offs of the clinical tests emerging from the univariable analysis in detecting CGD* [a]

	Optimal cut-off level [a]	**Sensitivity**	**Specificity**
NBQ	≥ 7.50	0.94	0.45
JPE $_{\text{after extension}}$ (°)	≥ 2.13	0.94	0.44
Tandem Gait (# steps)	≥ 10.50	0.83	0.48

[a] Optimal cut-off was calculated through maximising the Youden index (i.e., sensitivity + specificity - 1)
Abbreviations: **NBQ** = Neck Bournemouth Questionnaire; **JPE**= joint position error

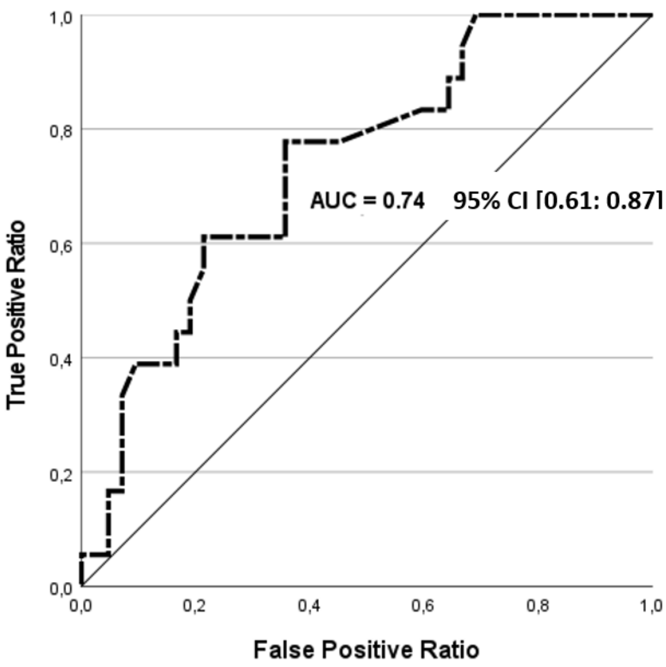
The multivariable model was fitted as described in the methods section. The final model included the variables neck pain-related disability (NBQ) and Tandem Gait as main predictors of CGD. The regression equation was [a] :

$$\text{Exp}(b_0 + b_1 * \text{NBQ} + b_2 * \text{Tandem Gait}) / (1 + \text{Exp}(b_0 + b_1 * \text{NBQ} + b_2 * \text{Tandem Gait}))$$

[a] b_0 = -2.8 (SE = 0.88); b_1 = 0.04 (SE = 0.02); b_2 = 0.07 (SE = 0.05)
Abbreviations: $\mathbf{b_0}$ = constant/intercept; $\mathbf{b_1}$ = regression coefficient for NBQ; $\mathbf{b_2}$ = regression coefficient for Tandem Gait; **NBQ** = Neck Bournemouth Questionnaire

Through ROC analysis (**FIGURE 1**), the discriminative ability of the multivariable model was evaluated and showed to be superior (AUC = 0.74, 95% CI [0.61; 0.87]) compared to the individual discriminative ability of JPE after extension, NBQ, and Tandem Gait.

__Figure 1.__ ROC curve of the multivariable logistic regression model [a]



[a] Abbreviations: **AUC** = area under the receiver operating curve; **CI** = confidence interval

5. Discussion

A first observation following from our results is that patients with chronic dizziness had more neck complaints compared to healthy controls. For patients with CGD, the presence of neck dysfunction is inherent to the pathology of CGD [10]. For dizzy patients without CGD, neck complaints often occur secondary to persistent dizziness [39]. One example is the 'head on trunk stiffness reaction' [40, 41], where patients tend to hold their head unnaturally still in order to reduce the dizziness and increase their gaze control.

A second observation is that patients with chronic dizziness had reduced balance control compared to healthy controls. This is in line with the literature which confirms that a perturbation of the proprioceptive information (as in patients with CGD) [15, 20] or vestibular information (as in most dizzy patients without CGD) may negatively affect balance [42, 43].

The third observation was the presence of visually induced dizziness in both dizzy patients with and without CGD. This finding adds to the literature that sensory reweighting towards the visual system, aimed at restoring balance control, does not only occur in patients with a vestibular dysfunction [44, 45], but also in patients with CGD.

In general, the results show that patients with and without CGD differ only very slightly on the clinical neck, balance, and visually induced dizziness tests. The literature confirms that there is overlap in the clinical fingerprint of many types of chronic dizziness [46]. Long-term dizziness is the result of a maladaptation process, and one often sees similar maladaptations occurring independently of the specific underlying cause (e.g., avoidance behaviour, head-on-trunk stiffness reaction, increased visual dependence, or psychological problems) [47]. It should also be noted that the clinical tests selected for this study are not CGD-specific, which may increase the overlap in results on the tests between dizzy patients with and without CGD. The rationale behind this selection is that these tests can be easily performed in clinical practice without the need for specific equipment. In contrast, CGD-specific tests such as the Smooth Pursuit Neck Torsion Test (SPNT) and Cervical Torsion Test (CTT) require videonystagmography [8, 25, 48], which reduces the general applicability.

For evaluation of the diagnostic value of the clinical tests, only the results of patients with chronic dizziness were considered. The univariable analyses showed that only higher JPE after extension, higher NBQ scores, and better Tandem Gait scores were individually significantly associated with higher odds of having CGD in patients with chronic dizziness. Each of these will be discussed below.

For JPE scores (with exception of the JPE after extension), differences between groups were limited. The literature, while inconclusive, shows a tendency for larger JPE in patients with (chronic) neck pain compared to healthy controls, especially in patients with whiplash trauma [49-51]. Patients with CGD have also been found to have increased JPE compared to patients with BPPV and healthy controls [19, 25]. The limited JPE differences in our study can be due to the small sample sizes in the three study groups. Another contributing factor may be that disturbed vestibular input in patients without CGD can also negatively affect the cervical joint position sense [52, 53]. The reason why JPE after extension could distinguish patients with CGD from those without CGD remains unclear. We suggest it may be linked with extension being the most provocative direction for CGD [54].

The NBQ scores were high in patients with CGD. Neck pain is a diagnostic criterion in CGD and has usually been present for a longer period of time than in dizzy patients without CGD [10]. This may explain the higher impact of neck pain on daily life, and thus the high NBQ scores for CGD patients.

For the Tandem Gait, patients with CGD scored better than dizzy patients without CGD. A possible reason for this is that the head is kept still during this test. While head movements are the main trigger for CGD [25, 55], patients with vestibular disorder may already feel imbalanced in the normal upright position. In contrast, scores on the FGA test, which includes head movements [35], did not differ between patients with and without CGD.

The specificity and cut-off levels of JPE after extension, NBQ, and Tandem Gait were low compared to the literature [32, 56-58]. This could be because other studies were looking at different study groups (e.g., patients with neck pain, or healthy persons). Our results indicate that
better JPE after extension, better NBQ, and worse Tandem Gait scores are reliable in ruling out the presence of CGD, but are not reliable diagnostic tools for detecting CGD in patients with chronic dizziness.

Multivariable analysis shows that the combination of the NBQ and Tandem Gait has more discriminative power for CGD than any of the tests separately. This indicates the possible added value to use a combination of tests.

5.1. Limitations

A first limitation is the rather limited sample size. A second possible limitation is that in order to measure cervical sensorimotor control, we used the head-to-neutral head position repositioning test. However, this test may be biased by interference from body systems other than the proprioceptive system, such as the vestibular system or centrally generated motor commands [59-61]. To eliminate the influence of the vestibular system in the future, the trunk instead of the head should be returned to the starting position [62]. A third limitation may be that the physiotherapist was not blinded to the healthy controls. However, we believe that the effect on the study results is minimal because in clinical practice focus lies on how CGD can be identified in patients with chronic dizziness, and because the physiotherapist was still blinded for the diagnosis in patients.

5.2. Clinical implications and further research

The clinical tests are easy and fast to perform during general examination in clinical practice. The high sensitivity of the clinical tests for CGD show that these clinical tests can be used to exclude the diagnosis of CGD. To confirm the diagnosis of CGD in patients with chronic dizziness, tests targeted at CGD should be used (e.g., SPNT, CTT) [8, 25, 48].

Since this study shows that it is still important to also perform CGD-specific tests to confirm the diagnosis of CGD, further research into clinical versions of these tests (i.e., not requiring the use of specific equipment such as videonystagmography/ video-oculography) is recommended [63, 64].

Lastly, as there are no fixed diagnostic criteria for CGD, the clinical presentations of patients with CGD from this study may differ slightly from those in other studies. For example, the presence of chronic neck pain and dizziness was a prerequisite for CGD in our study, which made it more difficult for our patients to remember when the dizziness and neck pain were linked in time [10]. More uniformity in the diagnostic criteria for CGD across studies is needed to determine which clinical tests have the most diagnostic value.

6. Conclusion

Results show that larger JPE after extension, higher NBQ scores, and better Tandem Gait scores were individually associated with higher odds of having CGD in patients with chronic dizziness. Their sensitivity for CGD was high, but their specificity low. The combined use of NBQ and Tandem Gait had the highest discriminative ability to detect CGD in patients with chronic dizziness.

7. Appendix

Table 7. Content, application and clinimetric properties of the measurement tools

Variable	Measurement tool	Measurement methods
DESCRIPTIVE VARIABLES		
Self-perceived dizziness-related disability (0-100)	Dizziness Handicap Inventory (DHI) questionnaire	Impact of dizziness on patients' emotional well-being (9 items), and physical (7 items) and functional (9 items) capacity were evaluated. All 25 items had to be rated on an ordinal 3-level scale ('no' = 0; 'sometimes' = 2; 'yes' = 4 points). The total maximum score was 100 points (0 = no disability; 100 = maximal disability). Based on the total score, a division can be made between patients with mild (0-30), moderate (31-60), and severe disability (61-100). The Dutch version of the DHI shows excellent internal consistency (Cronbach's alpha 0,81-0,93) and test-retest reliability (ICC 0,94-0,99), and the measurement error is below 10% of the scoring range ([-9; 7] 95% CI) [30, 65].
Anxiety (0-21) and depression (0-21)	Hospital Anxiety and Depression Scale (HADS) questionnaire	Seven anxiety (HADS-A) and seven depression (HADS-D) related questions were presented alternately. For each question, the participant had to indicate on an ordinal 4-level scale (0-3) which statement was the closest to how he/she had been feeling the past week. The score for anxiety and depression was calculated separately. The maximum total score for both the HADS-A and HADS-D was 21 points (0 = not present; 21 = maximally present). The degree of anxiety and depression can be classified as normal (0-7), or mildly (8-10), moderately (11-14) or severely elevated (15-21). The HADS shows sufficient internal consistency (Cronbach's alpha for HADS-A = 0,68-0,93, and Cronbach's alpha for HADS-D = 0,67 – 0,90), and good sensitivity and specificity (AUCs ≈ 0.80 at a cut-off score of ≥8) [31].
CLINICAL VARIABLES		
a. Neck-related variables		
Self-perceived neck pain-related disability (0-70)	Neck Bournemouth Questionnaire (NBQ)	Impact of neck pain on physical, functional and emotional domain were evaluated. A total of seven items had to be rated on a numeric rating scale (0-10). The maximum total score was 70 (0 = no disability; 70 = maximal disability). The test shows high test-retest reliability (ICC = 0,65) and internal consistency (Cronbach's alpha = 0,787 – 0,92) [32].
Cervical range of motion (CROM) (degrees)	Cervical Range Of Motion test	The participant, wearing a headband on his/her head to which a sensor is attached, was instructed to sit on a chair with the trunk firmly against the backrest, the head in its neutral position and the hands resting on the lap. Consecutively, the participant was asked to maximally flex, extend, and rotate the head left and right six times in each direction (without exceeding pain limits). The degree of range of motion in each movement direction was captured by the sensor and wirelessly sent to the computer software programme (NeckSmart®). For data-analysis, the mean CROM scores of six repetitions were calculated for flexion, extension, and left and right rotation. Normative values for cervical range of motion are provided by Swinkels et al. 2014 [66].

Joint position error (JPE) (degrees)	Head-to-neutral head position repositioning test (HRA-to-NHP)	The same test materials and starting position were used as for the CROM evaluation. For the HRA-to-NHP test, however, the participant was blindfolded with opaque goggles. Participants were instructed to reposition the head to their neutral head position from maximal flexion, extension, and rotation left and right, six times in each direction (without exceeding pain limits). Between each trial the researcher manually repositioned the head to the original neutral position. For data-analysis, the mean deviations in degrees from the neutral position (i.e., mean joint position error (JPE) scores) of six repetitions were calculated for flexion, extension, and left and right rotation. The HRA-to-NHP has sufficient intrarater reliability (ICC = 0,35 – 0,82) [67] and is recommended in differentiating asymptomatic persons from patients with neck pain (p=0.001, ANOVA) [68]. Normative values for head repositioning accuracy are provided by Dugailly et al. 2015 [69].
Deep neck flexor endurance (mmHg)	CranioCervical Flexion test (CCF)	The craniocervical flexion test (CCF) assesses the activation and isometric endurance of the deep cervical flexors. A pressure biofeedback unit (PBU; Stabilizer™, Chattanooga Group Inc., Hixson, TN, USA) is placed behind the patient's neck and inflated to a baseline of 20mmHg. From this baseline, the patient had to perform and maintain five consecutive stages of increasing craniocervical flexion (i.e., 22-24-26-28-30 mmHg) (i.e., a gentle nodding movement on the axis of rotation of motion segment C0-C1). Progression to the next stage was done when the current stage could be performed at least 3 times for 10 seconds without substitution strategies and with minimal activity of the superficial neck muscles, which were both evaluated by observation and palpation. The CCF was performed as described in the literature [33], using the same criteria for disturbed activation and/or endurance of the deep cervical flexors [33]. The highest stage that could be correctly performed and maintained (in mmHg) was retained and dichotomised for analysis (≥ 26 mmHg = normal; ≤ 24 mmHg = abnormal) The CCF test has high construct validity (linear mixed mode, F = 239,04; df = 36; p < 0,0001) [70], and high interrater (ICC = 0,91) [71] and intrarater reliability (ICC = 0,99) [72].

b. Balance-related variables

Static balance (seconds)	Static balance test	The static balance test was performed conform to the guidelines of Vereeck et al. 2008 [34]. The participant had to keep his/her balance during different static poses, which were: (1) feet side-by-side on a firm surface with the arms horizontally in front of the body and hands grasping each other (Romberg with Jendrassik maneuver), (2) feet 5 cm apart on a foam pad (NeuroCom International Inc., Clackamas, USA; 60kg/cm3 medium density; 45 x 45 x 12 cm) with the arms horizontally in front of the body and hands grasping each other (standing on foam with Jendrassik maneuver), (3) heel-to-toe tandem stance, and (4) standing on one leg. For all poses, balance had to be kept non-stop for 30 seconds: first with eyes open and then with eyes closed. A maximum of three attempts was allowed for each pose, but only the best score was retained for data analysis. The total static balance score is the sum of the best scores on the eight balance poses. The maximum score is 240 seconds (120 seconds for eyes open and 120 for eyes closed) indicating normal balance function. Normative values for static balance are provided by Vereeck et al. 2008 [34].
Dynamic balance (seconds)	Timed-Up and Go test (TUG)	The TUG was performed conform the guidelines of Vereeck et al. 2008 [34]. The patient had to stand up from a chair, walk 3m, turn around, walk back to the chair and sit down again. The test should be performed quickly but without running or risking safety. Three attempts were allowed and only the best score (i.e., fastest performance) was retained. Normative values for TUG are provided by Vereeck et al. 2008 [34].

Dynamic balance (steps)	Tandem Gait	The Tandem Gait was performed conform the guidelines of Vereeck et al. 2008 [34]. The patient had to take 20 heel-to-toe steps along a straight line with eyes open but without using any walking aids or other support. Three attempts were allowed and only the highest number of correctly performed steps was retained. Normative values for Tandem Gait are provided by Vereeck et al. 2008 [34].
Dynamic balance (0-30)	Functional Gait Assessment (FGA)	The FGA is an updated version of the Dynamic Gait Index of Shumway-Cook and Woollacott, 1995 [73] . The FGA was done conform the guidelines of Wrisley et al. 2004 [35]. Briefly, participants had to perform ten walking tasks within a 30 cm wide walkway of 6 meters long. The tasks focus on speed (e.g., timed 180° turn), head movements (e.g., walking with head rotations left and right), and precision (e.g., heel-to-toe walking). Each task was rated on a four-point rating scale (0-3). The total FGA score (0 = impaired balance; 30 = normal balance) is the sum of the scores on the ten individual tasks. Normative values for FGA are provided by Walker et al. 2007 [74].
c. Variable on visually induced dizziness		
Visually induced dizziness (0-100)	Visual Vertigo Analogue Scale questionnaire (VVAS)	Dizziness sensation was evaluated in nine recognisable visually provoking situations, such as walking in a supermarket, watching television or sitting in a car. Patients had to indicate how dizzy those situations made them by marking off a ten centimetre anchored line. If patients could not make an estimation, for example because they had never done a specific activity before, they checked off the box 'not applicable'. The VVAS score was calculated as the ratio between the sum of the rated items on the anchored line, and the number of answered items. This result was then multiplied by ten to form a total percentage (0 = no visually-induced dizziness; 100% = maximal visually-induced dizziness). As there is only an English version of the VVAS available, this questionnaire was translated and adapted from its original version to the Dutch language following an established double translation method [75]. The English version of the VVAS shows good internal consistency and reliability (Cronbach's alpha = 0,94) [36].

8. References

1. Sloane, P., D. Blazer, and L.K. George, *Dizziness in a community elderly population.* J Am Geriatr Soc, 1989. **37**(2): p. 101-8.
2. Bisdorff, A., et al., *The epidemiology of vertigo, dizziness, and unsteadiness and its links to co-morbidities.* Frontiers in Neurology, 2013. **4**.
3. Neuhauser, H.K., et al., *Burden of dizziness and vertigo in the community.* Arch Intern Med, 2008. **168**(19): p. 2118-24.
4. Jayarajan, V. and D. Rajenderkumar, *A survey of dizziness management in General Practice.* J Laryngol Otol, 2003. **117**(8): p. 599-604.
5. Yardley, L., *Overview of psychologic effects of chronic dizziness and balance disorders.* Otolaryngol Clin North Am, 2000. **33**(3): p. 603-16.
6. Weidt, S., et al., *Health-related quality of life and emotional distress in patients with dizziness: a cross-sectional approach to disentangle their relationship.* BMC Health Serv Res, 2014. **14**: p. 317.
7. Magnusson, M. and E.M. Malmström, *The conundrum of cervicogenic dizziness.* Handbook of clinical neurology, 2016. **137**: p. 365-369.
8. Reiley, A.S., et al., *How to diagnose cervicogenic dizziness.* Arch Physiother, 2017. **7**: p. 12.
9. Wrisley, D.M., et al., *Cervicogenic dizziness: A review of diagnosis and treament.* Journal of Orthopaedic and Sports Physical Therapy, 2000. **30**(12): p. 755-766.
10. Knapstad, M.K., *Clinical characteristics in patients with cervicogenic dizziness: A systematic review.* Health science reports, 2019. **2**(9): p. e134.
11. Pompeiano, O., *Neck and macular labyrinthine influences on the cervical spino-reticulocerebellar pathway.* Prog Brain Res, 1979. **50**: p. 501-14.
12. Peterson, B.W. and F.J. Richmond, *Control of head movement*. 1988: New York: Oxford University Press.
13. Van Ombergen, A., et al., *Altered functional brain connectivity in patients with visually induced dizziness.* Neuroimage Clin, 2017. **14**: p. 538-545.
14. Dieterich, M., et al., *Evidence for cortical visual substitution of chronic bilateral vestibular failure (an fMRI study).* Brain, 2007. **130**(Pt 8): p. 2108-16.
15. Yahia, A., et al., *Chronic neck pain and vertigo: Is a true balance disorder present?* Ann Phys Rehabil Med, 2009. **52**(7-8): p. 556-67.
16. Alund, M., et al., *Dynamic posturography among patients with common neck disorders. A study of 15 cases with suspected cervical vertigo.* J Vestib Res, 1993. **3**(4): p. 383-9.
17. Endo, K., H. Suzuki, and K. Yamamoto, *Consciously postural sway and cervical vertigo after whiplash injury.* Spine (Phila Pa 1976), 2008. **33**(16): p. E539-42.

18. Grande-Alonso, M., et al., *Biobehavioural analysis of the vestibular system and posture control in patients with cervicogenic dizziness. A cross-sectional study.* Neurologia, 2018. **33**(2): p. 121-128.
19. Heikkila, H., M. Johansson, and B.I. Wenngren, *Effects of acupuncture, cervical manipulation and NSAID therapy on dizziness and impaired head repositioning of suspected cervical origin: a pilot study.* Man Ther, 2000. **5**(3): p. 151-7.
20. Karlberg, M., et al., *Postural and symptomatic improvement after physiotherapy in patients with dizziness of suspected cervical origin.* Arch Phys Med Rehabil, 1996. **77**(9): p. 874-82.
21. Micarelli, A., et al., *Diagnostic route of cervicogenic dizziness: usefulness of posturography, objective and subjective testing implementation and their correlation.* Disability and Rehabilitation, 2019. **43**: p. 1-8.
22. Micarelli, A., et al., *Usefulness of postural sway spectral analysis in the diagnostic route and clinical integration of cervicogenic and vestibular sources of dizziness: A cross-sectional preliminary study.* Journal of vestibular research : equilibrium & orientation, 2021.
23. Treleaven, J., G. Jull, and N. Lowchoy, *Standing balance in persistent whiplash: a comparison between subjects with and without dizziness.* J Rehabil Med, 2005. **37**(4): p. 224-9.
24. Micarelli, A., et al., *Reciprocal roles of joint position error, visual dependency and subjective perception in cervicogenic dizziness.* Somatosens Mot Res, 2020. **37**(4): p. 262-270.
25. L'Heureux-Lebeau, B., et al., *Evaluation of paraclinical tests in the diagnosis of cervicogenic dizziness.* Otology & neurotology : official publication of the American Otological Society, American Neurotology Society [and] European Academy of Otology and Neurotology, 2014. **35**(10): p. 1858-1865.
26. Treleaven, J., et al., *Comparison of sensorimotor disturbance between subjects with persistent whiplash-associated disorder and subjects with vestibular pathology associated with acoustic neuroma.* Arch Phys Med Rehabil, 2008. **89**(3): p. 522-30.
27. Williams, K., A. Tarmizi, and J. Treleaven, *Use of neck torsion as a specific test of neck related postural instability.* Musculoskeletal Science and Practice, 2017. **29**: p. 115-119.
28. Bronstein, A.M., T. Lempert, and B.M. Seemungal, *Chronic dizziness: a practical approach.* Pract Neurol, 2010. **10**(3): p. 129-39.
29. Wuyts, F.L., V. Van Rompaey, and L.K. Maes, *"SO STONED": Common Sense Approach of the Dizzy Patient.* Frontiers in surgery, 2016. **3**: p. 32-32.
30. Vereeck, L., et al., *Test-retest reliability of the Dutch version of the Dizziness Handicap Inventory.* B-ent, 2006. **2**(2): p. 75-80.

31. Bjelland, I., et al., *The validity of the Hospital Anxiety and Depression Scale. An updated literature review.* J Psychosom Res, 2002. **52**(2): p. 69-77.
32. Bolton, J.E. and B.K. Humphreys, *The Bournemouth Questionnaire: a short-form comprehensive outcome measure. II. Psychometric properties in neck pain patients.* J Manipulative Physiol Ther, 2002. **25**(3): p. 141-8.
33. Jull, G.A., S.P. O'Leary, and D.L. Falla, *Clinical assessment of the deep cervical flexor muscles: the craniocervical flexion test.* J Manipulative Physiol Ther, 2008. **31**(7): p. 525-33.
34. Vereeck, L., et al., *Clinical assessment of balance: normative data, and gender and age effects.* Int J Audiol, 2008. **47**(2): p. 67-75.
35. Wrisley, D.M., et al., *Reliability, internal consistency, and validity of data obtained with the functional gait assessment.* Phys Ther, 2004. **84**(10): p. 906-18.
36. Dannenbaum, E., G. Chilingaryan, and J. Fung, *Visual vertigo analogue scale: an assessment questionnaire for visual vertigo.* J Vestib Res, 2011. **21**(3): p. 153-9.
37. Safari, S., et al., *Evidence Based Emergency Medicine; Part 5 Receiver Operating Curve and Area under the Curve.* Emerg (Tehran), 2016. **4**(2): p. 111-3.
38. *IBM Corp. Released 2020. IBM SPSS Statistics for Windows; Version 27.0* Armonk, NY.
39. Knapstad, M.K., et al., *Neck pain associated with clinical symptoms in dizzy patients-A cross-sectional study.* Physiother Res Int, 2020. **25**(2): p. e1815.
40. Balaban, C.D., M.E. Hoffer, and K.R. Gottshall, *Top-down approach to vestibular compensation: Translational lessons from vestibular rehabilitation.* Brain Research, 2012. **1482**: p. 101-111.
41. Lacour, M. and L. Bernard-Demanze, *Interaction between Vestibular Compensation Mechanisms and Vestibular Rehabilitation Therapy: 10 Recommendations for Optimal Functional Recovery.* Front Neurol, 2014. **5**: p. 285.
42. Baydan, M., O. Yigit, and S. Aksoy, *Does vestibular rehabilitation improve postural control of subjects with chronic subjective dizziness?* PLoS One, 2020. **15**(9): p. e0238436.
43. Kundakci, B., *The effectiveness of exercise-based vestibular rehabilitation in adult patients with chronic dizziness: A systematic review.* F1000Research, 2018. **7**.
44. Agarwal, K., et al., *Visual dependence and BPPV.* J Neurol, 2012. **259**(6): p. 1117-24.
45. Pavlou, M., R.A. Davies, and A.M. Bronstein, *The assessment of increased sensitivity to visual stimuli in patients with chronic dizziness.* J Vestib Res, 2006. **16**(4-5): p. 223-31.

46. Staab, J.P., *Chronic subjective dizziness.* Continuum (Minneap Minn), 2012. **18**(5 Neuro-otology): p. 1118-41.
47. Staab, J.P. and M.J. Ruckenstein, *Expanding the differential diagnosis of chronic dizziness.* Arch Otolaryngol Head Neck Surg, 2007. **133**(2): p. 170-6.
48. Tjell, C. and U. Rosenhall, *Smooth pursuit neck torsion test: a specific test for cervical dizziness.* Am J Otol, 1998. **19**(1): p. 76-81.
49. Stanton, T.R., et al., *Evidence of Impaired Proprioception in Chronic, Idiopathic Neck Pain: Systematic Review and Meta-Analysis.* Physical Therapy, 2016. **96**(6): p. 876-887.
50. de Vries, J., et al., *Joint position sense error in people with neck pain: A systematic review.* Man Ther, 2015. **20**(6): p. 736-44.
51. de Zoete, R.M.J., et al., *Sensorimotor Control in Individuals With Idiopathic Neck Pain and Healthy Individuals: A Systematic Review and Meta-Analysis.* Arch Phys Med Rehabil, 2017. **98**(6): p. 1257-1271.
52. Strupp, M., et al., *Perceptual and oculomotor effects of neck muscle vibration in vestibular neuritis. Ipsilateral somatosensory substitution of vestibular function.* Brain, 1998. **121 (Pt 4)**: p. 677-85.
53. Karlberg, M., et al., *Vibration-induced shift of the subjective visual horizontal: a sign of unilateral vestibular deficit.* Arch Otolaryngol Head Neck Surg, 2002. **128**(1): p. 21-7.
54. Mulligan Brian, R., *Manual Therapy," Nags","Snags","MWMS" etc*. 6 ed. New Zealand. 2010: Bateson Publishing Ltd
55. Reid, S.A., et al., *Utility of a brief assessment tool developed from the Dizziness Handicap Inventory to screen for Cervicogenic dizziness: A case control study.* Musculoskeletal Science and Practice, 2017. **30**: p. 42-48.
56. De Hertogh, W.J., et al., *The clinical examination of neck pain patients: the validity of a group of tests.* Man Ther, 2007. **12**(1): p. 50-5.
57. Revel, M., C. Andre-Deshays, and M. Minguet, *Cervicocephalic kinesthetic sensibility in patients with cervical pain.* Arch Phys Med Rehabil, 1991. **72**(5): p. 288-91.
58. Howell, D.R., et al., *Dual-Task Tandem Gait and Average Walking Speed in Healthy Collegiate Athletes.* Clin J Sport Med, 2019. **29**(3): p. 238-244.
59. Kelders, W.P., et al., *Compensatory increase of the cervico-ocular reflex with age in healthy humans.* J Physiol, 2003. **553**(Pt 1): p. 311-7.
60. Victor S. Gurfinkel, M.A.L., Yuri S. Levick, *What about the So-Called Neck Reflexes in Humans?*
61. Gandevia, S.C. and D. Burke, *Does the nervous system depend on kinesthetic information to control natural limb movements?* Behavioral and Brain Sciences, 2011. **15**(4): p. 614-632.
62. Chen, X. and J. Treleaven, *The effect of neck torsion on joint position error in subjects with chronic neck pain.* Man Ther, 2013. **18**(6): p. 562-7.

63. Treleaven, J., et al., *Normative Responses to Clinical Tests for Cervicogenic Dizziness: Clinical Cervical Torsion Test and Head-Neck Differentiation Test.* Phys Ther, 2020. **100**(1): p. 192-200.
64. Daly, L., et al., *Validity of clinical measures of smooth pursuit eye movement control in patients with idiopathic neck pain.* Musculoskelet Sci Pract, 2018. **33**: p. 18-23.

Chapter 2

Comparison of Clinical Balance and Visual Dependence Tests in patients with Chronic Dizziness With and Without Persistent Postural-Perceptual Dizziness: A Cross-Sectional Study

Published as: De Vestel C, De Hertogh W, Van Rompaey V, Vereeck L. Comparison of Clinical Balance and Visual Dependence Tests in Patients With Chronic Dizziness With and Without Persistent Postural-Perceptual Dizziness: A Cross-Sectional Study. Front Neurol. 2022 May 24;13:880714. doi: 10.3389/fneur.2022.880714. PMID: 35685740; PMCID: PMC9170888.

Appendix: Available at the end of this manuscript.

Highlights:

- Scores on static and dynamic balance tests were not significantly different between dizzy patients with and without PPPD.
- While facing rotating dots, postural sway was increased in dizzy patients with PPPD, dizzy patients without PPPD, and healthy persons. The largest increase in postural sway was observed in patients with PPPD.
- A higher VVAS score was associated with the presence of PPPD (odds ratio 1.04; 95% CI [1.01; 1.07]; p=0.010).

1. Abstract

Background: The diagnosis of persistent postural-perceptual dizziness (PPPD) is primarily based on medical history taking. Research on the value of clinical balance and visual dependence tests in identifying PPPD is scarce.

Objectives: [1] to contrast clinical balance and visual dependence tests between PPPD patients, dizzy non-PPPD patients, and healthy persons; and [2] to evaluate whether these clinical tests can help to identify PPPD in patients with chronic dizziness.

Methods: Consecutive patients with chronic dizziness (38 PPPD and 21 non-PPPD) and 69 healthy persons underwent Static Balance tests, the Timed Up and Go test, the Tandem Gait test, and the Functional Gait Assessment (FGA). Visual dependence tests included the Visual Vertigo Analogue Scale (VVAS), the Rod-and-Disc test (RDT), and postural sway while facing rotating dots. Groups were compared using ANOVA with post-hoc Tukey, or independent samples t-tests. The value of the clinical tests for PPPD identification was evaluated through logistic regression and Partial Least Squares Discriminant (PLS-DA) analyses.

Results: PPPD patients had significantly higher VVAS scores than dizzy non-PPPD patients ($p=0.006$). Facing rotating dots, PPPD and dizzy non-PPPD patients had increased postural sway compared to healthy persons (PPPD versus healthy: center of pressure (COP) velocity $p<0.001$, and COP area $p<0.001$; but non-PPPD versus healthy: COP velocity $p=0.116$ and COP area $p=0.207$). PPPD patients had no significantly increased postural sway compared to dizzy non-PPPD patients. PPPD and dizzy non-PPPD patients also scored significantly worse on balance tests compared to healthy persons (PPPD versus healthy: for all balance tests $p<0.001$; non-PPPD versus healthy: FGA $p<0.001$, for all other tests $p<0.05$). Differences were insignificant in balance scores between PPPD and dizzy non-PPPD patients, or in RDT scores between the three study groups. In patients with chronic dizziness, a higher VVAS score was most associated with PPPD (odds ratio 1.04; 95% CI [1.01; 1.07]; $p=0.010$). The cross-validated (CV) PLS-DA model with all clinical tests included, had fair discriminative ability (CVerror = 47%).

Conclusion: PPPD patients were more visually dependent, but did not have worse postural balance compared to dizzy non-PPPD patients. Elevated VVAS scores characterized PPPD most in patients with chronic dizziness.

Keywords: persistent postural-perceptual dizziness, chronic dizziness, vestibular diseases, balance, visual dependence

2. Introduction

Persistent postural-perceptual dizziness (PPPD), with a prevalence of up to 20% in patients with vestibular symptoms, is among the top five most common causes of vestibular complaints reported in tertiary care hospitals [1-3]. PPPD is designated by the Bárány Society as a separate vestibular disorder and an umbrella term for four subtypes: Phobic Postural Vertigo, Space-Motion Discomfort, Visual Vertigo, and Chronic Subjective Dizziness [4].

Patients with PPPD clinically present with non-rotatory vertigo and postural imbalance, which are present almost on a daily basis. The symptoms are worsened by upright posture, active or passive movements, and visual stimuli [4]. Visual stimulation is the most characteristic aggravating factor for PPPD [5].

The pathophysiological mechanism of PPPD and its four subtypes is still uncertain [6]. It is thought to result from maladaptation to a condition that caused vestibular symptoms [e.g., a peripheral or central vestibular disorder, vestibular migraine, or psychogenic dizziness] [6]. Previous research identified altered functional brain connectivity [7, 8]: i.e., reduced between the [pre]cuneus and the premotor cortex [8], and increased in the visual cortices [9]. The former impairs the regulation of body posture and movement [10, 11], while the latter leads to increased visual dependence [12]. Excessive reliance on visual information often causes dizziness and/or postural instability in visually disturbing situations [13].

The diagnosis of PPPD is currently primarily based on medical history taking [4]. The often vague symptoms in patients with chronic dizziness tend to correlate weakly with the results of standard vestibular tests, making diagnosis difficult [14].

Several clinical tests exist in the literature that allow for evaluation of postural balance and visual dependence in patients with a vestibular disorder [13, 15]. However, it is not yet clear whether these clinical tests can be used for identifying PPPD in patients with chronic dizziness.

The aim of this study was twofold: [1] to contrast clinical balance and visual dependence tests between PPPD patients, dizzy non-PPPD patients, and healthy persons; and [2] to evaluate whether these clinical tests can help to identify PPPD in patients with chronic dizziness.

3. Materials and methods

3.1. Design and setting

This study is a cross-sectional study consisting of consecutive patients enrolled between March 2019 and July 2020, either at the Department of Otolaryngology of the Antwerp University Hospital or in one of the two participating general hospitals (AZ Klina, Brasschaat and AZ Sint-Jozef, Malle). The control group consisted of healthy persons from the direct (employees) or indirect environment (family and friends) of the MOVANT research team. The study was performed in the M²OCEAN laboratory (Multidisciplinary Motor Centre Antwerp) of the Antwerp University Hospital.

The study report is drafted conform the 'Strengthening the Reporting of Observational studies in Epidemiology (STROBE)' guidelines for cross-sectional studies [16].

3.2. Ethical considerations

Ethical approval was obtained from the Medical Ethics Committees of the Antwerp University Hospital (reference number 18/586).

3.3. Participants

Patients' eligibility was assessed by an Ear-Nose-Throat (ENT) specialist through medical history taking (using the SO STONED method [17]), and through a micro-otoscopic, a vestibular (including video head impulse, sinusoidal harmonic acceleration, and binaural bithermal caloric testing) and an audiometric assessment. The inclusion criteria were: (1) speaking the Dutch language; (2) being at least 18 years old; and (3) suffering of chronic non-rotatory vertigo and/or unsteadiness for at least 15 days per month for a minimum of 3 months. The exclusion criteria were: (1) presence of an acute vestibular disorder; (2) balance problems not due to dizziness [e.g., neurological, orthopaedic, or other medical conditions]; (3) dizziness due to untreated metabolic or cardiac disease, hormonal disturbances, vasovagal syncope, hyperventilation, acute mental problems, or substance abuse; and (4) severe visual impairment, not correctable by e.g., wearing glasses.

Eligibility of healthy persons was verified by the researcher. Their inclusion criteria were (1) speaking the Dutch language; and (2) being at least 18 years old. The exclusion criteria were: (1) history of or currently suffering from rotatory vertigo; (2) frequent episodes of non-rotatory vertigo (more than one episode in three months); (3) balance problems; and (4) severe visual impairment, not correctable by e.g., wearing glasses.

3.4. Diagnosis of PPPD

A patient was diagnosed with PPPD if he or she met all five diagnostic criteria for PPPD as established by the Committee for Classification of Vestibular Disorders of the Bárány Society [4]. These are: (1) presence of chronic [≥ 3 months] non-spinning [rotatory] vertigo, dizziness or unsteadiness; (2) symptoms are aggravated by an upright position, active/passive body movements, and visual stimuli; (3) prior presence of a condition that caused dizziness or instability; (4) symptoms have a major impact on patients' mental or physical functioning; and (5) symptoms cannot be explained by another existing condition.

3.5. Outcome variables

3.5.1. Descriptive variables

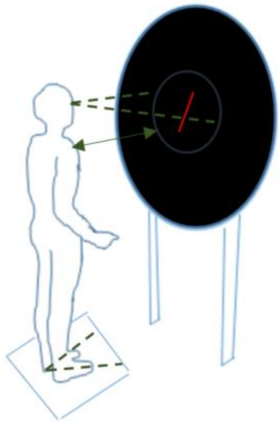
Age (years), gender, dizziness duration (years), and *ENT diagnosis* were collected from the electronic patient record.

The *Dizziness Handicap Inventory (DHI)* evaluates the physical, functional and emotional handicap experienced by patients as a result of their vestibular symptoms. For 25 statements, patients were asked to indicate the extent to which they applied to them ('no' = 0; 'sometimes' = 2; 'yes' = 4 points). The total DHI score was recorded, ranging from 0 (no impairment) to 100 (maximal impairment) [18, 19].

The *Hospital Anxiety and Depression Scale (HADS)* evaluates patients' emotional state by means of 7 anxiety-related (HADS-A) and 7 depression-related (HADS-D) questions answered on a 4-level ordinal scale. The total HADS-A and HADS-D scores, both ranging from 0 (no anxiety/depression) to 21 (maximal anxiety/depression), were retained [20].

The *Subjective Visual Vertical (SVV) test* measures patients' perception of verticality in the absence of visual reference points. The experimental setup is shown in **FIGURE 1**. The patient was asked to reposition a red line (6 cm length) on a black background until they felt it matched the true vertical. This was done using a handheld remote control and without moving the head or body. The test was done twice with the line initially tilted 20 degrees to the left, and twice with the line tilted 20 degrees to the right. More information on the test conditions can be found in the **Supplementary Material (Table 1)**. Performance was expressed as the mean absolute misalignment (in degrees) with the gravitational vertical (0°) for these four tests.

Figure 1. *Experimental setup for the Subjective Visual Vertical test, Rod-and-Disc test, and postural sway while facing rotating dots (screen display varied depending on the test condition)* [a, b]



[a] The participant stood upright, barefoot, with arms alongside the body, in a completely dark room. A television screen was placed at eye level at a distance of 40 cm, providing an almost full-field stimulus of 80%. A ring with an inner diameter of 54.5 was mounted on the television set to prevent the edges of the television screen from acting as a frame of reference.
[b] The feet were placed at an angle of 20 degrees with the inner malleoli 10 cm apart.

3.5.2. Clinical balance variables

The *Static Balance tests* measures the patients' balance while they were standing still and upright in four different foot positions with eyes closed: (1) feet together, combined with Jendrassik maneuver (i.e., fingers were interlocked with arms in abduction, and tension was created by pulling the hands apart); (2) feet 5 cm apart standing on a foam plate (NeuroCom International Inc., Clackamas, USA; 60 kg/cm3 medium density; 45 x 45 x 12 cm), combined with Jendrassik maneuver (i.e., the same hand grip as described above); (3) heel-to-toe tandem stance; and (4) standing on one leg. For each condition, the patient had three attempts to maintain the respective condition 30 seconds. Only the best score [in seconds] out of these three attempts was retained. The sum of these best scores for each of the four conditions constitutes the total static balance score, which ranges from 0 (markedly reduced balance) to 120 (excellent balance) [15].

The *Timed Up and Go test* evaluates how quickly a person can get up from a chair, walk 3m, turn around, walk back and sit back down on the chair. The fastest performance time (in seconds) of three attempts was retained [15].

The *Tandem Gait test* measures the number of correctly performed steps when walking heel-to-toe on a straight line. The highest number of steps of three attempts was retained. The maximal score was 20 steps [15].

The *Functional Gait Assessment (FGA)* evaluates balance control during ten different walking tasks (e.g., walking fast, or walking with head movements). The total FGA score ranges between 0 (markedly reduced balance) and 30 (normal balance) [21].

3.5.3. Clinical visual dependence variables

The *Visual Vertigo Analogue Scale (VVAS)* is a questionnaire consisting of nine statements describing different situations in daily life where disturbing visual stimuli are present (e.g., supermarket, or traffic at a busy intersection). For each statement, patients were asked to mark the extent to which they experienced dizziness on a 10 cm visual analogue scale. If a situation was not applicable for the patient, it was not marked and not included in the final score. The total VVAS score is the sum of the marks for each relevant situation, rescaled to a percentage where 100% indicates maximal visually induced dizziness [22].

The *Rod-and-Disc test (RDT)* measures the influence of visual disturbance on the perception of verticality. The experimental setup and the four test conditions were the same as for the SVV test, but for the RDT each test had to be performed twice with dots rotating clockwise [CW] and twice with dots rotating counter-clockwise (CCW) on the black screen. More information on the test conditions can be found in **APPENDIX (Table 6)**. The mean misalignment for the SVV test was used as baseline and subtracted from the differences in misalignment with the gravitational vertical (0°) for each of the CW and CCW rotating dots tests. These adjusted differences were then averaged out (after inverting the sign of the data for the CCW rotating dots, as the directions were mirrored), resulting in an indication of the overall impact of visual disturbance on the perception of verticality. A positive value means that the patient placed the line more in the direction of the rotating dots compared to the SVV, a negative value more opposite to the direction of the rotating dots.

Preliminary analyses showed that the Rod-and-Frame test - which was equivalent to the RDT, except that the dots were replaced by a frame tilted left or right - yielded less pronounced results than the RDT, and is therefore not retained for discussion. The test conditions and data are available in **APPENDIX (Table 7 and 8)**.

Postural sway while facing rotating dots was evaluated by measuring the displacement of patients' center of pressure (COP) first while looking at a black screen, and then during exposure to dots rotating CW and dots rotating CCW. The experimental setup differed from the SVV and RDT that no line was shown in any of the three tests, and that the patient stood on a force plate (AMTI type OR 6; 1000 fps, 46 x 50 x 8 cm). More information on the test conditions can be found as **Supplementary Material - Table 1**. Postural sway parameters for COP lean, COP velocity, and COP area were computed. The degree of visual dependence was calculated by subtracting the baseline value (black screen condition) from the values obtained during the CW and CCW rotating dots tests. More information is provided in **TABLE 1**.

Preliminary analyses showed that the postural sway while facing a tilted frame – which was equivalent to the postural sway while facing rotating dots, except that the dots were replaced by a frame tilted left or right - yielded less pronounced postural sway results compared to the rotating dots conditions, and are therefore not retained for discussion. The test conditions and data are available as **Supplementary Material - Table 2 and Table 3**.

Table 1. *Parameters of the postural sway while facing rotating dots* [a]

Postural sway parameters	Description
COP lean (mediolateral; mm)	Average deviation of the COP in mediolateral direction in relation to the starting position. Data were reversed for CCW rotating dots to average the data for CW and CCW rotating dots, resulting in an indication of the overall impact of visual disturbance on the COP lean. A positive value means that the body leaned in the direction of the rotating dots, a negative value indicates leaning in the opposite direction.
COP velocity (mediolateral; mm/s)	Average velocity of the COP in mediolateral direction. A positive value means that the COP velocity was larger during the rotating dots conditions compared to the baseline condition (black screen), while a negative value means the opposite.
COP area (mm^2)	Ellipse that contains 85% of the COP data. A positive value means that the COP area was larger during the rotating dots conditions compared to the baseline condition (black screen), while a negative value means the opposite.

[a] Abbreviations: COP = center of pressure; mm = millimeters; s = seconds

3.5.4. Data sources and measurement

The researcher is an accredited physiotherapist (Master's degree). The study took 2.5 hours per participant, using the following strict assessment order: first the questionnaires, then the clinical balance tests, and finally the visual dependence tests. The visual dependence tests (except the VVAS) were performed in a different randomised order for every participant to avoid a habituation effect on the results. Breaks were allowed between and during the different tests.

The next test was only started when the dizziness symptoms had returned to participant's baseline level. The data were collected pseudonymised in an IBM SPSS Statistics data file stored on a secure server of the University of Antwerp.

3.5.5. Blinding

During data collection, the researcher was blinded to the ENT diagnosis of each patient. Blinding to whether a participant was a patient or healthy person was not possible, as the healthy persons were recruited from the environment of the research team.

3.5.6. Statistical analyses

Descriptive statistics included means and standard deviations for quantitative variables, and frequencies and percentages for categorical variables. Shapiro-Wilk tests indicated whether quantitative variables were normally distributed [23].

Inter-group comparison of quantitative variables was carried out through one-way analysis of variance (ANOVA), using a Bonferroni-corrected significance level of $p < 0.006$ accounting for 9 comparisons, followed by post-hoc analysis with Tukey correction for multiple testing. For inter-group comparison of the categorical variables, chi-square ($\chi2$) tests were used. Two-group comparison of dizziness-related variables was carried out through independent samples t-tests.

Univariable logistic regression and Partial Least Squares Discriminant Analysis (PLS-DA) models were fitted to determine the predictors of PPPD in patients with chronic dizziness. The relation between the clinical tests and PPPD was expressed as odds ratios [95% confidence interval (CI)], area under the receiver operating characteristic curve (AUC), and optimal cut-off with corresponding sensitivity and specificity (according to maximization of the Youden index). For the PLS-DA model, the potential of each of the clinical tests to discriminate between PPPD and dizzy non-PPPD patients was evaluated through their loading values. The overall discriminative value of the PLS-DA model was 5-fold cross-validated (CV) [24]. In brief, for each fold we included 80% of the observations in the training set and 20% in the validation set. The training set was used to fit the PLS-DA models, with the number of components ranging from 2 to 10. Subsequently, these models predicted the outcome from the observations in the validation set, and the percentage of error (CVerror) was registered. This was carried out in five-fold, with each individual observation belonging to the validation set exactly one time. The five-fold CV was repeated 500 times to obtain the standard error of the CVerror.

Significance was set at $p < 0.05$, unless otherwise stated. Statistical analyses were performed using the SPSS software version 27.0 [25]. The PLS-DA was fitted with the R software (R Core Team, 2020) [26].

4. Results

4.1. Participants

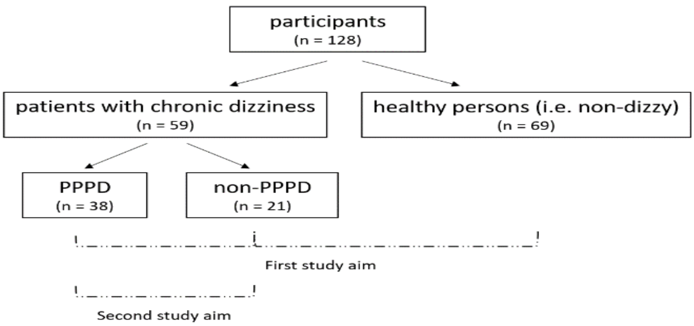
Seventy patients with chronic dizziness met the predefined study eligibility criteria as listed in the method section. Nine patients decided not to participate because of reduction of dizziness complaints with medication and/or physical therapy (2 patients), personal reasons (3 patients), or COVID outbreak (4 patients). The results of two other patients had to be excluded after the study because of unreliable test results due to disturbing background noise near the laboratory during the testing.

Of the 59 patients (mean age 57.34 ± 12.96) that successfully participated, 38 were diagnosed with PPPD. The 21 patients without PPPD were primarily diagnosed with vestibular hypofunction (4 patients), bilateral vestibulopathy (1 patient), proprioceptive cervicogenic dizziness (8 patients), multiple sensory deficits (3 patients), and mal de débarquement syndrome (1 patient). In four patients no cause could be found.

The control group consisted of 69 healthy non-dizzy persons (mean age 51,71 ± 17.24).

An overview of the recruited samples and the study aims are shown in **FIGURE 2**.

Figure 2. *Overview of the recruited samples and study aims* [a]



First study aim: Comparison of the clinical balance and visual dependence tests between PPPD patients, dizzy non-PPPD patients, and healthy persons.
Second study aim: Evaluation whether these clinical tests can help to identify PPPD in patients with chronic dizziness.

[a] Abbreviations: PPPD = persistent postural-perceptual dizziness

4.2. Sample characteristics

Gender numbers (p=0.453) were not significantly different between the three study groups.
All patients with chronic dizziness had significantly higher HADS-A (PPPD versus healthy, p<0.001; dizzy non-PPPD versus healthy, p=0.020) and HADS-D scores (PPPD versus healthy, p<0.001; dizzy non-PPPD versus healthy, p<0.001) compared to healthy persons. PPPD patients had significantly higher SVV scores (p=0.016) and dizzy non-PPPD patients were significantly older (p=0.037), both compared to healthy persons.

PPPD patients had significantly higher duration of dizziness complaints (p=0.003), but not significantly higher DHI (p=0.065), HADS (HADS-A, p=0.308; HADS-D, p=1.00) and SVV scores (p=0.406), compared to dizzy non-PPPD patients.

Data are provided in **TABLE 2**.

Table 2. *Results on descriptive variables of the included participants* [a, b]

Measurement tool (unit)	Mean ± SD or number (%)			Statistical analyses (p-values)			
	Chronic dizziness						
	With PPPD (n = 38)	Without PPPD (n = 21)	Healthy (n = 69)	3-group comparison	With PPPD vs without PPPD	With PPPD vs healthy	Without PPPD vs healthy
Age (years)	55.18 ± 12.31	61.23 ± 13.49	51.71 ± 17.24	**0.045** † *	0.320	0.503	**0.037** ¶ *
Female	24 (63.2)	10 (47.6)	34 (49.3)	0.453 §			
Dizziness duration (years)	7.84 ± 6.50	3.91 ± 3.24	N/A		**0.003** ‡ *		
DHI (0-100)	46.32 ± 18.18	36.95 ± 18.59	N/A		0.065 ‡		
HADS $_{anxiety}$ (0-21)	7.21 ± 3.89	5.86 ± 4.00	3.32 ± 2.25	**<0.001** † **	0.308 ¶	**<0.001** ¶ **	**0.020** ¶ *
HADS $_{depression}$ (0-21)	5.68 ± 3.43	5.67 ± 3.62	1.57 ± 1.63	**<0.001** † **	1.000 ¶	**<0.001** ¶ **	**<0.001** ¶ **
SVV (°)	1.73 ± 1.17	1.38 ± 0.90	1.18 ± 0.84	**0.022** † *	0.406 ¶	**0.016** ¶ *	0.707 ¶

[a] ANOVA test (†), Independent samples t-test (‡), Chi-squared test (§), post-hoc analysis with Tukey correction (¶) ANOVA: p<0.05 (*) and p<0.001 (**)
[b] Abbreviations: ° = degrees; DHI = Dizziness Handicap Inventory; HADS = Hospital Anxiety and Depression Scale; PPPD = persistent postural-perceptual dizziness; SD = standard deviation; SVV = Subjective Visual Vertical; vs = versus

4.3. Comparison of the clinical balance tests between PPPD patients, dizzy non-PPPD patients, and healthy persons

All patients with chronic dizziness had significantly worse static (PPPD versus healthy, p<0.001; dizzy non-PPPD versus healthy, p=0.002) and dynamic balance scores (Timed Up and Go, Tandem Gait, and FGA, PPPD versus healthy, p<0.001; dizzy non-PPPD versus healthy, p<0.05) compared to healthy persons.

Between PPPD and dizzy non-PPPD patients, no significant differences were found in either static (p=0.680) or dynamic balance scores (Timed Up and Go, p=0.846; Tandem Gait, p=0.954; and FGA, p=0.813).

Data are provided in **TABLE 3**.

Table 3. *Results on clinical balance tests of the included participants* [a, b]

	Mean ± SD			Statistical analyses (p-values)			
	Chronic dizziness						
Measurement tool (unit)	**With PPPD (n = 38)**	**Without PPPD (n = 21)**	**Healthy (n = 69)**	**3-group comparison**	**With PPPD vs without PPPD**	**With PPPD vs healthy**	**Without PPPD vs healthy**
Static Balance Test (0-120 sec)	64.22 ± 33.07	70.32 ± 27.09	93.30 ± 22.49	**<0.001** † **	0.680 ¶	**<0.001** ¶ ***	**0.002** ¶ *
Timed Up and Go test (sec)	8.07 ± 2.70	7.78 ± 2.57	6.34 ± 1.13	**<0.001** † **	0.846 ¶	**<0.001** ¶ ***	**0.012** ¶ *
Tandem gait (# steps)	13.47 ± 7.95	13.95 ± 8.23	18.84 ± 3.60	**<0.001** † **	0.954 ¶	**<0.001** ¶ ***	**0.004** ¶ *
FGA (0-30)	23.24 ± 4.38	23.81 ± 5.17	28.25 ± 1.82	**<0.001** † **	0.813 ¶	**<0.001** ¶ ***	**<0.001** ¶ ***

[a] ANOVA test (†), Independent samples t-test (‡), Chi-squared test (§), post-hoc analysis with Tukey correction (¶)
ANOVA Bonferroni cut-off: p<0.006 (**); other tests: p<0.05 (*) and p<0.001 (***)
[b] Abbreviations: # = amount; FGA = Functional Gait Assessment; PPPD = persistent postural-perceptual dizziness; SD = standard deviation; TUG = Timed Up and Go test; vs = versus

4.4. Comparison of the clinical visual dependence tests between PPPD patients, dizzy non-PPPD patients, and healthy persons

There was no significant difference in RDT results (p=0.431) between the three study groups. The RDT values were positive in all three groups, indicating that in all cases the perceived vertical had a larger offset in the same direction of the rotation of the dots compared to the SVV tests. The COP lean results (p=0.800) were not significantly different between the three study groups either. The COP lean values were small (≤1mm), indicating that the visual disturbance did not cause the participant to tilt more to one side.

Patients suffering from chronic dizziness had larger COP velocity values (PPPD versus healthy, p<0.001; dizzy non-PPPD versus healthy, p=0.116) compared to healthy persons. The COP velocity values were positive in all three study groups, indicating larger mediolateral sway in visually disturbing conditions compared to the SVV tests. Next to this, PPPD patients also showed a significantly higher COP area (p<0.001) compared to healthy persons. The COP area values were positive in all three study groups, indicating that the COP displacement was larger in visually disturbing conditions compared to the SVV condition.

PPPD patients had significantly higher VVAS scores (p=0.006), but not significantly larger COP velocity values (p=0.475) and COP area values (p=0.116), compared to dizzy non-PPPD patients.
Data are provided in **TABLE 4**.

Table 4. *Results on clinical visual dependence tests of the included participants* [a, b]

Measurement tool (unit)	Mean ± SD			Statistical analyses (p-values)			
	Chronic dizziness						
	With PPPD (n = 38)	Without PPPD (n = 21)	Healthy (n = 69)	3-group comparison	With PPPD vs without PPPD	With PPPD vs healthy	Without PPPD vs healthy
VVAS (0-100%)	33.87 ± 20.65	18.13 ± 20.08	N/A		**0.006** ‡ *		
RDT (degrees)	6.05 ± 3.96	6.09 ± 3.80	5.07 ± 4.21	0.431 †			
Postural sway analysis with rotating dots							
- COP lean (mm)	-0.05 ± 10.92	-0.32 ± 6.28	-1.01 ± 4.95	0.800 †			
- COP velocity (mm/s)	11.04 ± 15.32	7.68 ± 11.75	2.36 ± 5.12	**<0.001** † **	0.475 ¶	**<0.001** ¶ ***	0.116 ¶
- COP area (mm^2)	648.44 ± 1009.44	302.91 ± 648.15	31.38 ± 132.36	**<0.001** † **	0.116 ¶	**<0.001** ¶ ***	0.207 ¶

[a] ANOVA test (†), Independent samples t-test (‡), Chi-squared test (§), post-hoc analysis with Tukey correction (¶)
ANOVA Bonferroni cut-off: p<0.006 (**); other tests: p<0.05 (*) and p<0.001 (***)

[b] Abbreviations: COP = center of pressure; mm = millimeters; PPPD = persistent postural-perceptual dizziness; RDT = Rod-and-Disc test; s = seconds; SD = standard deviation; ; vs = versus; VVAS = Visual Vertigo Analogue Scale

4.5. Evaluation of the value of the clinical tests for PPPD identification in patients with chronic dizziness

Univariable logistic regression analyses of the clinical tests, displayed in **TABLE 5**, revealed that a higher VVAS score was associated with the presence of PPPD (odds ratio 1.04; 95% CI [1.01; 1.07]; p=0.010).

Table 5. *Univariable logistic regression of the clinical tests for the prediction of PPPD in patients with chronic dizziness* [a, b]

Measurement tools	**estimate**	**standard error**	**OR (95% CI)**	**p-value**
Static Balance tests (0-120 sec)	-0.007	0.009	0.99 [0.98 ; 1.01]	0.467
Timed Up and Go test (sec)	0.045	0.109	1.05 [0.85 ; 1.29]	0.678
Tandem Gait (# steps)	-0.008	0.035	0.99 [0.93 ; 1.06]	0.824
FGA (0-30)	-0.027	0.060	0.97 [0.87 ; 1.10]	0.648
VVAS (0-100%)	0.039	0.015	1.04 [1.01; 1.07]	**0.010 ***
RDT (°)	-0.003	0.076	1.00 [0.87 ; 1.16]	0.968
Postural sway while facing rotating dots				
- COP lean (mm)	0.003	0.030	1.00 [0.95 ; 1.06]	0.918
- COP velocity (mm/s)	0.019	0.023	1.02 [0.97 ; 1.07]	0.404
- COP area (mm2)	0.001	<0.001	1.00 [1.00 ; 1.001]	0.197

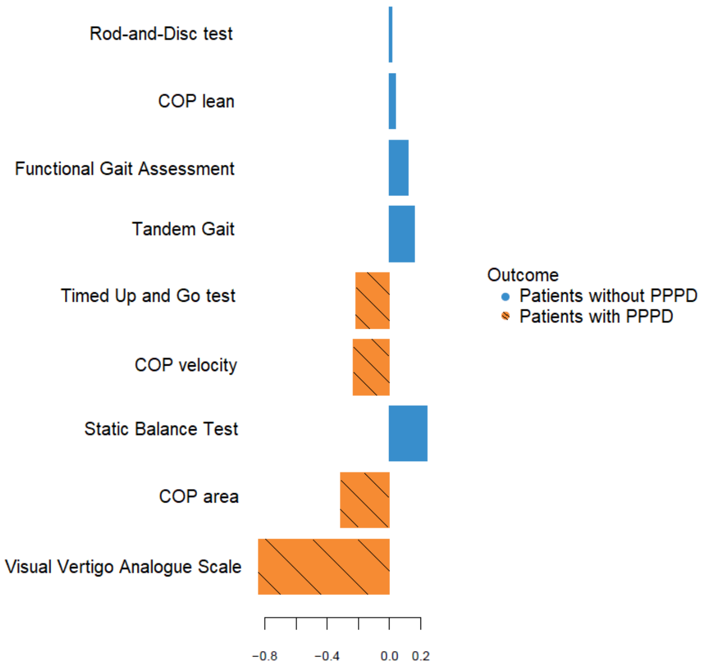
[a] p<0.05 (*)

[b] Abbreviations: COP = center of pressure; FGA = Functional Gait Assessment; mm = millimeters; OD = odds ratio; PPPD = persistent postural-perceptual dizziness; RDT = Rod-and-Disc test; s = seconds; TUG = Timed Up and Go test; ; vs = versus; VVAS = Visual Vertigo Analogue Scale

The ROC analysis of the VVAS showed fair discriminative accuracy (AUC = 0.72, 95% CI [0.57; 0.86]). The cut-off value for the VVAS (through maximisation of the Youden index) was 21.01 which resulted in a sensitivity of 0.74 and a specificity of 0.67 for identification of PPPD.

In addition, a PLS-DA model was built to classify patients with chronic dizziness into PPPD and non-PPPD based upon all clinical tests listed in Table 5. The highest loading in the first component of the PLS-DA model was observed for VVAS, which is in line with the result from the logistic regression analysis where VVAS showed the strongest positive association with PPPD. Loadings are graphically shown in **FIGURE 3**.

Figure 3. *Loading plot of the first component of the PLS-DA model [a, b]*



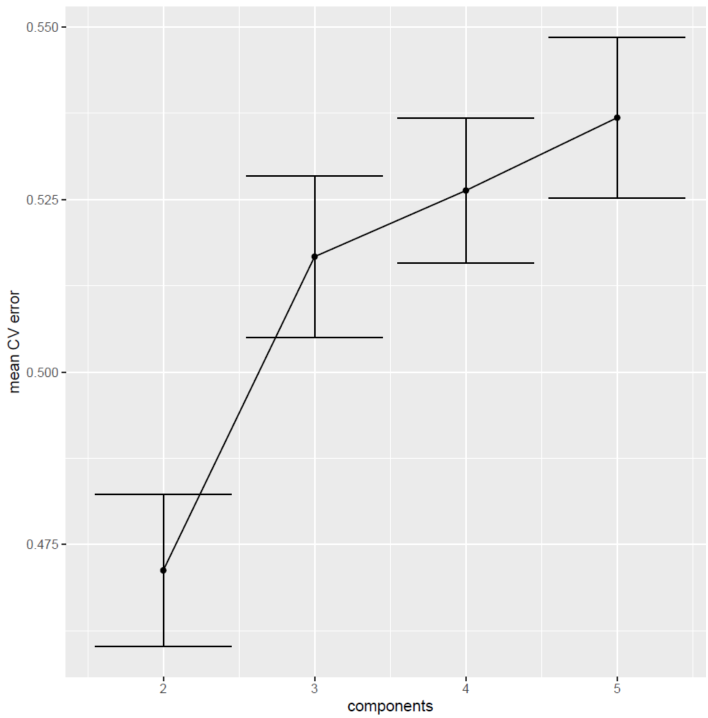
[a] Loadings of the original variables for the first PLS-DA component are represented on the X-axis. The color of the horizontal bars shows in which of the two groups (patients with or without PPPD) the mean value of the original variable is the largest. In this dataset, the original variables with a negative loading on the first PLSDA component all have a larger mean value in the patients with PPPD.

[b] Abbreviations: COP = center of pressure; PPPD = persistent postural-perceptual dizziness

The first two components of the PLS-DA accounted for 51% of the variance in the data (Kappa coefficient = 0.32; AUC of the ROC curve = 0.70). However, since the same observations were used to build the model and to test its predictive power, the prediction error is probably underestimated. To obtain an unbiased estimate of the prediction error of the PLS-DA model, and to find the optimal number of components to be included, 5-fold cross validation (CV) was carried out. The

CVerror was 47%, as presented in **FIGURE 4**, which indicates that the PLS-DA model performs fairly in distinguishing between PPPD patients and dizzy non-PPPD patients.

Figure 4. *Cross-validation error (5-fold) of 500 iterations* [a, b]



[a] This figure shows the cross-validation error of the models versus the number of components. The error bars represent the 95% confidence interval around the mean CV error (across 500 runs of 5-fold CV). The best performance is observed in the models with 2 components, with a CVerror of 47% (95% CI [0.46; 0.48]).
[b] Abbreviations: CV = cross-validation

5. Discussion

Our results show significantly reduced static and dynamic balance scores in patients with chronic dizziness compared to healthy subjects. However, no significant difference in any balance test results could be demonstrated between patients with and without PPPD. The literature indeed confirms reduced balance in all forms of chronic dizziness [6, 27-29]. This is attributed to ongoing sensory conflict between the visual, vestibular and proprioceptive systems that are responsible for maintaining postural balance [30]. Additionally, emotions (e.g., fear can cause conditioned avoidance) [31, 32] and musculoskeletal pain or dysfunction [33] are known triggers for balance problems. None of these triggers are specific to PPPD.

Furthermore, our results show increased postural sway while facing rotating dots compared to the baseline condition (black screen) in all three study groups, as indicated by the positive values for COP velocity and COP area. The largest increase in postural sway was found in PPPD patients. These results are in line with the literature which states that disturbing visual stimuli can reduce balance control, especially in persons who are less able to rely on their vestibular and proprioceptive systems in visually challenging conditions [i.e., increased visual dependence] [34].

In PPPD patients, this increased visual dependence can be expected as it is one of the diagnostic criteria of PPPD [4]. Increased visual dependence also occurs in patients with chronic dizziness of non-PPPD origin as it is a frequently used coping mechanism for reduced vestibular function, aimed at restoring postural balance [35-37]. On top of this, there is an inter-individual variability in visual susceptibility in the general population, which explains why participants without dizziness or balance complaints can have increased postural sway in visually challenging conditions [38].

The COP lean deviations were very limited (≤1mm), but in line with the low values reported in the literature [13], and not significantly different between the three groups. The lean effect could be strengthened in future research by: 1) only showing rotating dots in the peripheral field while keeping the center of the screen empty [13, 34], or 2) by showing more realistic visual materials [e.g., fairground carousel, passing traffic] [39].

Another finding was the larger SVV deviations in all patients with chronic dizziness (both PPPD and non-PPPD patients) compared to healthy persons, although in none of the three study groups the SVV values were pathological (i.e., they were within the normal limit of 2.5° [40-43]). The literature indicates that the upright SVV is sufficiently compensated in the chronic vestibular phase [44-46].

In our results, the SVV misalignment of RDT was not significantly different in PPPD patients compared to non-PPPD patients. This result agrees with earlier findings indicating that SVV misalignment of RDT is independent of the subtype of chronic dizziness, e.g., no significant differences in scores were found between visual vertigo and labyrinth-defective subjects [13], or between patients with vestibular neuritis with high versus low DHI scores [35]. In contrast to other studies, we could not observe significant differences in SVV misalignment of RDT between dizzy patients and healthy subjects [13, 35]. The higher SVV errors for healthy subjects in our study may be due to interindividual variability [34], resulting in a slightly higher visual sensitivity in our sample group. Lastly, the SVV misalignment of RDT of our results was always in the direction of the visual stimuli, which corresponds with previous results [47, 48].

Preliminary results showed that participants had less postural sway disturbances in presence of a tilted frame compared to the black screen condition. This adds to the literature that any reference frame, even if it deviates from the earth gravitational as in this study, provides the participant with a visual aid to maintain a more stable upright position. The perception of verticality was more disturbed in the RFT than in the SVV test, but less so than in the RDT. The literature confirms that rotating dots are a stronger visually disturbing stimulus than a tilted frame [38].

Lastly, this study aimed to identify PPPD in chronic dizziness patients by means of commonly used clinical tests. Balance and visual dependence tests were chosen, since poor balance and increased visual dependence have been reported in previous studies as indicators of PPPD [4, 6]. The results show that VVAS had the most, yet limited, discriminative value. These results complement the literature which already indicates duration of momentary worsening of dizziness, head roll-tilt SVV, and the Niigata PPPD questionnaire as useful tools in identifying PPPD. More specifically, duration of momentary worsening of dizziness can distinguish between PPPD and psychogenic chronic dizziness [49], the head roll-tilt SVV can help diagnosing PPPD in chronic vestibular disorders [50], and the Niigata PPPD questionnaire is useful in patients with other vestibular disorders (not specified as chronic) to detect PPPD [5].

5.1. Analysis of study strengths and weaknesses

Strengths of this study include [1] the meticulous elimination of visual fixation points during the visual dependence tests (e.g., completely darkened room, edges of the television screen covered by a ring), [2] preliminary analysis of the RFT, RDT and postural sway while facing a tilted frame versus rotating dots, and [3] the randomization of the visual dependence tests to eliminate a habituation effect on the results. Limitations of the study are [1] the limited sample size, [2] not having performed vestibular tests to confirm the absence of vestibular deficits in healthy persons, [3] the slightly younger age of the healthy persons, [4] the use of 'best of three attempts' for the Timed Up and Go and Tandem Gait tests which may have induced a ceiling effect, and [4] the administration time of the test protocol (2.5 hours) which may have caused fatigue in some patients.

5.2. Implications for clinical practice and future research

The VVAS was the most useful clinical test for the detection of PPPD of the balance and visual dependence tests examined in this study. Both PPPD and dizzy non-PPPD patients had significantly impaired balance and increased visual dependence compared to healthy persons. This shows the importance of evaluating balance and visual dependence in patients with chronic dizziness. The clinical tests can be useful to chart the patient's individual complaint profile. This profile can then be used to accentuate certain therapy elements, for example the degree of visual desensitisation training.

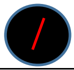
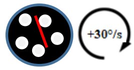
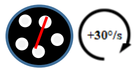
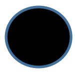
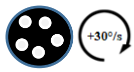
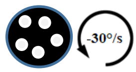
Further research can investigate the discriminative value of other clinical tests not discussed in this article, preferably in combination with the VVAS results.

6. Conclusion

PPPD patients were more visually dependent, but did not have worse postural balance compared to dizzy non-PPPD patients. The VVAS had the most, but limited, discriminative value for identifying PPPD in chronic dizziness. In clinical practice, evaluation of balance control and visual dependence is indicated in patients with chronic dizziness, and corresponding exercises should be integrated into their exercise program in a patient-tailored way.

7. Appendix

Table 6. *Test conditions of the Subjective Visual Vertical test, Rod-and-Disc test, and postural sway while facing rotating dots* [a]

Subjective Visual Vertical test			
Test condition	*Background*	*Line*	*Screen display*
Test condition 1 (1 trial)	Black	Left tilt (-20°)	
Test condition 2 (1 trial)	Black	Right tilt (+20°)	
Test condition 3 (1 trial)	Black	Left tilt (-20°)	
Test condition 4 (1 trial)	Black	Right tilt (+20°)	
Rod-and-Disc test			
Test condition	*Background*	*Line*	*Screen display*
Test condition 1 (2 trials)	CW rotating (+30°/sec)	Left tilt (-20°)	
Test condition 2 (2 trials)	CW rotating (+30°/sec)	Right tilt (+20°)	
Test condition 3 (2 trials)	CCW rotating (-30°/sec)	Left tilt (-20°)	
Test condition 4 (2 trials)	CCW rotating (-30°/sec)	Right tilt (+20°)	
Postural sway while facing rotating dots			
Test condition	*Background*	*Line*	*Screen display*
Test condition 1 (1 trial)	Black	No line displayed	
Test condition 2 (1 trial)	CW rotating (+30°/sec)	No line displayed	
Test condition 3 (1 trial)	CCW rotating (-30°/sec)	No line displayed	

[a] Abbreviations: CCW = counter-clockwise; CW = clockwise

Table 7. *Test conditions of the Rod-and-Frame test, and postural sway while facing a tilted frame*

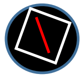
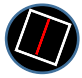
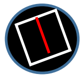
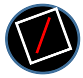
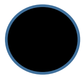
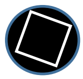
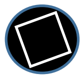
Rod-and-Frame test			
Test condition	*Background*	*Line*	*Screen display*
Test condition 1 (2 trials)	Right tilted frame (+20°)	Left tilt (-20°)	
Test condition 2 (2 trials)	Right tilted frame (+20°)	Right tilt (+20°)	
Test condition 3 (2 trials)	Left tilted frame (-20°)	Left tilt (-20°)	
Test condition 4 (2 trials)	Left tilted frame (-20°)	Right tilt (+20°)	
Postural sway while facing a tilted frame			
Test condition	*Background*	*Line*	*Screen display*
Test condition 1 (1 trial)	Black	No line displayed	
Test condition 2 (1 trial)	Right tilted frame (+20°)	No line displayed	
Test condition 3 (1 trial)	Left tilted frame (-20°)	No line displayed	

Table 8. *Results on Rod-and-Frame test and postural sway while facing a tilted frame of the included participants* [a, b]

Measurement tool (unit)	Mean ± SD			Statistical analyses (p-values)			
	Chronic dizziness						
	With PPPD (n = 38)	Without PPPD (n = 21)	Healthy (n = 69)	3-group comparison	With PPPD vs without PPPD	With PPPD vs healthy	Without PPPD vs healthy
RFT (°)	2.70 ± 1.77	2.99 ± 3.06	2.00 ± 1.84	0.100 †			
Postural sway while facing a tilted frame							
- COP lean (mm)	0.36 ± 8.33	0.004 ± 6.04	-0.03 ± 3.03	0.940 †			
- COP velocity (mm/s)	-0.76 ± 4.76	-1.05 ± 4.10	-1.89 ± 1.99	0.229 †			
- COP area (mm^2)	52.84 ± 301.65	-14.86 ± 161.40	-32.23 ± 64.16	0.072 †			

[a] ANOVA test (†), Independent samples t-test (‡), Chi-squared test (§), post-hoc analysis with Tukey correction (¶)
ANOVA Bonferroni cut-off: p<0.006 (**); other tests: p<0.05 (*) and p<0.001 (***)
[b] Abbreviations: COP = centre of pressure; mm = millimetres; PPPD = persistent postural-perceptual dizziness; RFT = Rod-and-Frame test; s = seconds; SD = standard deviation

8. References

1. Brandt, T. and M. Dieterich, *Phobischer attacken-schwankschwindel, ein neues syndrom.* Münch Med Wochenschr, 1986. **128**: p. 247-250.
2. Staab, J.P. and M.J. Ruckenstein, *Expanding the differential diagnosis of chronic dizziness.* Arch Otolaryngol Head Neck Surg, 2007. **133**(2): p. 170-6.
3. Xue, H., et al., *[Etiological analysis on patients with vertigo or dizziness].* Zhonghua Yi Xue Za Zhi, 2018. **98**(16): p. 1227-1230.
4. Staab, J.P., et al., *Diagnostic criteria for persistent postural-perceptual dizziness (PPPD): Consensus document of the committee for the Classification of Vestibular Disorders of the Barany Society.* J Vestib Res, 2017. **27**(4): p. 191-208.
5. Yagi, C., et al., *A Validated Questionnaire to Assess the Severity of Persistent Postural-Perceptual Dizziness (PPPD): The Niigata PPPD Questionnaire (NPQ).* Otol Neurotol, 2019. **40**(7): p. e747-e752.
6. Popkirov, S., J.P. Staab, and J. Stone, *Persistent postural-perceptual dizziness (PPPD): a common, characteristic and treatable cause of chronic dizziness.* Pract Neurol, 2018. **18**(1): p. 5-13.
7. Van Ombergen, A., et al., *Altered functional brain connectivity in patients with visually induced dizziness.* Neuroimage Clin, 2017. **14**: p. 538-545.
8. Li, K., et al., *Altered intra- and inter-network functional connectivity in patients with persistent postural-perceptual dizziness.* Neuroimage Clin, 2020. **26**: p. 102216.
9. Lee, J.O., et al., *Altered brain function in persistent postural perceptual dizziness: A study on resting state functional connectivity.* Hum Brain Mapp, 2018. **39**(8): p. 3340-3353.
10. Cavanna, A.E. and M.R. Trimble, *The precuneus: a review of its functional anatomy and behavioural correlates.* Brain, 2006. **129**(Pt 3): p. 564-83.
11. Margulies, D.S., et al., *Precuneus shares intrinsic functional architecture in humans and monkeys.* Proc Natl Acad Sci U S A, 2009. **106**(47): p. 20069-74.
12. Sohsten, E., R.S. Bittar, and J.P. Staab, *Posturographic profile of patients with persistent postural-perceptual dizziness on the sensory organization test.* J Vestib Res, 2016. **26**(3): p. 319-26.
13. Guerraz, M., et al., *Visual vertigo: symptom assessment, spatial orientation and postural control.* Brain, 2001. **124**(Pt 8): p. 1646-56.
14. Bronstein, A.M., T. Lempert, and B.M. Seemungal, *Chronic dizziness: a practical approach.* Pract Neurol, 2010. **10**(3): p. 129-39.
15. Vereeck, L., et al., *Clinical assessment of balance: normative data, and gender and age effects.* Int J Audiol, 2008. **47**(2): p. 67-75.

16. Cuschieri, S., *The STROBE guidelines.* Saudi J Anaesth, 2019. **13**(Suppl 1): p. S31-S34.
17. Wuyts, F.L., V. Van Rompaey, and L.K. Maes, *"SO STONED": Common Sense Approach of the Dizzy Patient.* Frontiers in surgery, 2016. **3**: p. 32-32.
18. Vereeck, L., et al., *Test-retest reliability of the Dutch version of the Dizziness Handicap Inventory.* B-ent, 2006. **2**(2): p. 75-80.
19. Vereeck, L., et al., *Internal consistency and factor analysis of the Dutch version of the Dizziness Handicap Inventory.* Acta Otolaryngol, 2007. **127**(8): p. 788-95.
20. Bjelland, I., et al., *The validity of the Hospital Anxiety and Depression Scale. An updated literature review.* J Psychosom Res, 2002. **52**(2): p. 69-77.
21. Wrisley, D.M., et al., *Reliability, internal consistency, and validity of data obtained with the functional gait assessment.* Phys Ther, 2004. **84**(10): p. 906-18.
22. Dannenbaum, E., G. Chilingaryan, and J. Fung, *Visual vertigo analogue scale: an assessment questionnaire for visual vertigo.* J Vestib Res, 2011. **21**(3): p. 153-9.
23. Mishra, P., et al., *Descriptive statistics and normality tests for statistical data.* Ann Card Anaesth, 2019. **22**(1): p. 67-72.
24. Ruiz-Perez, D., et al., *So you think you can PLS-DA?* BMC Bioinformatics, 2020. **21**(Suppl 1): p. 2.
25. *IBM Corp. Released 2020. IBM SPSS Statistics for Windows; Version 27.0* Armonk, NY.
26. *R Core Team (2020). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/.*
27. Herssens, N., et al., *A Systematic Review on Balance Performance in Patients With Bilateral Vestibulopathy.* Phys Ther, 2020. **100**(9): p. 1582-1594.
28. Giray, M., et al., *Short-term effects of vestibular rehabilitation in patients with chronic unilateral vestibular dysfunction: a randomized controlled study.* Arch Phys Med Rehabil, 2009. **90**(8): p. 1325-31.
29. Balci, B. and G. Akdal, *Imbalance, motion sensitivity, anxiety and handicap in vestibular migraine and migraine only patients.* Auris Nasus Larynx, 2020. **47**(5): p. 747-751.
30. Bronstein, A.M., *Multisensory integration in balance control.* Handb Clin Neurol, 2016. **137**: p. 57-66.
31. Balaban, C.D. and J.F. Thayer, *Neurological bases for balance–anxiety links.* Journal of Anxiety Disorders, 2001. **15**(1-2): p. 53-79.

32. Goto, F., et al., *Effect of anxiety on antero-posterior postural stability in patients with dizziness.* Neurosci Lett, 2011. **487**(2): p. 204-6.
33. Haukanes, L., et al., *Association between musculoskeletal function and postural balance in patients with long-lasting dizziness. A cross-sectional study.* Physiother Res Int, 2021. **26**(3): p. e1916.
34. Lee, S.C., *Relationship of visual dependence to age, balance, attention, and vertigo.* J Phys Ther Sci, 2017. **29**(8): p. 1318-1322.
35. Cousins, S., et al., *Visual dependency and dizziness after vestibular neuritis.* PLoS One, 2014. **9**(9): p. e105426.
36. Agarwal, K., et al., *Visual dependence and BPPV.* J Neurol, 2012. **259**(6): p. 1117-24.
37. Bisdorff, A.R., *Management of vestibular migraine.* Ther Adv Neurol Disord, 2011. **4**(3): p. 183-91.
38. Pavlou, M., et al., *The effect of repeated visual motion stimuli on visual dependence and postural control in normal subjects.* Gait Posture, 2011. **33**(1): p. 113-8.
39. Meyer, G.F., et al., *Modulation of visually evoked postural responses by contextual visual, haptic and auditory information: a 'virtual reality check'.* PLoS One, 2013. **8**(6): p. e67651.
40. Dieterich, M. and T. Brandt, *Ocular torsion and tilt of subjective visual vertical are sensitive brainstem signs.* Ann Neurol, 1993. **33**(3): p. 292-9.
41. Zwergal, A., et al., *A bucket of static vestibular function.* Neurology, 2009. **72**(19): p. 1689-92.
42. Friedmann, G., *The judgement of the visual vertical and horizontal with peripheral and central vestibular lesions.* Brain, 1970. **93**(2): p. 313-28.
43. Habs, M., et al., *Primary or secondary chronic functional dizziness: does it make a difference? A DizzyReg study in 356 patients.* J Neurol, 2020. **267**(Suppl 1): p. 212-222.
44. Vibert, D. and R. Hausler, *Long-term evolution of subjective visual vertical after vestibular neurectomy and labyrinthectomy.* Acta Otolaryngol, 2000. **120**(5): p. 620-2.
45. Cnyrim, C.D., et al., *Central compensation of deviated subjective visual vertical in Wallenberg's syndrome.* J Neurol Neurosurg Psychiatry, 2007. **78**(5): p. 527-8.
46. Kumagami, H., et al., *Subjective visual vertical test in patients with chronic dizziness without abnormal findings in routine vestibular function tests.* Acta Otolaryngol Suppl, 2009(562): p. 46-9.
47. Mittelstaedt, H., *A new solution to the problem of the subjective vertical.* Naturwissenschaften, 1983. **70**(6): p. 272-81.
48. Merfeld, D.M. and L.H. Zupan, *Neural processing of gravitoinertial cues in humans. III. Modeling tilt and translation responses.* J Neurophysiol, 2002. **87**(2): p. 819-33.

49. Ishizuka, K., et al., *The Clinical Key Features of Persistent Postural Perceptual Dizziness in the General Medicine Outpatient Setting: A Case Series Study of 33 Patients.* Intern Med, 2020. **59**(22): p. 2857-2862.
50. Yagi, C., et al., *Head Roll-Tilt Subjective Visual Vertical Test in the Diagnosis of Persistent Postural-Perceptual Dizziness.* Otol Neurotol, 2021. **42**(10): p. e1618-e1624.

Part 2

Treatment of patients with CGD and PPPD

Chapter 1

Systematic review and meta-analysis of the therapeutic management of patients with cervicogenic dizziness

Published as: De Vestel C, Vereeck L, Reid SA, Van Rompaey V, Lemmens J, De Hertogh W. Systematic review and meta-analysis of the therapeutic management of patients with cervicogenic dizziness. J Man Manip Ther. 2022 Apr 6:1-11. doi: 10.1080/10669817.2022.2033044. Epub ahead of print. PMID: 35383538.

Appendix: Available at the end of this manuscript.

Highlights:

- Based on moderate quality of evidence, upper cervical manual therapy is effective in reducing neck-related dizziness, neck symptoms, and postural imbalance.
- Based on low quality of evidence, a combination of manual therapy and exercise therapy is more effective than manual therapy alone in reducing neck-related dizziness, neck symptoms, and postural imbalance.
- There is considerable heterogeneity across studies regarding the diagnostic criteria for CGD.

1. Abstract

Background: Patients with cervicogenic dizziness (CGD) present with dizziness, cervical spine dysfunctions, and postural imbalance, symptoms that can significantly impact their daily functioning.

Objectives: To provide evidence-based recommendations for the management of patients with CGD.

Methods: Three databases were searched for randomized controlled trials (RCTs) (last search 15 May 2021). Outcome measures included dizziness, cervical spine, and balance parameters. Cochrane standard methodological procedures were used and included the RoB 2.0 and GRADE. Where possible, RCTs were pooled for meta-analysis.

Results: Thirteen RCTs (n=898 patients) of high (two RCTs), moderate (five RCTs), and low (six RCTs) methodological quality were analyzed. Six RCTs were included in the meta-analysis. Only three RCTs specified the cause of CGD. They showed inconsistent findings for the effectiveness of exercise therapy in patients with traumatic CGD. Manual therapy and manual therapy combined with exercise therapy may reduce CGD, cervical spine, and balance dysfunctions.

Conclusion: There is moderate quality of evidence that manual therapy reduces CGD, cervical spine, and balance symptoms. When manual therapy is combined with exercise therapy, the positive effect on CGD, cervical spine, and balance symptoms is even stronger. However, the quality of the evidence here is very low.

Keywords: dizziness, cervical vertebrae, exercise therapy, musculoskeletal manipulations

2. Introduction

Dizziness is a frequently occurring symptom with a lifetime prevalence between 15% and 35% in the general population [1-6]. There are many different causes of dizziness, including vestibular, cardiorespiratory, neurological, mental/psychiatric, and cervical [7]. Cervical-related dizziness can be divided further into dizziness caused by altered blood flow in the cervical arterial blood vessels, either by compression (e.g., vertebrobasilar insufficiency) or disruption (e.g., sympathetic plexus induced vasoconstriction) [8, 9], and dizziness caused by altered functioning of the cervical proprioceptors [10, 11]. The latter is called cervicogenic dizziness (CGD) and is the scope of this review.

The cervical proprioceptors are very densely concentrated in the cervical zygapophyseal joints of C1 to C3 and the deep segmental upper cervical muscles [12, 13]. They can become dysfunctional due to trauma [14], muscle fatigue [15], degenerative changes [10] and/or inflammation. In addition, due to the altered cervical proprioceptive information to the central nervous system, head and body posture control may be impaired, and dizziness may occur due to a sensory mismatch with the information from the vestibular and visual systems [11, 16].

Dizziness, cervical spine, and balance complaints can significantly impact patients' daily functioning [17, 18]. Therefore, it is essential to find adequate therapeutic methods for patients with CGD. Across studies, multiple interventions have been described. A frequently discussed therapeutic method is manual therapy. Manual therapy (both mobilization and manipulation techniques) targeting the upper cervical spine has been shown to not only reduce muscle spasms and restore zygapophyseal joint mobility and joint play, but also to promote the flow of afferent information, including proprioceptive input, towards the central nervous system [19-21]. This theoretical effectiveness of upper cervical manual therapy for CGD has been confirmed in clinical studies [22-24]. Furthermore, there is a theoretical framework for the use of vestibular rehabilitation for CGD as well. It has been postulated that vestibular exercises can stimulate the vestibulo-cerebellar system to compensate for the altered cervical afferent input [22, 25].

It remains, however, unclear what the effectiveness is compared to other therapeutic approaches in reducing CGD. In addition, no summary is available showing which therapeutic strategies are effective for cervical spine and balance complaints in patients with CGD.

Central sensitization or nociplastic pain (i.e., increased responsiveness of the central neurons to noxious input) is a common feature in patients with (whiplash) trauma [26-28]. Furthermore, this cervical sensory hypersensitivity has been linked to prolongation of postural balance complaints [29, 30] and can therefore complicate therapy. Therefore, to ascertain whether patients with and without traumatic CGD should require a different therapeutic approach, the results in this study are discussed separately for these two subgroups of patients.

This review aims to evaluate the average intervention effect of different therapeutic methods on dizziness, and secondarily on the cervical spine and balance symptoms in patients with CGD of both traumatic and non-traumatic origin.

3. Methods

This systematic review has been drafted according to the recommendations of The Cochrane Handbook for Systematic Reviews of Interventions [31] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [32]. A protocol of this study was submitted prospectively (PROSPERO - registration number CRD42020140301).

3.1. Information sources and search strategy

Electronic databases of PubMed, Embase and Web of Science were searched up to 15 May 2021. The search strategy (**APPENDIX – Table 4 and 5**), formulated in agreement with three subject matter experts (C.D.V., S.R., W.D.H.), included both terms (and synonyms) for CGD and for therapeutic methods. In addition, non-specific terms were used for therapeutic methods to allow a broad search in the literature. Additional terms were added to include only randomized controlled trials (RCTs).

3.2. Article selection

The study inclusion criteria were: (1) patients (≥ 18 years old) who presented with both dizziness and a cervical spine dysfunction, either reported as such or implied by mentioning cervical spine symptoms or cervical spine triggers for dizziness; (2) evaluation of the effectiveness of therapeutic methods on CGD (primary outcome measure), cervical spine and balance symptoms (secondary outcome measures); (3) RCT design; and (4) written in English or Dutch. RCTs that included patients suffering from strong sensations of spinning vertigo or whose dizziness could be explained by another disorder, were excluded. RCTs which discussed only preliminary findings were excluded as well.

All collected articles and predefined study selection criteria were imported into an excel template (available from: http://processbook.kce.fgov.be) by first author C.D.V. and provided to all reviewers (J.L. and W.D.H.). After each reviewer screened all articles separately, the findings were compared to form a consensus.

The reference lists were checked manually for additional relevant RCTs of all RCTs included through consensus.

3.3. Data collection process

The following data were extracted from the included RCTs: (1) study characteristics (authors, year of publication, and sample size); (2) patient characteristics (age, gender, and criteria for CGD); (3) therapeutic characteristics (type, intensity, and duration); and (4) therapeutic effect on CGD and, if mentioned, on the cervical spine and balance symptoms. In case of unclear or missing data, the corresponding authors were contacted.

Data extraction was performed independently using a pre-formatted excel spreadsheet by C.D.V. and J.L. Results were compared afterward, and any discrepancies were discussed to reach a final consensus. If needed, a third reviewer (W.D.H.) provided additional feedback.

To facilitate insight into the study results, the collected data were discussed separately depending on the cause of CGD mentioned (traumatic versus non-traumatic) and the type of therapy investigated (e.g., physiotherapeutic techniques, medication).

3.4. Risk of bias assessment

For the risk of bias (RoB) assessment, the RoB 2.0 tool was used [33, 34]. Each RCT was screened for bias in five domains: the randomization procedure, the intervention, handling missing outcome data, the measurement of the outcome, and the reported results. The RoB assessment was performed individually by the reviewers (C.D.V. and J.L.) in the manner described in the RoB 2.0 guidelines. The individual assessments of C.D.V. and J.L. were compared, and where they disagreed, a third reviewer (W.D.H.) made the final decision.

3.5. Statistical analysis

For each of the included RCTs, the within-group differences (i.e., the differences between baseline and post-therapy results) were first calculated for both the intervention and control groups separately. Then, these within-group differences in the outcome parameter were compared between intervention and control groups to measure the magnitude of the therapeutic effects. Means and standard deviations were extracted from the RCTs. Non-reported standard deviations were calculated based on the reported confidence intervals (CI), standard errors, or p-values. Other calculations performed were merging of data results of similar experimental interventions within the same RCT, merging of data results related to the same plane of movement (e.g., rotation left and right), and conversion of outcome results into the units of the most commonly used instrument if needed [35]. Along with the difference in means (MD), the equivalent 95% CI was also computed.

A meta-analysis, using the random-effects method [36], was performed provided that a minimum of three RCTs had comparable patient and therapeutic characteristics. Heterogeneity among these RCTs was measured with the Cochran Q test. Significant heterogeneity was present if $Chi^2 < 0.10$. The Higgins I^2 test expressed the amount of heterogeneity. The I^2 ranges between 0 and 100%, whereby a higher value means more heterogeneity across studies [37]. Results were graphically displayed through forest plots.

Significance was set at a p-value of less than 0.05. Statistical analyses were performed using the software package Review Manager 5.3 [31].

3.6. Minimal clinically important difference

Information on the minimal clinically important difference (MCID) is available in the literature for the Dizziness Handicap Inventory questionnaire (DHI 0-100 points = 18 points) [38], neck pain visual analogue scale (VAS 0-100 mm = varied between 4.6 to 21.4 mm) [39], and cervical range of motion (CROM flexion-extension = 4-6°; CROM rotation = 5-10°) [40].

3.7. GRADE assessment

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach was used to rate the quality of the retrieved evidence. The following five domains were assessed: within-study risk of bias, inconsistency, indirectness, imprecision, and publication bias [41]. Information on the interpretation of the quality of evidence score is provided in **TABLE 1**. The GRADE was performed by C.D.V. and J.L. separately. Their findings were compared. In case of disagreements, a third reviewer (W.D.H.) made the final decision.

Table 1. *Interpretation of the quality of evidence (the GRADE method)* [a, b]

Quality	Explanation
High	There is high confidence that the true effect lies close to that of the estimate of the effect.
Moderate	There is moderate confidence in the effect estimate. The true effect is likely to be close to the estimate of the effect but there is a possibility that is it substantially different.
Low	There is limited confidence in the effect estimate. The true effect may be substantially different from the estimate of the effect.
Very low	There is little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of the effect.

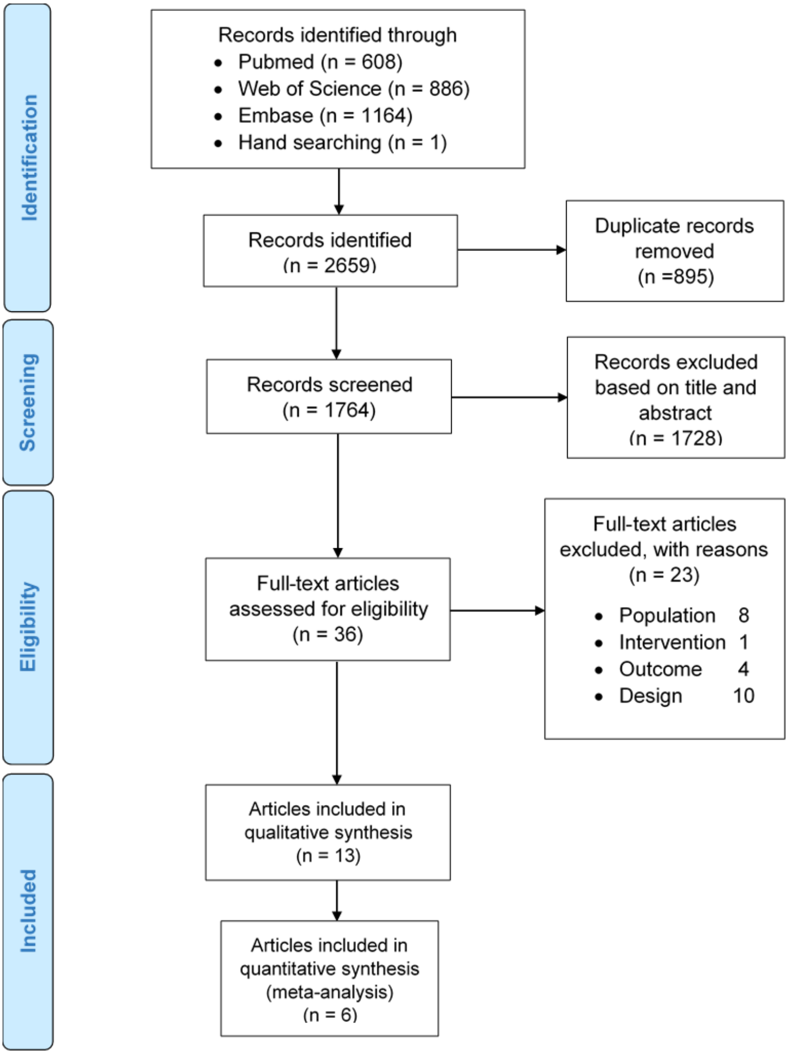
[a] Abbreviations: GRADE = Grading of Recommendations, Assessment, Development and Evaluations

[b] Guyatt, G.H., et al., GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. British Medical Journal, 2008. 336(7650): p. 924-6.

4. Results

The search yielded 2658 articles. Manual search resulted in one additional article [42]. Of those, thirty-six articles were screened on full text resulting in 13 RCTs representing 11 unique studies (n=898), meeting all eligibility criteria [42-54]. Flowchart of study selection and characteristics of excluded articles are available in **FIGURE 1** and **APPENDIX (Table 8)**, respectively.

Figure 1. *PRISMA Flow Diagram*



4.1. Characteristics of the included RCTs

Characteristics of the included RCTs are presented in **APPENDIX (Table 6 and 7)**.

The main criteria for a CGD diagnosis were non-rotatory dizziness and neck pain [45-54]. Only three RCTs (n=169) specified the cause of CGD, all of which were of traumatic origin (i.e., whiplash-associated disorder) [42-44].

Twelve of the 13 RCTs discussed physiotherapeutic techniques [42-53]. Six RCTs focused on manual therapy and investigated traction-manipulations [46] and sustained natural apophyseal glides (SNAGs) of the upper cervical segments in the dizziness provoking movement directions [48, 50], or a combination of SNAGs and mobilizations [51-53]. Three RCTs that did specify the cause of CGD, focused on exercise therapy and investigated vestibular rehabilitation [42, 43] and cervical spine exercises (including motor relearning, stabilization, and endurance training) with or without behavioral approach [44]. In three RCTs, exercise therapy was combined with dry needling (trapezius and sternocleidomastoid muscles) [45], or manual therapy. The manual therapy consisted of DennerollTM cervical spine traction [49], or soft tissue and passive mobilization techniques [47]. The exercise therapy included cervical spine stretching, strengthening and stabilization exercises, relaxation techniques, and trunk stabilization exercises. One RCT discussed an alternative therapy, Shi-style cervical spine mobilizations [54].

Control interventions were usually sham or no therapy [42, 43, 46-48, 50-53]. Yet, the control intervention was physiotherapeutic techniques in three RCTs (i.e., general physical activity [44], cervical spine exercises [45] or a multimodal cervical program [49]), or traditional massage in one RCT [54].

Dizziness outcome measures were intensity, frequency, and impact on quality of life. Cervical spine outcome measures were reported in ten RCTs [42, 44, 46-53] and included cervical spine pain, mobility, repositioning accuracy, trigger points, sagittal alignment, and impact on quality of life. Static and dynamic balance outcome measures were reported in nine RCTs [42, 44-48, 50, 52, 53].

Follow-up periods ranged from 48 hours to 1 year. In addition, six RCTs, which did not specify the cause of CGD and discussed manual therapy, provided data for meta-analyses [46, 48, 50-53].

4.2. Risk of bias of the individual RCTs

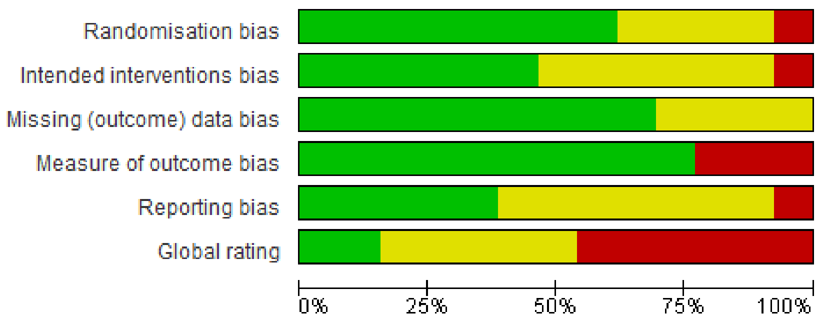
Risk of bias was high or unclear for the randomization procedure (5 RCTs) [42, 45, 47, 50, 51], the intervention (7 RCTs) [42-45, 47, 49, 54], handling missing outcome data (4 RCTs) [43, 46, 48, 54], the measurement of the outcome (3 RCTs) [44, 45, 47], and the reported results (8 RCTs) [42, 43, 45, 47, 50-52, 54]. The overall RoB was low in 2 RCTs [49, 53], moderate in 5 RCTs [46, 48, 50-52] and high in 6 RCTs [42-45, 47, 54] (**TABLE 2** and **TABLE 3**).

Table 2. *Risk of bias summary: review authors' judgements about each risk of bias item for each included RCT* [a]

	Yao et al (2019)	Treleaven et al (2016)	Reid et al (2015)	Reid et al (2014 Sept)	Reid et al (2014 April)	Reid et al (2008)	Moustafa et al (2017)	Micarelli (2021)	Karlberg et al (1996)	Hansson et al (2013)	Hansson et al (2006)	Carrasco-Uribarren (2021)	Aydin et al (2019)
Randomisation bias	+	+	+	+	?	?	+	+	?	+	?	+	−
Intended interventions bias	?	?	+	+	+	+	?	+	−	?	?	+	?
Missing (outcome) data bias	?	+	+	+	+	+	+	?	+	?	+	?	+
Measure of outcome bias	+	−	+	+	+	+	+	+	−	+	+	+	−
Reporting bias	−	+	+	?	?	?	+	+	?	?	?	+	?
Global rating	−	−	+	?	?	?	+	?	−	−	−	?	−

[a] Interpretation: + = Low risk of bias; ? = Moderate risk of bias; − = High risk of bias

Table 3. *Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included RCTs* [a]



[a] Interpretation: + = Low risk of bias; ? = Moderate risk of bias; − = High risk of bias

4.3. Results of the individual RCTs and syntheses

The results are available in **APPENDIX (Table 9)**. The GRADE assessment is provided in **APPENDIX (Table 10)**.

4.3.1. RCTs specifying the cause of CGD (traumatic origin in all cases)

Dizziness. There is only a very low quality of evidence (GRADE) for the effectiveness of exercise therapy in reducing CGD. In comparison with controls, cervical spine exercises with or without behavioral therapy may reduce dizziness intensity (10cm visual analogue scale (VAS); at rest: MD -6.46 [-10.93; -1.99] 95% CI, p<0.005 ; during activity: MD -6.93 [-12.79; -1.07] 95% CI, p=0.02) and impact on quality of life (University of California Los Angeles dizziness questionnaire; MD -2.65 [-4.82; -0.48] 95% CI, p=0.02) up to 1-year follow-up [44]. Vestibular rehabilitation may not affect CGD [42, 43].

Cervical spine. There is only very low quality of evidence (GRADE) for the effectiveness of exercise therapy in reducing cervical spine symptoms. In comparison with controls, cervical spine exercises with or without behavioral therapy may improve head repositioning accuracy towards rotation (MD -1.53 [-2.71; -0.35] 95% CI, p=0.01) and reduce Neck Disability Index score (MD -2.26 [-4.04; -0.48] 95% CI, p=0.01) up to 1-year follow-up. However, cervical spine exercises with or without behavioral therapy may have no effect on neck pain (10cm VAS; MD at 1-year follow-up: -4.73 [-10.77 ; 1.31] 95% CI, p=0.13) although the MD exceeds the MCID [44]. Vestibular rehabilitation may not affect cervical spine symptoms [42, 43].

Balance. Based on a very low level of evidence (GRADE), exercise therapy may have no effect on static or dynamic balance compared with the control intervention [42-44].

4.3.2. RCTs not specifying the cause of CGD

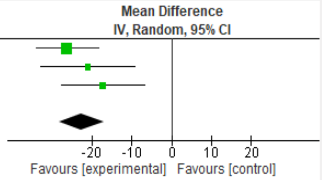
Dizziness. Based on moderate level of evidence (GRADE) and in comparison with controls, manual therapy likely reduces CGD (i.e., intensity [46, 50, 51, 53], frequency [51, 53], and impact on quality of life [46, 48, 50, 51, 53]) up to 1-year follow-up. Meta-analyses confirm the overall beneficial effect of manual therapy in reducing dizziness intensity (10cm VAS, MD at 4-6 weeks follow-up: -22.56 [-

28.11; -17.01] 95% CI ; p<0.001; I^2=0%; **FIGURE 2**) [46, 50, 51, 53], and the impact of dizziness on quality of life (Dizziness Handicap Inventory scale (DHI), MD at 4-6 weeks follow-up: -10.04 [-16.36; -3.73] 95% CI ; p=0.002; I^2=79%; **FIGURE 3**) even though the MD does not exceed the MCID in this case [46, 50, 51, 53, 55]. Furthermore, based on very low level of evidence (GRADE) and in comparison with controls, combined exercise therapy and manual therapy may reduce CGD (i.e., intensity [47, 49], frequency [49], and impact on quality of life [49]), and combined exercise and dry needling therapy may reduce the impact of CGD on quality of life [45] up to 1-year follow-up. Shi-style cervical mobilizations probably do not reduce CGD compared to the control intervention, which is based on a moderate level of evidence (GRADE) [54].

Figure 2. *Forest plot demonstrating the effectiveness of manual therapy on Dizziness intensity at 4-6 weeks post-therapy* [a, b]

Study or Subgroup	Experimental (MT) Mean	SD	Total	Control (sham) Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Carrasco-Uribarren (2021)	-28.9	12.6	20	-2.7	12.7	20	50.2%	-26.20 [-34.04, -18.36]
Reid (2008)	-29.1	15.2	16	-8.1	19.2	17	22.2%	-21.00 [-32.78, -9.22]
Reid (2014 April+2015)	-21.8	24.1	58	-4.6	23.1	28	27.6%	-17.20 [-27.77, -6.63]
Total (95% CI)			**94**			**65**	**100.0%**	**-22.56 [-28.11, -17.01]**

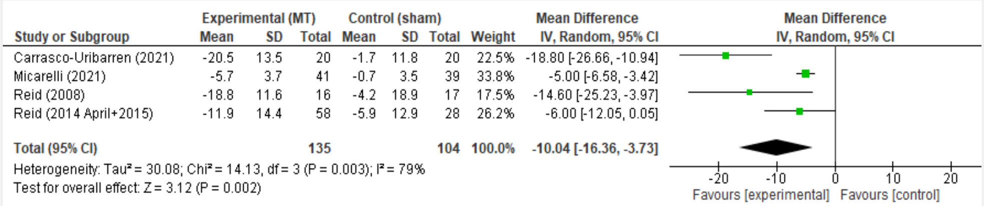
Heterogeneity: Tau² = 0.00; Chi² = 1.88, df = 2 (P = 0.39); I² = 0%
Test for overall effect: Z = 7.96 (P < 0.00001)



(1) Carrasco-Uribarren (2021) = traction-manipulation
(2) Reid (2008) = sustained natural apophyseal glides
(3) Reid (2014 April+2015) = sustained natural apophyseal glides and cervical mobilizations

[a] Dizziness intensity: 0-100mm VAS; the higher the VAS, the higher the dizziness intensity
[b] Abbreviations: CI = confidence interval; df = degrees of freedom; IV = inverse variance; MT = manual therapy; SD = standard deviation

Figure 3. *Forest plot demonstrating the effectiveness of manual therapy on Dizziness Handicap Inventory (DHI) at 4-6 weeks post-therapy* [a, b]



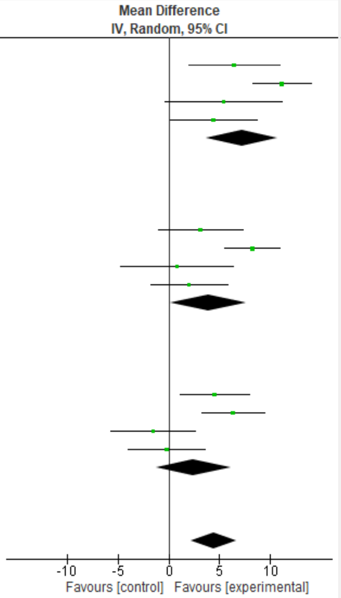
(1) Carrasco-Uribarren (2021) = traction-manipulation
(2) Micarelli (2021) = sustained natural apophyseal glides
(3) Reid (2008) = sustained natural apophyseal glides
(4) Reid (2014 April+2015) = sustained natural apophyseal glides and cervical mobilizations

[a] DHI: 0-100 points; the higher the DHI score, the higher the impact of dizziness on quality of life
[b] Abbreviations: CI = confidence interval; df = degrees of freedom; DHI = Dizziness Handicap Inventory; IV = inverse variance; MT = manual therapy; SD = standard deviation

Cervical spine. Based on moderate level of evidence (GRADE) and in comparison with controls, manual therapy likely improves cervical spine symptoms (i.e., pain [46, 48, 50], mobility [46, 48, 50], and impact on quality of life [48]) up to 1-year follow-up. Meta-analyses confirm the overall beneficial effect of manual therapy in improving mobility (MD at 4-6 weeks follow-up for CROM flexion-extension: 7.18 [3.65; 10.70] 95% CI, p<0.0001, I^2=65%; MD for CROM rotation 3.88 [0.18; 7.59] 95% CI, p=0.04, I^2=73%; **FIGURE 4**) [46, 48, 50, 52, 53] and pain intensity (10cm VAS, MD at 4-6 weeks follow-up: -14.01 [-22.77; -5.26] 95% CI, p=0.002, I^2=81%; **FIGURE 5**) [46, 48, 50, 51, 53]. Here, the MDs for CROM flexion-extension and cervical spine pain intensity exceed their respective MCIDs. Furthermore, based on very low level of evidence (GRADE) and in comparison with controls, combined exercise and manual therapy may improve cervical spine pain [47, 49], head repositioning accuracy [49], and sagittal alignment [49], and combined exercise and dry needling therapy may improve cervical spine pain, pressure pain threshold and head repositioning accuracy [45] up to 1-year follow-up. No information is available on the effectiveness of Shi-style cervical mobilizations in improving neck symptoms [54].

Figure 4. *Forest plot demonstrating the effectiveness of manual therapy on cervical range of motion (CROM) at 4-6 weeks post-therapy* [a, b]

Study or Subgroup	Experimental (MT) Mean	SD	Total	Control (sham) Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.1.1 Flexion-extension								
Carrasco-Uribarren (2021)	3.9	7.4	20	-2.5	7	20	7.8%	6.40 [1.94, 10.86]
Micarelli (2021)	11.6	6.3	41	0.5	6.8	39	9.5%	11.10 [8.22, 13.98]
Reid (2008)	4.1	8.7	16	-1.3	8.1	17	6.5%	5.40 [-0.34, 11.14]
Reid (2014 Sept+2015)	6.7	10	58	2.3	9.1	28	8.0%	4.40 [0.16, 8.64]
Subtotal (95% CI)			**135**			**104**	**31.9%**	**7.18 [3.65, 10.70]**
Heterogeneity: Tau² = 8.21; Chi² = 8.51, df = 3 (P = 0.04); I² = 65%								
Test for overall effect: Z = 3.98 (P < 0.0001)								
1.1.3 Rotation								
Carrasco-Uribarren (2021)	4.3	5.9	20	1.2	7.4	20	8.1%	3.10 [-1.05, 7.25]
Micarelli (2021)	8.6	6.3	41	0.4	5.9	39	9.7%	8.20 [5.53, 10.87]
Reid (2008)	3.4	8.9	16	2.6	7.1	17	6.7%	0.80 [-4.71, 6.31]
Reid (2014 Sept+2015)	6.5	8.3	58	4.5	8.5	28	8.5%	2.00 [-1.80, 5.80]
Subtotal (95% CI)			**135**			**104**	**33.1%**	**3.88 [0.18, 7.59]**
Heterogeneity: Tau² = 10.11; Chi² = 10.93, df = 3 (P = 0.01); I² = 73%								
Test for overall effect: Z = 2.05 (P = 0.04)								
1.1.5 Lateroflexion								
Carrasco-Uribarren (2021)	2.6	5.5	20	-1.9	5.4	20	9.0%	4.50 [1.12, 7.88]
Micarelli (2021)	6.6	7	41	0.3	7	39	9.3%	6.30 [3.23, 9.37]
Reid (2008)	1.7	5.5	17	3.2	6.8	17	8.1%	-1.50 [-5.66, 2.66]
Reid (2014 Sept+2015)	3.6	11.5	58	3.8	6.2	28	8.6%	-0.20 [-3.95, 3.55]
Subtotal (95% CI)			**136**			**104**	**35.0%**	**2.45 [-1.18, 6.08]**
Heterogeneity: Tau² = 10.39; Chi² = 12.50, df = 3 (P = 0.006); I² = 76%								
Test for overall effect: Z = 1.32 (P = 0.19)								
Total (95% CI)			**406**			**312**	**100.0%**	**4.39 [2.15, 6.63]**
Heterogeneity: Tau² = 11.56; Chi² = 46.17, df = 11 (P < 0.00001); I² = 76%								
Test for overall effect: Z = 3.84 (P = 0.0001)								
Test for subgroup differences: Chi² = 3.54, df = 2 (P = 0.17), I² = 43.4%								



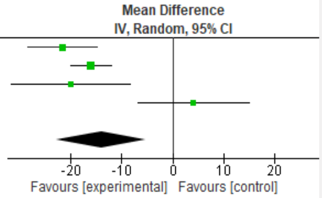
(1) Carrasco-Uribarren (2021) = traction-manipulation
(2) Micarelli (2021) = sustained natural apophyseal glides
(3) Reid (2008) = sustained natural apophyseal glides
(4) Reid (2014 Sept+2015) = sustained natural apophyseal glides and cervical mobilizations

[a] CROM: degrees; the higher the CROM, the higher the cervical mobility
[b] Abbreviations: CI = confidence interval; CROM = cervical range of motion; df = degrees of freedom; IV = inverse variance; MT = manual therapy; SD = standard deviation

Figure 5. *Forest plot demonstrating the effectiveness of manual therapy on neck pain intensity at 4-6 weeks post- therapy* [a, b]

Study or Subgroup	Experimental (MT) Mean	SD	Total	Control (sham) Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Carrasco-Uribarren (2021)	-23.7	9.7	20	-2.1	12.2	20	27.2%	-21.60 [-28.43, -14.77]
Micarelli (2021)	-16.9	9.3	41	-0.9	8.6	39	30.6%	-16.00 [-19.92, -12.08]
Reid (2008)	-31	15.1	16	-11	18.8	17	20.7%	-20.00 [-31.60, -8.40]
Reid (2014 April+2015)	-15.5	24.8	58	-19.6	24	28	21.6%	4.10 [-6.84, 15.04]
Total (95% CI)			**135**			**104**	**100.0%**	**-14.01 [-22.77, -5.26]**

Heterogeneity: Tau² = 61.29; Chi² = 15.99, df = 3 (P = 0.001); I² = 81%
Test for overall effect: Z = 3.14 (P = 0.002)



(1) Carrasco-Uribarren (2021) = traction-manipulation
(2) Micarelli (2021) = sustained natural apophyseal glides
(3) Reid (2008) = sustained natural apophyseal glides
(4) Reid (2014 April+2015) = sustained natural apophyseal glides and cervical mobilizations

[a] Neck pain intensity: 0-100mm VAS; the higher the VAS score, the higher the neck pain intensity
[b] Abbreviations: CI = confidence interval; df = degrees of freedom; IV = inverse variance; MT = manual therapy; SD = standard deviation; VAS = visual analogue scale

Balance. Based on a moderate level of evidence (GRADE) and in comparison with controls, manual therapy likely improves balance (i.e., static [48, 50, 52, 53] and dynamic balance [46, 52, 53]) up to 1-year follow-up. Compared with controls, combined exercise and manual therapy may improve static balance [47], and combined exercise and dry needling therapy may improve fall index [45]). However, the level of evidence for this finding is very low (GRADE). No information is available on the effectiveness of Shi-style cervical mobilizations on balance [54].

5. Discussion

Thirteen RCTs with a total of 898 patients were included in this systematic review [42-54]. However, the cause of CGD was specified in only three RCTs, all of which investigated exercise therapy [42-44].

5.1. Summary of main results

The effectiveness of manual therapy (aimed at the upper cervical segments in the dizziness-provoking directions) was investigated in six RCTs [46, 48, 50-53]. We found a moderate quality of evidence supporting the use of upper cervical manual therapy in reducing CGD, which is consistent with the literature [23, 24]. What has not been previously synthesized is that there is also moderate evidence for the effectiveness of upper cervical manual therapy in reducing cervical spine and balance symptoms in patients with CGD. Based on the MCIDs, this includes a clinically significant improvement of symptoms for cervical spine pain and ROM from the patients' perspective. The literature confirms cervical spine dysfunction, such as reduced range of motion [56-58], and postural imbalance [59-61] in patients with CGD, especially those with a whiplash-associated disorder. Theoretical background to support the positive effect on cervical spine symptoms is that manual therapy induces a chain of neurophysiological effects (e.g., decreasing muscle spasm, reducing inflammatory mediators) in the cervical spine [62, 63]. In addition, manual therapy also affects direct and indirect neural pathways between the cervical spine and the central nervous system (including the vestibular and visual systems), which may explain the positive effects of manual therapy on balance function [63].

Results of the only three RCTs investigating the effectiveness of exercise therapy in patients with whiplash-related CGD were of very low quality of evidence and provided conflicting results [42-44]: cervical spine exercises, preferably with a behavioral approach, may be effective in reducing CGD and cervical spine symptoms, including a clinically relevant reduction of neck pain as reported by the patient based on its MCID. However, vestibular rehabilitation would have no positive effects at all in patients with whiplash-related CGD. In the literature, the evidence for the use of (cervical spine) exercises to improve cervical spine symptoms in chronic whiplash-associated disorder is modest [64, 65], and study results on the added value of behavioral therapy are unclear [66, 67]. A possible explanation for the uncertainty about the effectiveness of behavioral therapy may be that studies include both patients with and without central sensitization in their intervention group. It could be that patients with central sensitization benefit most from behavioral therapy [68]. Another possible explanation may be that behavioral therapy should be given before exercise therapy [68]. Vestibular rehabilitation is an effective therapy for many vestibular disorders [69]. However, research on the effectiveness of vestibular rehabilitation in patients with neck pain or CGD is very limited. Only two RCTs could be included, of very low methodological quality [42, 43]. Given that there is a rationale for the effectiveness of vestibular rehabilitation in CGD [22], further high-quality research is indicated.

Thus far, upper cervical manual therapy seems to be the most promising therapy in patients with CGD. However, this review identified that a combination of manual therapy and exercise therapy is more effective than manual therapy alone in reducing CGD and both cervical spine and balance symptoms. The effectiveness of combined manual and exercise therapy has only been summarized in the context of patients with neck pain without dizziness [70-72].

Not all objectives of this review could be addressed thoroughly. It is still not clear whether therapy should be different depending on the cause of CGD. This is because only three of the included RCTs specified the cause of CGD [42-44]. Further complicating this issue is the heterogeneity in the diagnostic criteria used for CGD.

5.2. Evidence quality of the review

Several factors reduced confidence in the review's effect estimates because of limitations in the included RCTs, such as: (1) moderate to high RoB in most RCTs, (2) multicomponent interventions, which increase the indirectness of the evidence (i.e., it is not clear to what extent the individual therapeutic components contribute to the overall therapeutic effect), (3) wide confidence intervals in the RCTs with a small sample size or large variability in the standard deviation of measurements between individuals, and (4) heterogeneity of diagnostic criteria for CGD, outcome measures and control interventions.

5.3. Potential biases in the review process

Even though the methodological procedures (Cochrane) and reporting guidelines (PRISMA) were rigorously adhered to, bias cannot be excluded. First, bias may have been introduced by the predefined restrictions on study eligibility (i.e., language and study design). Additionally, although the methods for the meta-analysis were discussed with a statistics expert from the University of Antwerp, a professional librarian with expertise in systematic review methodology was not involved.

5.4. Recommendations for future research

Further research into the optimal therapy methods in patients with CGD is needed. It is important that all studies use the same diagnostic criteria for CGD. In addition, a distinction should be made between patients with traumatic and non-traumatic origin for CGD. Furthermore, it is important that the studies correctly follow the methodological study procedures to guarantee that the measured therapy effect is reliable.

6. Conclusions

Based on the moderate quality of evidence, manual therapy effectively reduces CGD, neck, and balance symptoms. Combined manual and exercise therapy maybe even more effective in reducing CGD, cervical spine, and balance symptoms, but the quality of evidence for this is currently very low. Further research of high methodological quality is needed, including evaluating whether the cause for CGD should be considered.

7. Appendix

Articles were retrieved from the electronic databases of PubMed, Embase and Web of Science up to May 15, 2021. The search strategy included terms (and synonyms) for CGD and therapeutic modalities. The latter contained only non-specific terms in order to retain all therapeutic modalities described in the literature.

Table 4. *Search strategy - Database: Embase*

1. ('cervicogenic dizziness'/exp
2. ((‘cervical’:ab,ti
3. ‘cervicogenic’:ab,ti
4. ‘proprioceptive’:ab,ti)
5. “OR” Boolean between 1-4
6. (‘dizziness’:ab,ti
7. ‘vertigo’:ab,ti
8. ‘lightheadedness’:ab,ti
9. ‘light-headedness’:ab,ti
10. ‘light headedness’:ab,ti
11. ‘unsteadiness’:ab,ti
12. ‘imbalance’:ab,ti
13. ‘instability’:ab,ti
14. ‘disorientation’:ab,ti
15. ‘disequilibrium’:ab,ti
16. ‘dysequilibrium’:ab,ti
17. 'vertigo'/exp
18. 'dizziness'/exp)))
19. “OR” Boolean between 6-18
20. (‘therapy’:ab,ti
21. ‘therapies’:ab,ti
22. “manual therapy”:ab,ti
23. ‘therapeutic’:ab,ti
24. ‘treatment’:ab,ti
25. ‘treatments’:ab,ti
26. ‘rehabilitation’:ab,ti
27. ‘management’:ab,ti
28. ‘mobilisation’:ab,ti
29. ‘mobilization’:ab,ti
30. ‘manipulation’:ab,ti
31. ‘chiropractic’:ab,ti
32. ‘behavior’:ab,ti
33. ‘behaviour’:ab,ti
34. ‘behavioral’:ab,ti
35. ‘behavioural’:ab,ti
36. ‘physiotherapy’:ab,ti
37. ‘physiotherapies’:ab,ti
38. “physical therapy”:ab,ti
39. “physical therapies”:ab,ti
40. ‘modality’:ab,ti
41. ‘modalities’:ab,ti
42. 'therapy'/exp
43. 'rehabilitation'/exp)
44. “OR” Boolean between 20-43
45. ((((‘controlled’:ab,ti
46. ‘control’:ab,ti
47. ‘placebo’:ab,ti
48. ‘placebos’:ab,ti
49. ‘versus’:ab,ti
50. ‘vs’:ab,ti
51. ‘comparison’:ab,ti
52. ‘compared’:ab,ti
53. ‘cross-over’:ab,ti
54. ‘crossover’:ab,ti)
55. “OR” between 45-54
56. (‘trial’:ab,ti
57. ‘study’:ab,ti))
58. ((‘single’:ab,ti
59. ‘double’:ab,ti
60. ‘triple’:ab,ti)
61. “OR” Boolean between 56-60
62. (‘masked’:ab,ti
63. ‘blind’:ab,ti
64. ‘blinded’:ab,ti)))
65. 'controlled clinical trial'/exp)
66. “AND” Boolean between 5 ; 19 ; 44 ; 55 ; 61

__Table 5.__ Search strategy - Database: Web of Science

1. ((cervical
2. cervicogenic
3. proprioceptive)
4. “OR” Boolean between 1-3
5. (dizziness
6. vertigo
7. lightheadedness
8. light-headedness
9. light headedness
10. unsteadiness
11. imbalance
12. instability
13. disorientation
14. disequilibrium
15. dysequilibrium))
16. “OR” Boolean between 5-15
17. (therapy
18. therapies
19. “manual therapy”
20. therapeutic
21. treatment
22. treatments
23. rehabilitation
24. management
25. mobilisation
26. mobilization
27. manipulation
28. chiropractic
29. behavior
30. behaviour
31. behavioral
32. behavioural
33. physiotherapy
34. physiotherapies
35. “physical therapy”
36. “physical therapies”
37. modality OR modalities)
38. “OR” Boolean between 17-37
39. (((controlled
40. control
41. placebo
42. placebos
43. versus
44. vs
45. comparison
46. compared
47. cross-over
48. crossover)
49. “OR” Boolean between 39-48
50. (trial
51. study))
52. ((single
53. double
54. triple)
55. “OR” Boolean 50-54
56. (masked
57. blind
58. blinded)))
59. “OR” Boolean 56-58
60. “AND” Boolean between 4 ; 16 ; 38 ; 49 ; 55 ; 59

Table 6. *Included articles (RCTs): patient characteristics [a]*

A. Articles specifying the cause of CGD (traumatic origin in all cases)

Author (year)	**Group**	**Sample size**	**Demographic data** (age & gender) *	**Criteria for CGD**
Hansson (2006 + 2013) [42, 43]	EG CG	n = 16 (Lost: 8) n = 13 (Lost: 3)	40 (22 -73); 10 females 43 (23 76); 10 females	Inclusion: WAD (grade II / III) with dizziness Exclusion: not mentioned
Treleaven (2016) [44]	EG_1 EG_2 CG	n = 41 (Lost: 9) n = 44 (Lost: 8) n = 55 (Lost: 13)	37.6 ± 12.4; 35 females 41.2 ± 11.8; 30 females 43.3 ± 10.9; 32 females	Inclusion: 18-63 years; WAD II and III; dizziness > 20 mm (100 mm VAS) and neck disability > 20% (NDI) between 6 months and 3 years post WAD; ≥ 5 UCLA-DQ Exclusion: known or suspected serious pathology; earlier neck fracture/subluxation/trauma with persistent injury; neck surgery; neck pain causing > 1 month work' absence the year before the trauma; signs of TBI at the time of the WAD; not neck-related generalized or heavy pain; diseases or injuries affecting full participation; diagnosed severe psychiatric disorder; known drug abuse

B. Articles not specifying the cause of CGD

Author (year)	**Group**	**Sample size**	**Demographic data** (age and gender)*	**Criteria for CGD**
Aydin (2019) [45]	EG CG	n = 30 (Lost: 1) n = 25 (Lost: 5)	36.9 ± 8.5; 30 females 40.1 ± 7.9; 25 females	Inclusion: women, 18-50 years; > 3 months dizziness; neck pain diagnosed as myofascial pain syndrome Exclusion: objective findings on otolaryngological or neurological tests; central or vestibular-induced dizziness; orthostatic hypotension; psychosomatic disorders; heart diseases; cerebrovascular diseases; neoplastic diseases; neck trauma or instability; cervical facet osteoarthritis; neck surgery; use of medication or alcohol
Carrasco-Uribarren (2021) [46]	EG CG	n = 20 (Lost: 0) n = 20 (Lost: 0)	55.90 ± 11.96; 16 females 52.10 ± 16.03; 16 females	Inclusion: > 18 years; dizziness, neck stiffness or pain; positive flexion rotation test; indications for traction manipulation Exclusion: other causes for dizziness (e.g., vestibular dysfunction); presence of red flags; inability to tolerate flexion rotation test

[a]Abbreviations: **AHT** = anterior head translation; **ARA** = absolute rotation angle; **CG** = control group; **CGD** = cervicogenic dizziness; **CNS** = central nervous system; **EG** = experimental group; **IG** = intervention group; **Lost** = lost to follow-up; **mm** = millimeter; **n** = number; **NDI** = neck disability index; **TBI** = traumatic brain injury; **UCLA-DQ** = University of California Los Angeles Dizziness Questionnaire; **VAS** = visual analogue scale; **WAD** = whiplash associated disorder
*Age is reported as median (range) or mean ± SD

B. Articles not specifying the cause of CGD (TABLE 6. Continued)

Author (year)	**Group**	**Sample size**	**Demographic data** (age & gender) *****	**Criteria for CGD**
Karlberg (1996) [47]	EG CG	n = 9 (Lost: 0) n = 8 (Lost: 0)	39 ± 8; 8 females 37 ± 4; 7 females	**Inclusion**: ≤ 55 years; recent onset of neck pain and simultaneous complaints of dizziness; **Exclusion**: history of central nervous system disease; CNS/neck trauma; ear disease; arteriosclerotic disease; psychiatric disease; major injuries of the lower limbs; extracervical causes for dizziness and neck pain
Micarelli (2021) [48]	EG CG	n = 41 (Lost: 0) n = 39 (Lost: 0)	44.3 ± 14.8; 22 females 43.8 ± 13.9; 21 females	**Inclusion**: 18-65 years; ≥ 3 months subjective perception of dizziness associated with pain, motion, stiffness, or specific positions of the neck (clear link in time and severity of neck pain and dizziness is needed); cervical pain, trauma, or disease; in case of neck trauma, temporal relation present between neck injury and start of dizziness; **Exclusion**: extracervical causes for dizziness; recent head/neck/chest trauma or surgery
Moustafa (2017) [49]	EG CG	n = 36 (Lost: 5) n = 36 (Lost: 6)	49.3 ± 4.7; 14 females 50.4 ± 4.9; 11 females	**Inclusion**: > 15 mm AHT distance; < 25° ARA; > 3 months dizziness; dizziness provoked by neck movement/positions; non-rotatory dizziness; dizziness associated with stiff or painful neck ; **Exclusion**: extracervical causes for dizziness; history of stroke; bleeding disorder; current anticoagulation treatment; inflammatory joint disease; infection; tumor; neck fracture; neck pain related to central vascular/neurologic condition; drug abuse
Reid (2008) [50]	EG CG	n = 16 (Lost: 2) n = 17 (Lost: 1)	63.4 ± 13.1; 11 females 63.6 ± 13.7; 10 females	**Inclusion**: 18-90 years; > 3 months; non-rotatory dizziness; dizziness provoked by neck movement/positions or stiff/painful neck; **Exclusion**: extracervical causes for dizziness; cardiovascular disorder; CNS disorder; inflammation; spinal cord pathology; cervical spine cancer or infection; bony disease or marked osteoporosis/disc protrusion; acute cervical nerve root symptoms; neck surgery
Reid (2014 + 2014 + 2015) [51, 52, 53]	EG_1 EG_2 CG	n = 29 (Lost: 1) n = 29 (Lost: 3) n = 28 (Lost: 1)	60.0 ± 10.1; 15 females 61.0 ± 15.7; 18 females 65.6 ± 11.0; 10 females	**Inclusion**: 18-90 years; ≥ 3 months non-rotatory dizziness; history of neck pain/stiffness; dizziness provoked by neck movement/positions; **Exclusion**: extracervical causes for dizziness; other causes of poor balance
Yao (2019) [54]	EG CG	n = 174 (Lost: 20) n = 172 (Lost: 21)	46.3 ± 11.8; 136 females 43.7 ± 12.5; 142 females	**Inclusion**: 18-60 years; non-rotatory dizziness; dizziness provoked by neck movement/positions; stiff/painful neck; **Exclusion**: extracervical causes for dizziness; severe systematic disease

[a]Abbreviations: **AHT** = anterior head translation; **ARA** = absolute rotation angle; **CG** = control group; **CGD** = cervicogenic dizziness; **CNS** = central nervous system; **EG** = experimental group; **IG** = intervention group; **Lost** = lost to follow-up; **mm** = millimeter; **n** = number; **NDI** = neck disability index; **TBI** = traumatic brain injury; **UCLA-DQ** = University of California Los Angeles Dizziness Questionnaire; **VAS** = visual analogue scale; **WAD** = whiplash associated disorder

*Age is reported as median (range) or mean ± SD

Table 7. *Included articles (RCTs): intervention characteristics [a]*

A. Articles specifying the cause of CGD (traumatic origin in all cases)					
Author (year)	**Group**	**Treatment**	**Administration**	**Intensity**	**Description**
Hansson (2006 + 2013) [42, 43]	EG	Vestibular rehabilitation	Therapist-assisted	2 group sessions per week for 6 weeks; each session = 50 min	Balance exercises with eye, head, and trunk movements
	CG	No intervention	N/A	N/A	N/A
Treleaven (2016) [44]	EG_1	Neck-specific exercises	Therapist-assisted + at home	2 supervised sessions per week + home training for 12 weeks; thereafter physical activity was added, and behavioural therapy removed	Cervical motor relearning, stabilisation, and endurance training
	EG_2	Neck-specific exercises with behavioural approach	Therapist-assisted + at home		Neck-specific exercises combined with pain education, graded activity, emotion regulation and coping strategies
	CG	General physical activity	At home	for 12 weeks	e.g., walking, exercise bike, swimming (customised)
B. Articles not specifying the cause of CGD					
Author (year)	**Group**	**Treatment**	**Administration**	**Intensity**	**Description**
Aydin (2019) [45]	EG	Dry needling with neck exercises	Therapist-assisted + at home	2 dry-needling sessions per week + 5x/week neck exercises (2 sessions of 20 min per day) for 4 weeks	· Dry needling: needle (0.25 x 25 mm) was inserted into the M. trap and M. SCM, turned around and removed after 20 minutes · Neck exercises: stretching M. SCM and M. TRAP, cervical isometric strengthening exercises (non-customised)
	CG	Neck exercises	At home	5x/week (2 sessions of 20 min per day) for 4 weeks	Stretching M. SCM and M. TRAP, cervical isometric strengthening exercises (non-customised)
Carrasco-Uribarren (2021) [46]	EG	Traction-manipulation	Therapist-assisted	3 sessions on alternate days; each session = 11 minutes	· First: premanipulative techniques and suboccipital muscle massage · Then: traction-manipulation = high speed and low amplitude techniques at the C0-C1, C1-C2, C2-C3 levels · Finally: relaxed supine position
	CG	Sham intervention	Therapist-assisted	3 sessions on alternate days; each session = 11 minutes	Relaxed supine position

[a]Abbreviations: see page 119

B. Articles not specifying the cause of CGD (TABLE 7. Continued)

Author (year)	Group	Treatment	Administration	Intensity	Description
Karlberg (1996) [47]	EG	Spinal therapy	Therapist-assisted + at home	over a period of 5 to 20 weeks	Soft tissue treatment, cervical spine and trunk stabilisation, active and passive mobilizations, relaxation techniques, ergonomic advice, non-specified home exercises (no balance or vestibular exercises were included) (customised)
	CG	No intervention	N/A	N/A	N/A
Micarelli (2021) [48]	EG	SNAG - Mulligan	Therapist-assisted	6 sessions over 4 weeks	SNAG in the direction of those movements which predominantly cause dizziness (end-range position was held for up to 10 sec)
	CG	Sham intervention	Therapist-assisted	6 sessions over 4 weeks	Detuned laser
Moustafa (2017) [49]	EG	Multimodal cervical program with Denneroll™ traction	Therapist-assisted	3 sessions per week for 10 weeks; each session = 60 min	Cervical traction: Supine position for ± 3 to 20 min with a Denneroll™ behind the neck (positioned at the mid or lower cervical region) Multimodal program: Pain relief (TENS/hot packs), cervical Maitland mobilizations, cervical myofascial release, and therapeutic exercises (deep cervical flexor endurance, scapular retraction exercises, postural education, low-load cervical flexion and extension resistive exercises)
	CG	Multimodal cervical program	Therapist-assisted	3 sessions per week for 10 weeks; each session = 60 min	The same multimodal cervical program as for the EG
Reid (2008) [50]	EG	SNAG - Mulligan	Therapist-assisted	4 to 6 sessions for 4 weeks	Spinal natural apophyseal glides in the direction of those movements which predominantly cause dizziness (end-range position was held for up to 10 sec)
	CG	Sham intervention	Therapist-assisted	20 sec for each neck location; 4 to 6 sessions for 4 weeks	Detuned laser

[a]Abbreviations:**ENS** = Transcutaneous electrical nerve stimulation

B. Articles not specifying the cause of CGD (TABLE 7. Continued)

Author (year)	Group	Treatment	Administration	Intensity	Description
Reid (2014 + 2014 + 2015) [51, 52, 53]	EG_1	SNAG - Mulligan	At home	SNAG = 6 reps for each segment per day; mobilization = 3 reps for each movement per day; for 6 weeks	Self-administered SNAG in the direction of those movements which predominantly cause dizziness (end-range position was held for up to 10 sec; using fingertips or strap)
	EG_2	Self-administered cervical mobilizations	At home	SNAG = 6 reps for each segment per day; mobilization = 3 reps for each movement per day; for 6 weeks	Range of motion exercises into flexion, extension, rotation and lateral flexion
	CG	Sham intervention	Therapist-assisted	2 min on 3 different neck locations; 2 to 6 sessions for 6 weeks	Detuned laser
Yao (2019) [54]	EG	Shi-style cervical mobilizations	Therapist-assisted	6 sessions of 20 min; 3 sessions per week	Soothing tendon (kneading), mobilization (oscillatory movements), dredging collateral steps (shaking)
	CG	Traditional massage	Therapist-assisted	6 sessions of 20 min; 3 sessions per week	Release (kneading acupoints), adjustment (pulling force acupoints), finishing step (stimulating acupoints)

[a]Abbreviations: **C0** = occipital bone; **C1** = first cervical vertebra; **C2** = second cervical vertebra; **C3** = third cervical vertebra; **CG** = control group; **CGD** = cervicogenic dizziness; **EG** = experimental group; **min** = minutes; **M. TRAP** = musculus trapezius; **M. SCM** = musculus sternocleidomastoideus; **N/A** = not applicable. **SNAG** = sustained natural apophyseal glides; **TENS** = Transcutaneous electrical nerve stimulation

Table 8. *Excluded articles* [a]

	Author (year)	Title	Reason for exclusion
1	Ahadi (2019) [73]	Vestibular-Balance Rehabilitation in Patients with Whiplash-Associated Disorders.	Study population (explanation: dizziness is not reported as a required inclusion criterion)
2	Aigner (2006) [74]	Adjuvant laser acupuncture in the treatment of whiplash injuries: a prospective, randomized placebo-controlled trial	Study population (explanation: no dizziness present)
3	Bernal-Utrera (2019) [75]	Manual therapy versus therapeutic exercise in non-specific chronic neck pain: study protocol for a randomized controlled trial	(1) Study population (explanation: no dizziness present) (2) Study design (explanation: study protocol)
4	Bracher (2000) [76]	A Combined Approach for the Treatment of Cervical Vertigo	Study design (explanation: non-RCT, all patients received the same treatment)
5	Florio (1999) [77]	The sequelae of cervical whiplash injury	(1) Study design (explanation: non-RCT, no information available on the randomization procedure) (2) Study methods and findings are not clearly formulated
6	Gang (2015) [78]	Subtle adjustment of the cervical spine combined with Shu Jing Ding Xuan Decoction for cervical vertigo	Study population (explanation: patients with vertebrobasilar insufficiency)
7	Gu (2016) [79]	Effect of three vertigo-stopping needles on neurohumor of patients with cervical vertigo: a controlled trial	Study population (explanation: patients with vertebrobasilar insufficiency)
8	Hahn (2018) [80]	Response to Cervical Medial Branch Blocks In Patients with Cervicogenic Vertigo	Study design (explanation: non-RCT, all patients received the same treatment)

[a] Abbreviations: **NSAID** = Non-Steroidal Anti-Inflammatory Drugs; **RCT** = randomized controlled trial

Table 8. *(Continued)* [a]

	Author (year)	Title	Reason for exclusion
9	He (2021) [81]	Cervicogenic dizziness alleviation after coblation discoplasty: a retrospective study	Study design (explanation: non-RCT, patients who rejected surgery were recruited as the conservative group)
10	Heikkila (2000) [82]	Effects of acupuncture, cervical manipulation and NSAID therapy on dizziness and impaired head repositioning of suspected cervical origin: a pilot study	Study design (explanation: non-RCT, single-subject experiment in which all patients received three different treatments in random order; and pilot study)
11	Jung (2017) [83]	Clinical Decision Making in the Management of Patients With Cervicogenic Dizziness: A Case Series	Study design (explanation: non-RCT, case series)
12	Kendall (2018) [84]	Chiropractic treatment including instrument-assisted manipulation for non-specific dizziness and neck pain in community-dwelling older people: a feasibility randomized sham-controlled trial	Study design (explanation: pilot study)
13	Krabak (2000) [85]	Chronic cervical myofascial pain syndrome: Improvement in dizziness and pain with a multidisciplinary rehabilitation program. A pilot study.	Study design (explanation: pilot study; and non-RCT, all patients received the same treatment)
14	Lin (2012) [86]	Immediate effects of ischemic compression on neck function in patients with cervicogenic cephalic syndrome. Journal of manipulative and physiological therapeutics	Study population (explanation: patients with cephalic syndrome)
15	Liu (2016) [87]	Clinical research on a myofascial pain trigger point combining baihui acupoint therapy of myofascial pain syndrome and living quality analysis	Study population (explanation: dizziness is not reported as a required inclusion criterion)
16	Malmström (2007) [88]	Cervicogenic dizziness: Musculoskeletal findings before and after treatment and long-term outcome	Study design (explanation: non-RCT, single-subject experiment in which all patients received the same treatment)

[a] Abbreviations: **NSAID** = Non-Steroidal Anti-Inflammatory Drugs; **RCT** = randomized controlled trial

Table 8. *(Continued)*

	Author (year)	Title	Reason for exclusion
17	Michels (2007) [89]	Cervical vertigo - cervical pain: an alternative and efficient treatment.	Study design (explanation: non-RCT, one treatment method is investigated between two different subgroups of patients)
18	Minguez-Zuazo (2016) [90]	Therapeutic patient education and exercise therapy in patients with cervicogenic dizziness: a prospective case series clinical study	Study design (explanation: case series clinical study)
19	Peng (2018) [91]	The effectiveness of anterior cervical decompression and fusion for the relief of dizziness in patients with cervical spondylosis	Study design (explanation: non-RCT, patients who declined surgery received conservative treatment)
20	Shikora (2010) [92]	Influence of cervical spine stabilization via Stiff Neck on the postural system in healthy patients: compensation or decompensation of the postural system?	Study population (explanation: no patients with cervicogenic dizziness)
21	Shin (2018) [93]	Can a Traditional Korean Manual Therapy Be a Complementary and Alternative Strategy for Cervicogenic Dizziness? A Study Protocol for a Randomized Controlled Trial.	Study design (explanation: study protocol)
22	Strunk (2009) [94]	Effects of chiropractic care on dizziness, neck pain, and balance: a single-group, pre-experimental, feasibility study	Study design (explanation: non-RCT, single-subject experiment; and feasibility study)
23	Zeng (2006) [95]	Jinger moxibustion for treatment of cervical vertigo - A report of 40 cases.	(1) Study population (explanation: patients with vertebrobasilar insufficiency) (2) Study design (explanation: case series)

[a] Abbreviations: **NSAID** = Non-Steroidal Anti-Inflammatory Drugs; **RCT** = randomized controlled trial

Table 9. *Results of individual articles*

A. Articles specifying the cause of CGD (traumatic origin in all cases)								
Author (year)	**Study type**	**N**	**Experimental intervention (EG)**	**Comparator (CG)**	**Outcomes**			
					Follow-up	**Dizziness**	**Cervical spine**	**Balance**
Hansson (2006 + 2013) [42, 43]	RCT	29	Vestibular rehabilitation	No intervention	T0: baseline T1: 6 wks T2: 12 wks	DHI (0-100 points)	▪ CROM (i.e., flexion, extension, lateral flexion and rotation) (degrees) ▪ Pain intensity (0-100 mm VAS)	Static: ▪ Tandem stance (EO + EC) (sec) ▪ Standing on one leg (EO + EC) (sec) Dynamic: ▪ Figure 8 walking (steps outside line) ▪ Walking heel-to-toe (steps outside line)
						Results: INTERGROUP: Dizziness, neck and balance scores were not sig improved in EG compared to CG at T1 and at T2 (Comment: confidence intervals include the null value which means that there is no statistically significant difference between groups)		
Treleaven (2016) [44]	RCT	140	Neck specific exercises with or without behavioural approach	General physical activity (customized)	T0: baseline T1: 12 wks T2: 24 wks T3: 1 yr	▪ Intensity at rest (0-100 mm VAS) ▪ Intensity during activity (0-100 mm VAS) ▪ UCLA-DQ (0-25 points)	▪ HRA rotation (to neutral head position) (degrees) ▪ NDI (0-50 points) ▪ Pain intensity (0-100 mm VAS)	Static: ▪ Tandem stance (EC) (sec) Dynamic: ▪ Figure 8 walking (steps outside line)
						Results: INTRAGROUP: sig total main effects over time in dizziness, neck, and balance scores (except in static balance) for EG (p<0.001 – 0.04) INTERGROUP: dizziness intensity (at T1 and T3)), UCLA-DQ (at T3), HRA (at T2 and T3) and NDI (at T1, T2 and T3) were sig lower in EG compared to CG (Comment: one hundred and eight (77%) of the patients received therapies for their WAD before participating in the present study)		

[a]Abbreviations: see page 127

B. Articles not specifying the cause of CGD (Table 9. Continued)

Author (year)	Study type	N	Experimental intervention (EG)	Comparator (CG)	Outcome: Follow-up	Outcome: Dizziness	Outcome: Cervical spine	Outcome: Balance
Aydin (2019) [45]	RCT	55	Dry needling with neck exercises (non-customised)	Neck exercises (non-customised)	T0: baseline T1: 4 wks T2: 16 wks	DHI (0-100 points)	▪ Pain intensity (0-10 points NRS) ▪ Pressure-pain threshold algometry (M. TRAP and M. SCM) (kg/cm²)	Fall index score (based on static posturography) (0-100 points NRS)
						Results: INTRAGROUP: sig improvements in dizziness, neck and balance scores for both groups at all time points follow-up (p<0.05) INTERGROUP: DHI total score, neck pain intensity and fall index score were sig improved in EG compared to CG at T1 and T2, and pressure-pain threshold at T2. (Comment: letter to the editor has been sent by the author panel [96])		
Carrasco-Uribarren (2021) [46]	RCT	40	Traction-manipulation	Sham intervention (i.e., relaxed supine position)	T0: baseline T1: 48 h T2: 4 wks	▪ Intensity (0-100 mm VAS) ▪ DHI (0-100 points)	▪ Pain intensity (0-100 mm VAS) ▪ CROM (i.e., flexion, extension, lateroflexion and rotation) (degrees)	Static: ▪ Upright posture (EO + EC) (anteroposterior and mediolateral postural displacement (mm) and confidence ellipse area (mm²)) Dynamic: ▪ Upright posture on unstable surface (EO + EC) (anteroposterior and mediolateral postural displacement (mm) and confidence ellipse area (mm²))
						Results: INTRAGROUP: sig improvement in dizziness intensity (at T1 and T2), DHI (at T1 and T2), neck pain intensity (at T1 and T2), CROM towards flexion (at T1), CROM towards rotation (at T2), CROM towards extension (at T1 and T2) and balance scores (p=0.001-0.032) for EG INTERGROUP: DHI total score, dizziness intensity, neck pain intensity, CROM towards extension and dynamic balance scores were sig improved in EG compared to CG at T1 and T2. CROM towards rotation was sig improved in EG compared to CG only at T1 and CROM lateroflexion only at T2. (p=0.001-0.032)		

[a] Abbreviations: see page 127

B. Articles not specifying the cause of CGD (Table 9. Continued)

Author (year)	Study type	N	Experimental intervention (EG)	Comparator (CG)	Outcome: Follow-up	Outcome: Dizziness	Outcome: Cervical spine	Outcome: Balance
Karlberg (1996) [47]	RCT	17	Spinal therapy (customised)	No intervention	T0: baseline T1: between 5 and 20 wks	▪ Intensity (0-4 points) ▪ Frequency (0-4 points)	▪ Pain intensity (0-100 mm VAS)	Static: ▪ Upright posture with and without vibration (calf/occipital muscles) (EO + EC) (postural sway variance and sway velocity) ▪ Upright posture with galvanic stimulation (vestibular nerves) (EC) (postural sway variance and sway velocity)
						Results: INTRAGROUP: sig improvement in dizziness intensity (p=0.01), neck pain intensity and some balance scores (i.e., velocity parameters) (p<0.05) for EG. No sig improvement in dizziness frequency for EG (p=0.22).		
Micarelli (2021) [48]	RCT	80	Sustained natural apophyseal glides (SNAG)	Sham intervention	T0: baseline T1: 4 wks	DHI (0-100 points)	▪ CROM (i.e., flexion, extension, lateroflexion and rotation) (degrees) ▪ NDI (0-50 points) ▪ Pain intensity (0-100 mm VAS)	Static: ▪ Upright posture (EO + EC) (anteroposterior and mediolateral postural displacement (mm), confidence ellipse area (mm^2) and trace length (mm))
						Results: INTERGROUP: DHI (p=0.005), CROM (p=0.004-0.007), NDI (p=0.05), neck pain intensity (p=0.003) and some balance scores (p=0.005-0.008) were sig improved in EG compared to CG		
Moustafa (2017) [49]	RCT	72	Multimodal cervical program with Denneroll™ traction	Multimodal cervical program	T0: baseline T1: 10 wks T2: 1 yr	▪ Intensity (0-100 mm VAS) ▪ Frequency (0-5 points) ▪ DHI (0-100 points)	▪ HRA (to target head position) (degrees) ▪ Cervical sagittal alignment (absolute rotation angle (degrees) and anterior head translation (cm)) ▪ Pain intensity (0-10 points NRS)	N/A
						Results: INTRAGROUP: sig improvements in dizziness and neck scores (except neck pain intensity at T2 for CG (p=0.4)) for both groups at T1 and T2 INTERGROUP: dizziness scores were not sig lower in EG compared to CG at T1, but neck scores, however, did sig improve. At T2, dizziness (p<0.001) and neck scores were sig improved in EG compared to CG.		

[a] Abbreviations: see page 127

B. Articles not specifying the cause of CGD (Table 9. Continued)

Author (year)	Study type	N	Experimental intervention (EG)	Comparator (CG)	Outcome			
					Follow-up	Dizziness	Cervical spine	Balance
Reid (2008)[50]	RCT	33	Sustained natural apophyseal glides (SNAG)	Sham intervention	T0: baseline T1: 4 wks T2: 6wks T3: 12 wks	▪ Intensity (0-100 mm VAS) ▪ Frequency (0-5 points) ▪ DHI (0-100 points)	▪ Pain intensity (0-100 mm VAS) ▪ CROM (i.e., flexion, extension, lateroflexion and rotation) (degrees)	Static: ▪ Upright posture (EO + EC) (postural sway index (cm)) ▪ Upright posture cervical extension (postural sway index (cm))
						Results: INTRAGROUP: sig improvements in dizziness (p<0.01-003) and neck scores (p<0.001), but not in balance scores, at all time points follow-up for EG. Sig improvements in DHI (at T3, p=0.01) and neck pain intensity (T3) for CG. INTERGROUP: dizziness intensity and DHI (but not dizziness frequency) were sig improved in EG compared to CG at all time points follow-up. Neck pain intensity (T2), CROM towards extension (T1 and T3) and balance scores (T1 and T3) were also sig improved in EG compared to CG.		

[a]Abbreviations: see page 127

B. Articles not specifying the cause of CGD (Table 9. Continued)

Author (year)	Study type	N	Experimental intervention (EG)	Comparator (CG)	Outcome			
					Follow-up	Dizziness	Cervical spine	Balance
Reid (2014 +2014 + 2015) [51, 52, 53]	RCT	86	Self-administered sustained natural apophyseal glides (SNAG) or cervical mobilisations	Sham intervention	T0: baseline T1: 6 wks T2: 12 wks T3: 1 yr	▪ Intensity (0-100 mm VAS) ▪ Frequency (0-5 points) ▪ DHI (0-100 points)	▪ HRA (to neutral head position) (degrees) ▪ CROM (i.e., flexion, extension, lateroflexion and rotation) (degrees) ▪ Pain intensity (0-100 mm VAS)	Static: ▪ Upright posture (EO + EC) (postural sway index (cm)) ▪ Upright posture cervical extension (EO) (postural sway index (cm)) ▪ Upright posture cervical left rotation (EO) (postural sway index (cm)) ▪ Upright posture cervical right rotation (EO) (postural sway index (cm)) Dynamic: ▪ Upright posture on unstable surface (EO) (postural sway index (cm))
						Results: INTRAGROUP: sig improvements in dizziness scores, neck pain intensity and CROM scores for EG. No sig improvements in most HRA and balance scores for EG. INTERGROUP: DHI, dizziness frequency, CROM towards flexion-rotation-lateroflexion and some balance scores were sig improved in EG compared to CG up to 1-yr follow-up. Dizziness intensity was only sig lower in EG compared to CG up to 12-wks follow-up.		
Yao (2019) [54]	RCT	346	Shi-style cervical mobilisations	Traditional massage	T0: baseline T1: 2 wks T2: 4 wks T3: 12 wks T4: 24 wks	DHI (0-100 points)	N/A	N/A
						Results: INTRAGROUP: sig improvements in DHI total score and subscores for both groups at all time points follow-up (p<0.001) INTERGROUP: DHI total score and subscores were not sig lower in EG compared to CG at all time points follow-up (p = 0.182 – 0.993)		

[a]Abbreviations: **CG** = control group; **CGD** = cervicogenic dizziness; **CROM** = cervical range of motion; **DHI** = Dizziness Handicap Inventory; **EC** = eyes closed; **EG** = experimental group; **EO** = eyes open; **HRA** = head repositioning accuracy; **IG** = intervention group; **M. TRAP** = musculus trapezius; **M. SCM** = musculus sternocleidomastoideus; **N/A** = not applicable; **NDI** = Neck Disability Index; **NRS** = numeric rating scale; **RCT** = randomised controlled trial; sig = significant; **T0** = baseline assessment; **T1/2/3/4** = first/second/third/fourth assessment post-therapy; **UCLA-DQ** = University of California Los Angeles Dizziness Questionnaire; **VAS** = Visual Analogue Scale; **WAD** = whiplash associated disorder; **wk(s)** = week(s); **yr** = year

Table 10. *GRADE - Importance of outcomes* [a]

Dizziness outcome	9	Of **most** importance	**Critical** for making a decision (included in evidence profile)
	8		
	7		
Cervical spine outcome	6		**Important**, but not critical for making a decision (included in evidence profile)
Balance outcome	5		
	4		
	3		**Of limited importance** for making a decision (not included in evidence profile)
	2		
	1	Of **least** importance	

[a] Abbreviations: Grading of Recommendations, Assessment, Development and Evaluation

***Table 11.** Summary of findings table*

A. RCTs specifying the cause of CGD (traumatic origin in all cases)

a. Dizziness outcome

Treatment	RCTs	No. of patients	RoB	Inconsistency	Indirectness	Imprecision	Publication bias	GRADE	Importance
Exercise therapy	3 RCTs [42-44]	169	Serious [a,b,c,d,e]	Not serious [f]	Serious [h]	Serious [i]	None	Very low	Critical

b. Cervical spine outcome

Treatment	RCTs	No. of patients	RoB	Inconsistency	Indirectness	Imprecision	Publication bias	GRADE	Importance
Exercise therapy	3 RCTs [42-44]	169	Serious [a,b,c,d,e]	Not serious [f]	Serious [h]	Serious [i]	None	Very low	Important

c. Balance outcome

Treatment	RCTs	No. of patients	RoB	Inconsistency	Indirectness	Imprecision	Publication bias	GRADE	Effectiveness
Exercise therapy	3 RCTs [42-44]	169	Serious [a,b,c,d,e]	Not serious [f]	Serious [h]	Serious [i]	None	Very low	Important

Abbreviations: **CGD** = cervicogenic dizziness; **GRADE** = Grading of Recommendations, Assessment, Development and Evaluation; **No** = number; **RCT** = randomized controlled trial; **RoB** = risk of bias

[a] randomization bias
[b] intended intervention bias
[c] missing outcome bias
[d] reporting bias
[e] measure of outcome bias
[f] inconsistency can be explained by differences in control intervention
[g] inconsistency can be explained by differences in RoB
[h] multicomponent interventions and therefore difficult to allocate the most effective treatment part
[i] small sample size
[j] sufficient sample size, however, the 95% CI includes no effect

Summary of findings table (Table 11. Continued)

B. RCTs not specifying the cause of CGD									
a. Dizziness outcome									
Treatment	**RCTs**	**No. of patients**	**RoB**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**GRADE**	**Importance**
Manual therapy	6 RCTs [46,48,50-53]	239	Not serious	Not serious	Not serious	Serious [i]	None	Moderate	Critical
Combined manual and exercise therapy	3 RCTs [45,47,49]	144	Serious [a,b,d,e]	Not serious [f, g]	Serious [h]	Serious [i, j]	None	Very low	Critical
Alternative therapy	1 RCT [54]	346	Serious	Not serious	Not serious	Not serious	None	Moderate	Critical
b. Cervical spine outcome									
Treatment	**RCTs**	**No. of patients**	**RoB**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**GRADE**	**Importance**
Manual therapy	6 RCTs [46,48,50-53]	239	Not serious	Not serious	Not serious	Serious [i]	None	Moderate	Important
Combined manual and exercise therapy	3 RCTs [45,47,49]	144	Serious [a,b,d,e]	Not serious [f, g]	Serious [h]	Serious [i, j]	None	Very low	Important
c. Balance outcome									
Treatment	**RCTs**	**No. of patients**	**RoB**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**GRADE**	**Importance**
Manual therapy	6 RCTs [46,48,50-53]	239	Not serious	Not serious	Not serious	Serious [i]	None	Moderate	Important
Combined manual and exercise therapy	2 RCTs [45,47]	72	Serious [a,b,d,e]	Not serious [f, g]	Serious [h]	Serious [i, j]	None	Very low	Important

Abbreviations: **CGD** = cervicogenic dizziness; **GRADE** = Grading of Recommendations, Assessment, Development and Evaluation; **No** = number; **RCT** = randomized controlled trial; **RoB** = risk of bias

[a] randomization bias
[b] intended intervention bias
[c] missing outcome bias
[d] reporting bias
[e] measure of outcome bias
[f] inconsistency can be explained by differences in control intervention
[g] inconsistency can be explained by differences in RoB
[h] multicomponent interventions and therefore difficult to allocate the most effective treatment part
[i] small sample size
[j] sufficient sample size, however, the 95% CI includes no effect

8. References

1. Yardley, L., et al., *Prevalence and presentation of dizziness in a general practice community sample of working age people.* British Journal of General Practice, 1998. **48**(429): p. 1131-1135.
2. Kroenke, K., *Symptoms in the Community.* Archives of Internal Medicine, 1993. **153**(21).
3. Hannaford, P.C., et al., *The prevalence of ear, nose and throat problems in the community: results from a national cross-sectional postal survey in Scotland.* Fam Pract, 2005. **22**(3): p. 227-33.
4. Gopinath, B., et al., *Dizziness and vertigo in an older population: the Blue Mountains prospective cross-sectional study.* Clin Otolaryngol, 2009. **34**(6): p. 552-6.
5. Wiltink, J., et al., *Dizziness: anxiety, health care utilization and health behavior--results from a representative German community survey.* J Psychosom Res, 2009. **66**(5): p. 417-24.
6. Mendel, B., J. Bergenius, and A. Langius-Eklof, *Dizziness: A common, troublesome symptom but often treatable.* J Vestib Res, 2010. **20**(5): p. 391-8.
7. Post, R.E. and L.M. Dickerson, *Dizziness: A Diagnostic Approach.* American Family Physician, 2010. **82**(4): p. 361-368.
8. Knapstad, M.K., *Clinical characteristics in patients with cervicogenic dizziness: A systematic review.* Health science reports, 2019. **2**(9): p. e134.
9. Yacovino, D.A. and T.C. Hain, *Clinical characteristics of cervicogenic-related dizziness and vertigo.* Seminars in Neurology, 2013. **33**(3): p. 244-255.
10. Yang, L., et al., *Mechanoreceptors in Diseased Cervical Intervertebral Disc and Vertigo.* Spine (Phila Pa 1976), 2017. **42**(8): p. 540-546.
11. Kristjansson, E. and J. Treleaven, *Sensorimotor function and dizziness in neck pain: implications for assessment and management.* J Orthop Sports Phys Ther, 2009. **39**(5): p. 364-77.
12. Hulse, M., *Disequilibrium, caused by a functional disturbance of the upper cervical spine. Clinical aspects and differential diagnosis.* Manual Medicine, 1983. **1**(1): p. 18-23.
13. Sterling, M., et al., *Development of motor system dysfunction following whiplash injury.* Pain, 2003. **103**(1): p. 65-73.
14. Treleaven, J., G. Jull, and M. Sterling, *Dizziness and unsteadiness following whiplash injury: characteristic features and relationship with cervical joint position error.* J Rehabil Med, 2003. **35**(1): p. 36-43.
15. Abdelkader, N.A., et al., *Decreased neck proprioception and postural stability after induced cervical flexor muscles fatigue.* Journal of Musculoskeletal Neuronal Interactions, 2020. **20**(3): p. 421-428.

16. Wrisley, D.M., et al., *Cervicogenic dizziness: A review of diagnosis and treatment.* Journal of Orthopaedic & Sports Physical Therapy, 2000. **30**(12): p. 755-766.
17. Dros, J., et al., *Impact of dizziness on everyday life in older primary care patients: a cross-sectional study.* Health Qual Life Outcomes, 2011. **9**: p. 44.
18. Fejer, R., K.O. Kyvik, and J. Hartvigsen, *The prevalence of neck pain in the world population: a systematic critical review of the literature.* Eur Spine J, 2006. **15**(6): p. 834-48.
19. Rogers, R.G., *The effects of spinal manipulation on cervical kinesthesia in patients with chronic neck pain: a pilot study.* J Manipulative Physiol Ther, 1997. **20**(2): p. 80-5.
20. Sterling, M., G. Jull, and A. Wright, *Cervical mobilisation: concurrent effects on pain, sympathetic nervous system activity and motor activity.* Man Ther, 2001. **6**(2): p. 72-81.
21. Pickar, J.G., *Neurophysiological effects of spinal manipulation.* Spine J, 2002. **2**(5): p. 357-71.
22. Lystad, R.P., et al., *Manual therapy with and without vestibular rehabilitation for cervicogenic dizziness: a systematic review.* Chiropr Man Therap, 2011. **19**(1): p. 21.
23. Yaseen, K., et al., *The effectiveness of manual therapy in treating cervicogenic dizziness: a systematic review.* J Phys Ther Sci, 2018. **30**(1): p. 96-102.
24. Reid, S.A. and D.A. Rivett, *Manual therapy treatment of cervicogenic dizziness: a systematic review.* Man Ther, 2005. **10**(1): p. 4-13.
25. Hansson, E.E., *Vestibular rehabilitation – For whom and how? A systematic review.* Advances in Physiotherapy, 2009. **9**(3): p. 106-116.
26. Malfliet, A., et al., *Lack of evidence for central sensitization in idiopathic, non-traumatic neck pain: a systematic review.* Pain Physician, 2015. **18**(3): p. 223-36.
27. Van Oosterwijck, J., et al., *Evidence for central sensitization in chronic whiplash: a systematic literature review.* Eur J Pain, 2013. **17**(3): p. 299-312.
28. Chimenti, R.L., L.A. Frey-Law, and K.A. Sluka, *A Mechanism-Based Approach to Physical Therapist Management of Pain.* Phys Ther, 2018. **98**(5): p. 302-314.
29. Treleaven, J., G. Jull, and H. Grip, *Head eye co-ordination and gaze stability in subjects with persistent whiplash associated disorders.* Manual Therapy, 2011. **16**(3): p. 252-257.
30. Huntley, A.H., J.Z. Srbely, and J.L. Zettel, *Experimentally induced central sensitization in the cervical spine evokes postural stiffening strategies in healthy young adults.* Gait and Posture, 2015. **41**(2): p. 652-657.

31. Higgins JPT, T.J., Chandler J, Cumpston M, Li T, Page MJ, Welch VA., *Cochrane Handbook for Systematic Reviews of Interventions version 6.2.* Cochrane Database of Systematic Reviews, 2021.
32. Liberati, A., et al., *The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration.* PLoS Med, 2009. **6**(7): p. e1000100.
33. Ma, L.L., et al., *Methodological quality (risk of bias) assessment tools for primary and secondary medical studies: what are they and which is better?* Mil Med Res, 2020. **7**(1): p. 7.
34. Sterne, J.A.C., et al., *RoB 2: a revised tool for assessing risk of bias in randomised trials.* BMJ, 2019. **366**: p. l4898.
35. Johnston, B.C., et al., *Patient-reported outcomes in meta-analyses-part 2: methods for improving interpretability for decision-makers.* Health Qual Life Outcomes, 2013. **11**: p. 211.
36. DerSimonian, R. and N. Laird, *Meta-analysis in clinical trials.* Control Clin Trials, 1986. **7**(3): p. 177-88.
37. Higgins, J.P., et al., *Measuring inconsistency in meta-analyses.* BMJ, 2003. **327**(7414): p. 557-60.
38. Jacobson, G.P. and C.W. Newman, *The development of the Dizziness Handicap Inventory.* Arch Otolaryngol Head Neck Surg, 1990. **116**(4): p. 424-7.
39. MacDowall, A., et al., *Validation of the visual analog scale in the cervical spine.* J Neurosurg Spine, 2018. **28**(3): p. 227-235.
40. Jorgensen, R., et al., *Responsiveness of clinical tests for people with neck pain.* BMC Musculoskelet Disord, 2017. **18**(1): p. 548.
41. Guyatt, G.H., et al., *GRADE: an emerging consensus on rating quality of evidence and strength of recommendations.* Bmj, 2008. **336**(7650): p. 924-6.
42. Ekvall Hansson, E., et al., *Dizziness among patients with whiplash-associated disorder: a randomized controlled trial.* J Rehabil Med, 2006. **38**(6): p. 387-90.
43. Hansson, E.E., L. Persson, and E.M. Malmstrom, *Influence of vestibular rehabilitation on neck pain and cervical range of motion among patients with whiplash-associated disorder: a randomized controlled trial.* J Rehabil Med, 2013. **45**(9): p. 906-10.
44. Treleaven, J., et al., *Balance, dizziness and proprioception in patients with chronic whiplash associated disorders complaining of dizziness: A prospective randomized study comparing three exercise programs.* Man Ther, 2016. **22**: p. 122-30.
45. Aydin, T., et al., *The Effectiveness of Dry Needling and Exercise Therapy in Patients with Dizziness Caused By Cervical Myofascial Pain Syndrome;*

Prospective Randomized Clinical Study. Pain Medicine, 2019. **20**(1): p. 153-160.

46. Carrasco-Uribarren, A., et al., *Short-term effects of the traction-manipulation protocol in dizziness intensity and disability in cervicogenic dizziness: a randomized controlled trial.* Disabil Rehabil, 2021: p. 1-9.
47. Karlberg, M., et al., *Postural and symptomatic improvement after physiotherapy in patients with dizziness of suspected cervical origin.* Arch Phys Med Rehabil, 1996. **77**(9): p. 874-82.
48. Micarelli, A., et al., *Postural and clinical outcomes of sustained natural apophyseal glides treatment in cervicogenic dizziness patients: A randomised controlled trial.* Clin Rehabil, 2021: p. 2692155211012413.
49. Moustafa, I.M., A.A. Diab, and D.E. Harrison, *The effect of normalizing the sagittal cervical configuration on dizziness, neck pain, and cervicocephalic kinesthetic sensibility: a 1-year randomized controlled study.* Eur J Phys Rehabil Med, 2017. **53**(1): p. 57-71.
50. Reid, S.A., et al., *Sustained natural apophyseal glides (SNAGs) are an effective treatment for cervicogenic dizziness.* Man Ther, 2008. **13**(4): p. 357-66.
51. Reid, S.A., et al., *Comparison of mulligan sustained natural apophyseal glides and maitland mobilizations for treatment of cervicogenic dizziness: a randomized controlled trial.* Phys Ther, 2014. **94**(4): p. 466-76.
52. Reid, S.A., et al., *Effects of cervical spine manual therapy on range of motion, head repositioning, and balance in participants with cervicogenic dizziness: a randomized controlled trial.* Arch Phys Med Rehabil, 2014. **95**(9): p. 1603-12.
53. Reid, S.A., et al., *Manual therapy for cervicogenic dizziness: Long-term outcomes of a randomised trial.* Man Ther, 2015. **20**(1): p. 148-56.
54. Yao, M., et al., *Shi-Style Cervical Mobilizations Versus Massage for Cervical Vertigo: A Multicenter, Randomized, Controlled Clinical Trial.* J Altern Complement Med, 2019.
55. Micarelli, A., et al., *Usefulness of postural sway spectral analysis in the diagnostic route and clinical integration of cervicogenic and vestibular sources of dizziness: A cross-sectional preliminary study.* Journal of vestibular research : equilibrium & orientation, 2021.
56. Sjolander, P., et al., *Sensorimotor disturbances in chronic neck pain--range of motion, peak velocity, smoothness of movement, and repositioning acuity.* Man Ther, 2008. **13**(2): p. 122-31.
57. Rudolfsson, T., M. Bjorklund, and M. Djupsjobacka, *Range of motion in the upper and lower cervical spine in people with chronic neck pain.* Man Ther, 2012. **17**(1): p. 53-9.
58. Vogt, L., et al., *Movement behaviour in patients with chronic neck pain.* Physiother Res Int, 2007. **12**(4): p. 206-12.

59. Treleaven, J., *Dizziness, Unsteadiness, Visual Disturbances, and Sensorimotor Control in Traumatic Neck Pain.* Journal of Orthopaedic & Sports Physical Therapy, 2017. **47**(7): p. 492-502.
60. Treleaven, J., G. Jull, and N. LowChoy, *The relationship of cervical joint position error to balance and eye movement disturbances in persistent whiplash.* Man Ther, 2006. **11**(2): p. 99-106.
61. Saadat, M., et al., *Postural stability in patients with non-specific chronic neck pain: A comparative study with healthy people.* Med J Islam Repub Iran, 2018. **32**: p. 33.
62. Bialosky, J.E., et al., *The mechanisms of manual therapy in the treatment of musculoskeletal pain: a comprehensive model.* Man Ther, 2009. **14**(5): p. 531-8.
63. Bishop, M.D., et al., *What effect can manual therapy have on a patient's pain experience?* Pain Manag, 2015. **5**(6): p. 455-64.
64. Southerst, D., et al., *Is exercise effective for the management of neck pain and associated disorders or whiplash-associated disorders? A systematic review by the Ontario Protocol for Traffic Injury Management (OPTIMa) Collaboration.* Spine J, 2016. **16**(12): p. 1503-1523.
65. Michaleff, Z.A., et al., *Comprehensive physiotherapy exercise programme or advice for chronic whiplash (PROMISE): a pragmatic randomised controlled trial.* The Lancet, 2014. **384**(9938): p. 133-141.
66. Söderlund, A. and P. Lindberg, *Cognitive behavioural components in physiotherapy management of chronic whiplash associated disorders (WAD)--a randomised group study.* G Ital Med Lav Ergon, 2007. **29**(1 Suppl A): p. A5-11.
67. Ludvigsson, M.L., et al., *The effect of neck-specific exercise with, or without a behavioral approach, on pain, disability, and self-efficacy in chronic whiplash-associated disorders: a randomized clinical trial.* Clin J Pain, 2015. **31**(4): p. 294-303.
68. Nijs, J. and K. Ickmans, *Chronic whiplash-associated disorders: to exercise or not?* The Lancet, 2014. **384**(9938): p. 109-111.
69. Han, B.I., H.S. Song, and J.S. Kim, *Vestibular rehabilitation therapy: review of indications, mechanisms, and key exercises.* J Clin Neurol, 2011. **7**(4): p. 184-96.
70. Akhter, S., et al., *Role of manual therapy with exercise regime versus exercise regime alone in the management of non-specific chronic neck pain.* Pak J Pharm Sci, 2014. **27**(6 Suppl): p. 2125-8.
71. Miller, J., et al., *Manual therapy and exercise for neck pain: A systematic review.* Manual Therapy, 2010. **15**(4): p. 334-354.
72. Hidalgo, B., et al., *The efficacy of manual therapy and exercise for treating non-specific neck pain: A systematic review.* J Back Musculoskelet Rehabil, 2017. **30**(6): p. 1149-1169.

Chapter 2

How do patients with chronic dizziness experience a web-based home rehabilitation programme for customised vestibular therapy ('WeBaVeR')? A qualitative study.

Published as: De Vestel, C., et al., *How do patients with chronic dizziness experience a web-based home rehabilitation programme for customised vestibular therapy ('WeBaVeR')? A qualitative study.* International Journal of Medical Informatics, 2023. **170**: p. 104927.

Appendix: Available at the end of this manuscript.

Highlights:

- WEb-BAsed VEstibular Rehabilitation therapy (WeBaVeR) allows patients, with the help of a booklet and access to a web application, to perform customized vestibular exercises (including visual desensitisation therapy) at home.
- Patients with chronic dizziness considered WeBaVeR as useful, acceptable, satisfactory, and of good quality.
- The main areas for improvement of the tool, according to patients, were the user interface, interactive functions, health awareness, and patients' accessibility to healthcare providers.

Note: Although the primary aim was to investigate the user experience of WeBaVeR in patients with PPPD, the target population was broadened to include patients with chronic dizziness in general. This choice was made for two reasons: firstly, on the research findings from part 1 of this doctoral thesis, which show that visually induced dizziness occurs not only in PPPD, but also in other forms of chronic dizziness. Secondly, both the visual desensitisation therapy component and the neck exercises can be added or removed depending on the patient, making WeBaVeR useful for a large range of patients with chronic dizziness. Since the aim of this study was to investigate the overall user experience of WeBaVeR for its target population, and not to evaluate the effect of a particular therapy plan (e.g., visual desensitisation therapy), patients with chronic dizziness were considered in recruitment.

1. Abstract

Background: Vestibular rehabilitation therapy (VRT) is the first choice approach for chronic dizziness. However, current home treatment programmes often lack attention to the individual needs of the patient and the integration of visual desensitisation therapy. We therefore developed a customised web-based VRT programme containing visual desensitisation exercises.

Objective: To assess the user experience (usability, satisfaction, acceptability, and quality) of patients with chronic dizziness with the customised **WE**b-**BA**sed **VE**stibular **R**ehabilitation, further called 'WeBaVeR'.

Methods: Patients with chronic dizziness, attending the Department of Otorhinolaryngology of the Antwerp University Hospital (period September 2021 to May 2022), received a customised programme, i.e. exercises supported by our web application and booklet. The programme lasted 6 weeks, with weekly supervision by phone. Patients' user experience was examined with the System Usability Scale (SUS), Client Satisfaction Questionnaire (CSQ), Service User Technology Acceptability Questionnaire (SUTAQ), and the User version of the Mobile Application Rating Scale (uMARS).

Results: Twelve patients with chronic dizziness (mean age: 45.33 ± 13.26 years) participated. The overall rated level of perceived usability (mean SUS score: 78.75 ± 8.95 points), satisfaction (mean CSQ score: 33.08 ± 3.37 points), acceptability (mean SUTAQ score: 105.67 ± 13.40 points) and quality (mean uMARS score: 94.58 ± 10.69 points) was good. The main remarks concerned the user interface and the interactive capabilities of the web application, and that WeBaVeR does not increase health awareness, or accessibility to health care providers.

Conclusion: Patients with chronic dizziness consider WeBaVeR as useful, acceptable, satisfactory and of good quality. To facilitate implementation in practice, further optimisation of WeBaVeR based on the feedback received, is useful.

Keywords: User Experience, Chronic Dizziness, Vestibular Rehabilitation, Internet, Home Care

2. Introduction

Dizziness is a major health problem in our society. Not only is dizziness common, it is also associated with important dysfunctions at the physical (e.g., fall risk), psychological (e.g., anxiety and depression), and social levels (e.g., social isolation) [1]. Those who are anxious or avoidant about their dizziness are prone to developing persistent dizziness symptoms [2].

Vestibular rehabilitation therapy (VRT) is the therapy of choice to break the vicious cycle of chronic dizziness and its secondary effects on the individual [3-5]. Through balance and gaze stabilisation training and repeated exposure to the movements and situations that trigger dizziness (also known as "habituation"), central adaptation and compensation occurs which is necessary for the recovery process [6]. However, despite its proven effectiveness, VRT is still underutilised in primary care settings [7]. An important reason for this may be the lack of tools to perform these exercises in the home environment. Indeed, VRT needs to be performed daily (2-3 exercise sessions per day) for several weeks (guideline duration is at least 6 weeks) [8]. In many countries, an exclusively office-based approach is not feasible, given the physical (e.g., living too far from the clinic) and financial burden on patients.

Research shows that a home rehabilitation programme in the form of a web application or booklet is effective [9-12] and no more expensive than usual care for the treatment of chronic dizziness [13, 14]. However, these booklets and web applications mainly consist of generic (head) movement exercises, and do not offer materials for visual desensitisation therapy.

There is sufficient theoretical support that customised VRT is more effective than a generic exercise regimen, especially in people with delayed central compensation [15]. It also provides higher patient motivation and increased transfer of the exercises to everyday life [16, 17]. Several options for customised VRT have been described in the literature (e.g., for gaze stabilisation [18], balance [19] and habituation training [20, 21]). In addition, studies show the importance of integrating visual desensitisation in VRT [22]. This may be explained by the fact that over-reliance on visual information is a common malcompensation that contributes to persistent dizziness symptoms, and thus should be treated [23-25].

Despite recent new studies on VRT [12, 26-28], the feasibility and effectiveness of a home VRT tool, which offers tailored exercises and accompanying assisting materials for gaze stabilisation, balance, movement habituation and visual desensitization therapy, have not yet been adequately investigated [29]. We therefore developed our own customised **We**b-**Ba**sed **Ve**stibular **R**ehabilitation therapy, further referred to as 'WeBaVeR'

The purpose of this study was to evaluate the user experience (usability, satisfaction, acceptability, and quality [30]) of patients with chronic dizziness with the customised WeBaVeR.

3. Methods

3.1. Design and setting

This study was designed according to the STROBE guidelines for cohort studies [31]. The study protocol was approved by the Medical Ethics Committees of the Antwerp University Hospital (reference number 18/586).

Patients visiting the Department of Otorhinolaryngology of the Antwerp University Hospital (Belgium) during the period September 2021 to May 2022 were recruited. Study investigations took place at the Multidisciplinary Motor Centre Antwerp (M2OCEAN), which is the movement analysis lab of the University of University of Antwerp/MOVANT. Participation was voluntary, and could be discontinued at any time at the patient's request. Participating patients signed the informed consent form.

3.2. Participants

To participate, the patient had to (1) suffer from chronic non-rotatory dizziness (i.e., have vestibular symptoms at least 15 days per month for at least 3 months); (2) be at least 18 years old; and (3) be Dutch-speaking. In the presence of any of the following criteria, the patient was refused: (1) acute vestibular dysfunction; (2) dizziness due to hormonal disorders, untreated metabolic or cardiac disorders, vasovagal syncope, hyperventilation, acute psychological problems, or substance abuse; (3) balance problems other than those caused by dizziness (such as orthopaedic and neurological disorders); (4) significant visual disturbances that cannot be corrected by, for example, wearing glasses; and (5) not having an email account or access to the Internet.

Patients' eligibility was checked by an Ear-Nose-Throat (ENT) doctor through anamnesis (according to the SO STONED method [32]), and through micro-otoscopic, vestibular (includes video head impulse, sinusoidal harmonic acceleration, and binaural bithermal caloric testing) and audiometric screening. If eligible, patients were referred to the study investigator (licensed physiotherapist at master's degree).

3.3. Study procedure

The study investigator performed a baseline assessment for each patient (i.e., Dizziness Handicap Inventory, DHI; Visual vertigo Analogue Scale, VVAS; Static Balance Tests; and Functional Gait Assessment, FGA; as described in [33]). This served as the basis for an individualised VRT programme. WeBaVeR (TABLE 1) was supported by a booklet with customised vestibular exercises (i.e. gaze stabilisation, balance, movement habituation, visual desensitisation and neck exercises; depending on the patient's needs), and the web application for which the patients received a secure login (FIGURE 1, a-c). In addition, all patients received an information brochure and a diary.

For example, individualised exercises meant that if the baseline assessment showed high levels of visually induced dizziness (VVAS ≥ 30%), visual desensitisation exercises were included; if it was found that turning in bed, looking up or bending (on the DHI questionnaire) or turning in standing (on the FGA) provoked vestibular symptoms, habituation exercises were included for training these specific movements. An example of how exercises were selected and progressively increased in difficulty for patients with high versus low VVAS scores can be found in APPENDIX A.

The patient was followed up by the study investigator. Each component of WeBaVeR was verbally explained to the patient at the start. The patient was informed to perform the exercises (4 à 6 in total) independently at home for 6 weeks twice a day, 7 days per week (with each session lasting 10 to 15 minutes). The required exercise intensity (e.g., frequency, speed and duration) was determined by mild to moderate provocation of the dizziness, provided the patient could tolerate it. In order to maintain sufficient exercise intensity, the content and progression of the exercises were adjusted weekly via telephone supervision (+/- 30 minutes), depending on the change in the patient's clinical condition. This meant that exercises that no longer caused dizziness or caused little dizziness were made more difficult (e.g., by increasing speed, number of repetitions, or addition of double tasks and visual disturbance), or were replaced by a different exercise. Patients could also contact the study investigator at any time within working hours (8:30 am to 7:00 pm). After the 6 weeks, patients were allowed to continue to use WeBaVeR without further follow-up from the study investigator.

Table 1. *Content of WeBaVeR* [a]

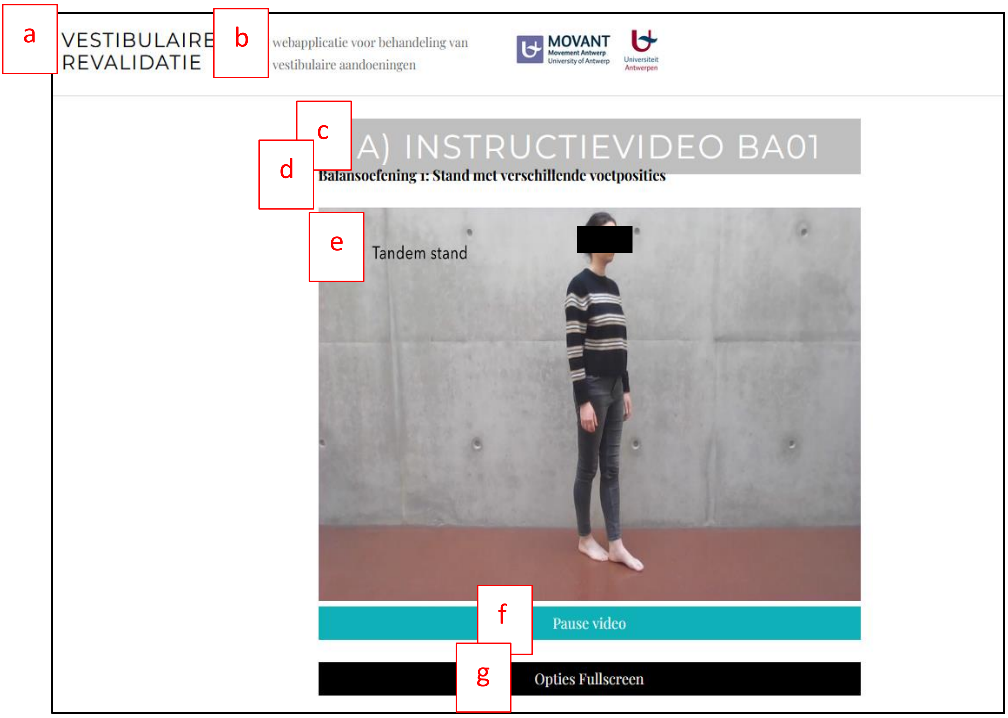
Components	Description
Information brochure	The brochure provides background information on the development of vestibular symptoms and the importance of vestibular exercises. For example, it explains that exercises that elicit vestibular symptoms are necessary to obtain vestibular compensation; that vestibular symptoms may initially worsen but will diminish as the exercise program is continued; and that it is important to remain physically active. In case of any adverse events (e.g., head/ear pain, double vision, tinnitus), although rare, contacting the Ear-Nose-Throat doctor and/or general practitioner is recommended.
Diary	The diary was designed to record daily what exercises were performed, at what intensity, and to what extent vestibular symptoms occurred with each exercise and after completion of the exercise session. In addition, physical activities performed (e.g., cycling, swimming, walking) and other remarks could be noted. The diary was sent to the study investigator 1 day before the telephone consult, in order to be discussed with the patient.
Booklet	The booklet contains 4 to 6 patient-tailored exercises to be chosen (by the study investigator) from the categories of Gaze Stabilisation, Balance, Habituation, Visual Desensitisation and/or Neck, depending on the patient's needs. Each exercise and how to perform it is described in detail to the patient with an accompanying figure. Various progression options (e.g., speed, duration, dual task) are also listed, which are chosen in consultation with the study investigator. 1) Category '*Gaze Stabilisation*' Aiming to improve the ability to focus the gaze during head movements. There is a choice of oculomotor (e.g., saccades, smooth pursuit), vestibulo-ocular reflex (e.g., VOR x1, VOR x2) and cervico-ocular reflex exercises. 2) Category '*Balance*' Aiming to improve static and dynamic balance. There is a choice of various exercises in which balance is challenged by, for example, changing the base of support, swinging the arms, or throwing an object. 3) Category '*Habituation*' Aiming to improve tolerance to head and/or body movements. There is a choice of various movements, for example, shaking the head, bending over, turning in a lying or standing position. 4) Category '*Visual Desensitisation*'

	Aiming to reduce hypersensitivity to visual stimuli. There is a choice of different static and dynamic images that can be either realistic or abstract (more information, see component 'Web Application'). 5) Category '*Neck'* Aiming to reduce secondary neck complaints. Various exercises for neck mobilisation and motor control can be selected.
Web application (**FIGURE 1, a-c**)	The web application contains instructional videos and exercise materials to support the booklet. An instructional video (with spoken instructions) is available for each exercise to visually clarify how the exercises should be performed. In addition, exercise materials are available for performing the gaze stabilisation and visual desensitisation exercises. (a) For gaze stabilisation, one or more targets can be placed on the screen and different background images can be selected. Various adjustment parameters are available (e.g., colour, size, speed, and addition of text or metronome). (b) For visual desensitisation, static and dynamic images can be selected, which can be realistic (e.g., patterned floor, fruit basket, supermarket) or abstract (e.g., tunnel, dots, stripes).

[a] VOR = vestibulo-ocular reflex; WeBaVeR = customised **We**b-**Ba**sed **Ve**stibular **R**ehabilitation therapy

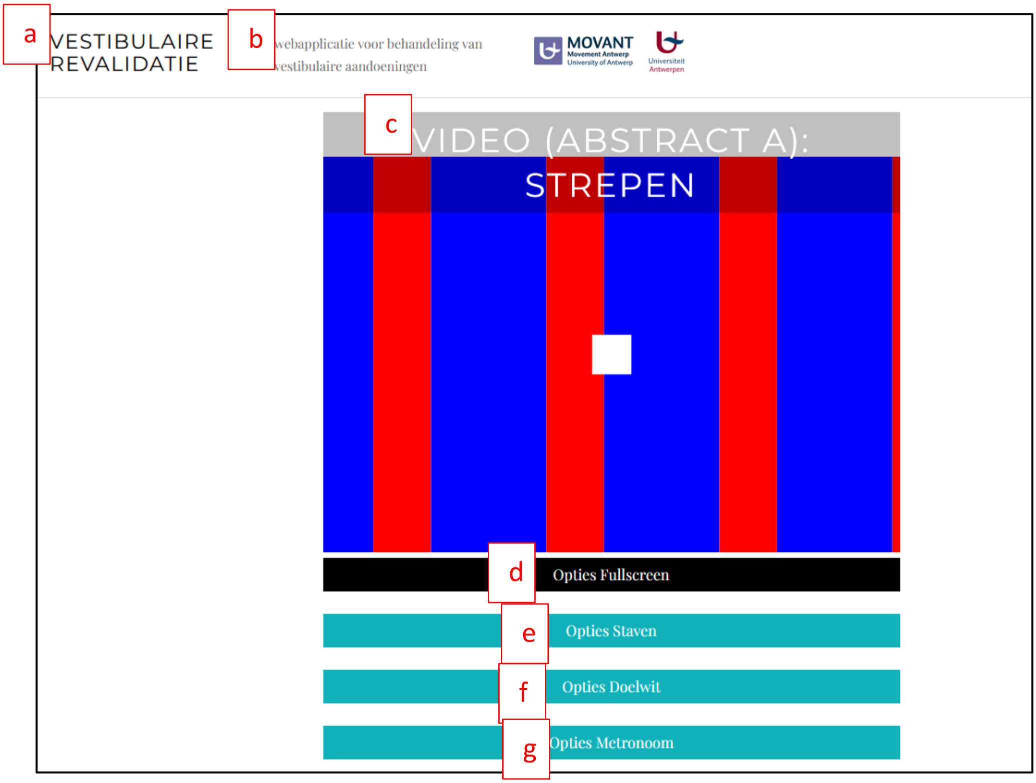
Figure 1. *The designed web application as a support for the vestibular booklet.* [a]

a) Example of an instructional video from the category 'Balance' [a]



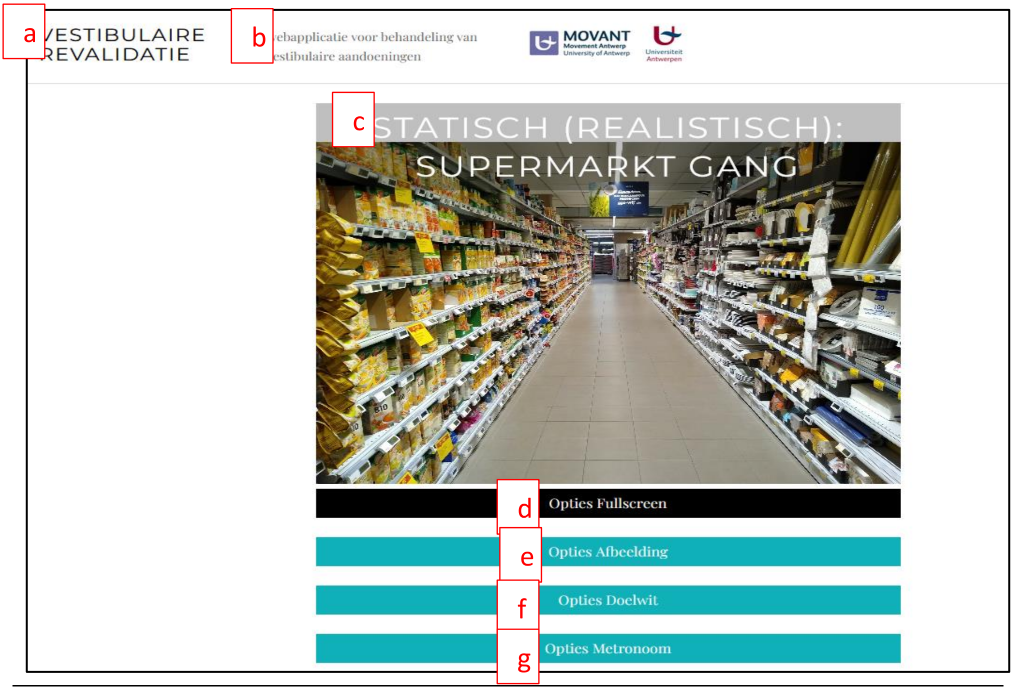
[a] Translation from Dutch to English: (a) Vestibular rehabilitation; (b) Web application for treatment of vestibular disorders; (c) Instructional video BA01; (d) Balance exercise 1: Standing with different foot positions; (e) Tandem stance; (f) pause the video; (g) full screen option

b) Example of exercise material from the category 'Gaze Stabilisation' [a]



[a] Translation from Dutch to English: (a) Vestibular rehabilitation; (b) Web application for treatment of vestibular disorders; (c) Video (abstract A): stripes; (d) Full screen options; (e) Options for stripes; (f) Options for target; (g) Options for metronome

c) Example of exercise material from the category 'Visual desensitisation' [a]



[a] Translation from Dutch to English: (a) Vestibular rehabilitation; (b) Web application for treatment of vestibular disorders; (c) Static (realistic): supermarket aisle; (d) Full screen options; (e) Options for image; (f) Options for target; (g) Options for metronome

After 6 weeks of therapy, patients were asked to indicate their user experience with WeBaVeR through four questionnaires (See '3.4. Outcome variables'). The completed questionnaires were delivered electronically to the study investigator, who checked whether all questions had been answered and, if not, contacted the patient to complete them further.

3.4. Outcome variables

3.4.1. Descriptive variables

Demographic data on *age (years)*, *gender*, *dizziness duration (years)*, and *ENT diagnosis* were taken from the patient's electronic medical record.

Baseline assessment data were collected on the *DHI*, *VVAS*, *Static balance tests*, and *FGA*, as described in [33].

3.4.2. User experience variables

The *System Usability Scale (SUS)* assesses the perceived usability of WeBaVeR by asking about the complexity of the content and the need for prior training or support. It contains a total of 10 questions, each to be scored using a 5-point Likert scale (ranging from strongly disagree (1) to strongly agree (5)). For questions 1,3,5,7 and 9, the score contribution is the "scale position minus 1", and for questions 2,4,6,8 and 10, the score contribution is "5 minus the scale position". The sum of the scores on all questions, multiplied by 2.5, constitutes the total SUS score [34]. The total score is between 0 and 100 where the higher the score the higher the perceived usefulness of WeBaVeR. Of the various methods available to interpret the total SUS score, the grading and adjective methods are used (see **FIGURE 2**) [35].

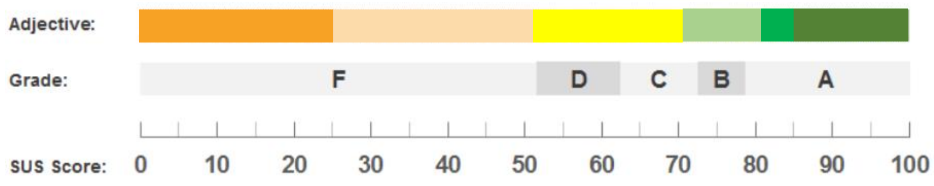


Figure 2. *The grading and adjective methods to interpret the SUS scores.* [a, b, c]

---

[a] Legend: ■ Best imaginable ■ Excellent ■ Good ■ Fair ■ Poor ■ Worst imaginable
A = superior performance; B = good performance; C = average performance; D = reduced performance; F = failing performance
[b] Figure adapted from https://measuringu.com/interpret-sus-score [35]
[c] SUS = System Usability Scale

The *Client Satisfaction Questionnaire (CSQ)* measures satisfaction with WeBaVeR by evaluating, for example, the service received and the therapy duration. It contains a total of 10 questions, each scored on a 4-point Likert scale (ranging from strongly not satisfied (1) to strongly satisfied (4)). The total score ranges between 10 and 40, with a higher score indicating higher satisfaction [36].

The *Service User Technology Acceptability Questionnaire (SUTAQ)* assesses the acceptability of WeBaVeR using 22 questions that can be broken down in 6 sub-items: 'enhanced care' (5 items), 'increased accessibility' (4 items), 'privacy and discomfort' (4 items), 'caregiver concerns' (3 items), 'WeBaVeR as substitution' (3 items) and 'satisfaction' (3 items). Each question should be scored using a 6-point Likert scale ranging from strongly disagree (1) to strongly agree (6). However, the sub-items 'privacy and discomfort' and 'caregiver concerns' contain negative statements, meaning that the lower the score here, the higher the acceptability. The total score on the SUTAQ was calculated by first reversing the scores for the negative statements, and then summing up the scores on the 22 questions. The total score ranged between 22 and 132, with the higher the score the higher the acceptability [37].

The *User version of the Mobile Application Rating Scale (uMARS)* focuses solely on evaluating the quality of WeBaVeR's web application. 'Objective quality' is estimated with 16 questions that can be divided into 4 domains: 'Engagement' (5 items), 'Functionality' (4 items), 'Aesthetics' (3 items), and 'Information' (4 items). In addition, there are 4 questions on 'subjective quality', which can be used to estimate whether the patient would use this web application in the future. Finally, there are 6 questions that gauge the possible positive effect of the web application on health habits, i.e. 'Perceived impact'. Each of the 26 questions was scored on a 5-point Likert scale. An average score for objective quality, subjective quality and perceived impact was calculated separately, as well as the total score on the uMARS. In each case, the higher the score the higher the quality, and/or positive effect of the web application on health habits was estimated [38].

3.5. Established double translation method

Only an English version of the SUS, SUTAQ, and uMARS was available in the literature. Therefore, these questionnaires were translated into Dutch using an established double translation method [39]. The forward translation was done by an informed (i.e. who was aware of the concept measured by the questionnaires) and an uninformed bilingual translator whose mother tongue was Dutch. Translation differences were limited and discussed between the translators until a consensus was reached. Then, these Dutch versions of the questionnaires were translated back into English by an informed and an uninformed bilingual translator whose native language was English (British). The differences in translation were limited here as well, and there were no changes in meaning between the agreed English versions and the original questionnaires. Consequently, these Dutch-language versions of the questionnaires were used in this study.

3.6. Data analysis

All data were collected pseudonymised in a Microsoft Excel 2016 spreadsheet. Statistical analyses were then performed via SPSS software version 27.0 [40]. All documents remained localised on the secure server of the University of Antwerp.

The sub/total scores on the user experience questionnaires were calculated according to the guidelines from the literature (SUS [35], CSQ [36], SUTAQ [37], en uMARS [38]).

The descriptive data and results on the user experience questionnaires were analysed using means and standard deviations (SD) for all quantitative variables, and frequencies and percentages for all categorical variables.

4. Results

4.1. Study participants

A total of 12 patients with chronic dizziness aged 23 to 65 years, with a mean age of 45.33 ± 13.26 years, participated in this study. All patients were diagnosed with PPPD, with the precipitating events being varied: vestibular migraine (N=4), bilateral vestibulopathy (N=2), vestibular neuritis (N=1), benign paroxysmal positional dizziness (N=1), vestibular schwannoma (N=1), cardiovascular event (N=1), SARS-CoV-2 infection (N=1), and concussion (N=1). Their demographic and baseline characteristics are presented in **TABLE 2**.

Table 2. *Demographic and baseline assessment data of the participants (N=12)* [a]

Variables	Mean ± SD or number (%)
Age (years)	45.33 ± 13.26
Female	4 (33.3)
Dizziness duration (months)	31.00 ± 43.45
Dizziness Handicap Inventory (0-100 points)	48.50 ± 11.79
Visual Vertigo Analogue scale (%)	52.24 ± 23.24
Static balance tests (0-120s)	83.32 ± 27.11
Functional Gait Assessment (0-30 points)	26.67 ± 2.15

[a] SD = standard deviation (+/- 1 SD)

4.2. Patients' experience with WeBaVeR

For a detailed overview of the scores given per questionnaire by the patients, please consult the **APPENDIX B**.

4.2.1. Evaluation of the usability

TABLE 3 presents the mean scores (± SD) for each question.

The mean total score on the SUS was 78.75 ± 8.95 points, which means that, based on the grading and adjective scoring methods, the perceived usability of WeBaVeR was generally considered as good [35]. All patients felt confident in using WeBaVeR, and almost all felt that WeBaVeR was easy to use, without the need of a technical person. The different components of WeBaVeR were considered to be well integrated. Most discordance was present on whether much learning was required to use WeBaVeR.

Table 3. *Mean scores (± SD) for each question on the SUS* [a, b, c]

Sub-items	**Mean ± SD**
SUS 1	3.83 ± 0.72
SUS 2	1.92 ± 0.67
SUS 3	4.08 ± 0.90
SUS 4	1.33 ± 0.65
SUS 5	4.08 ± 0.51
SUS 6	1.58 ± 0.79
SUS 7	3.92 ± 0.90
SUS 8	1.92 ± 0.51
SUS 9	4.58 ± 0.51
SUS 10	2.25 ± 1.36
Total score (0-100 points)	78.75 ± 8.95

[a] SD = standard deviation (+/- 1 SD); SUS = System Usability Scale

[b] Questions: **SUS_1**: I think I would like to use WeBaVeR frequently; **SUS_2**: I found WeBaVeR unnecessarily complex; **SUS_3**: I thought WeBaVeR was easy to use; **SUS_4**: I think that I would need the support of a technical person to be able to use WeBaVeR; **SUS_5**: I found the various parts in WeBaVeR were well integrated; **SUS_6**: I thought there was too much inconsistency in WeBaVeR; **SUS_7**: I would imagine that most people would learn to use WeBaVeR very quickly; **SUS_8**: I found WeBaVeR very awkward to use; **SUS_9**: I felt very confident using WeBaVeR; **SUS_10**: I needed to learn a lot of things before I could get going with WeBaVeR.

[c] More information on the SUS scoring can be found in *3.4.2. User experience variables*.

4.2.2. Evaluation of the satisfaction

TABLE 4 presents the mean scores (± SD) for each question.

With a mean total CSQ score of 33.08 ± 3.37 points, satisfaction was high (the minimum CSQ score is 10 and the maximum score is 40; a higher score means a higher degree of satisfaction). A small minority felt that the exercise period was too short and that the termination of the exercise program was therefore not a joint decision between the patient and study investigator.

Table 4. *Mean scores (± SD) for each question on the CSQ* [a, b, c]

Sub-items	**Mean ± SD**
CSQ 1	3.25 ± 0.62
CSQ 2	3.33 ± 0.65
CSQ 3	3.08 ± 0.67
CSQ 4	3.50 ± 0.67
CSQ 5	3.25 ± 1.06
CSQ 6	3.33 ± 0.49
CSQ 7	3.25 ± 0.62
CSQ 8	3.42 ± 0.67
CSQ 9	3.17 ± 0.72
CSQ 10	3.50 ± 0.67
Total score (10-40 points)	33.08 ± 3.37

[a] SD = standard deviation (+/- 1 SD); CSQ = Client Satisfaction Questionnaire

[b] Questions: **CSQ_1**: How do you find the quality of WeBaVeR?; **CSQ_2**: Was this the kind of help you were hoping to get?; **CSQ_3**: To what extent has WeBaVeR met your needs?; **CSQ_4**: If an acquaintance needed the same help, would you recommend our WeBaVeR?; **CSQ_5**: Overall, did you find the length of the exercise period sufficient?; **CSQ_6**: Did you feel you were able to practice adequately?; **CSQ_7**: Did WeBaVeR help you cope better with your problems?; **CSQ_8**: Overall, how satisfied are you with WeBaVeR you received?; **CSQ_9**: To what extent was the conclusion of treatment a joint decision between you and the caregiver?; **CSQ_10**: Suppose you ever seek help again, would you come back to us?

[c] More information on the CSQ scoring can be found in *3.4.2. User experience variables*.

4.2.3. Evaluation of the acceptability

TABLE 5 presents the mean scores (± SD) for each sub-item.

WeBaVeR was generally considered highly acceptable. The mean total score on the SUTAQ was 105.67 ± 13.40 points (the minimum SUTAQ score is 22 and the maximum score is 132; a higher score means a higher degree of acceptance).

Sub-item *Enhanced Care*: Patients' involvement in their care was generally considered to have increased with WeBaVeR. Two items were scored slightly lower, namely whether this tool could be used to better monitor the patient and their condition, and whether it could make the patient less anxious about their health/social care.

Sub-item *Increased Accessibility*: There was some ambiguity as to whether WeBaVeR increases accessibility, for example to health and social care professionals, and saves time compared to a physical consultation. Nevertheless, patients considered WeBaVeR to be beneficial to their health.

Sub-item *Privacy and Discomfort*: There was unanimity that there was no invasion of privacy. However, it was reported that WeBaVeR could possibly affect daily routine and lead to uncomfortable feelings (e.g., emotionally or physically).

Sub-item *Care personnel Concerns*: There was a high level of confidence in the expertise of the caregivers involved in the patient's treatment with WeBaVeR. However, three patients indicated that WeBaVeR may interfere with the continuity of their received care in general.

Sub-item *Satisfaction*: There was a high degree of satisfaction with WeBaVeR.

Sub-item *WeBaVeR as Substitution*: There was uncertainty about whether WeBaVeR can replace regular face to face consultations, or other regular health or social care. There was some agreement that WeBaVeR causes patients to worry less about their health status.

__Table 5__. Mean scores (± SD) on the six sub-items of the SUTAQ [a, b]

Sub-items (score range)	**Mean ± SD**
1) Enhanced Care (5-30 points)	24.58 ± 3.23
2) Increased accessibility (4-24 points)	17.00 ± 5.44
3) Privacy and discomfort (4-24 points)	7.33 ± 3.00
4) Care personnel concerns (3-18 points)	4.67 ± 1.78
5) Satisfaction (3-18 points)	16.50 ± 2.02
6) WeBaVeR as substitution (3-18 points)	11.08 ± 3.34
Total score (22-132 points)	105.67 ± 13.40

[a] SD = standard deviation (+/- 1 SD); SUTAQ = Service User Technology Acceptability Questionnaire; WeBaVeR = customised **We**b-**Ba**sed **Ve**stibular **R**ehabilitation

[b] More information on the SUTAQ scoring can be found in *3.4.2. User experience variables*.

4.2.4. Evaluation of the quality

TABLE 6 presents the mean scores (± SD) for the objective quality (including the 4 domains), the subjective quality, and the positive effect of WeBaVeR on health habits.

With a mean total score on the uMARS of 94.58 ± 10.69 points, the web application was generally considered to be of sufficient quality. Strengths of the web application were its clear and reliable content, with good visual support, which was adapted to its target group. The application would also be recommended by the patients to others with the same pathological condition.

The main drawback of the web application was that there were few interactive features and the application was not very attractive visually.

Contradictions in the responses were present on whether or not the web application has a positive effect on health awareness and habits. There was also discussion about the degree of possible customisation (e.g., notifications), and whether they would continue to use the web application and pay for it.

__Table 6__. Mean scores (± SD) on the three sub-items of the uMARS [a, b]

Sub-items (score range)	**Mean ± SD**
1) Objective quality (16-80 points)	59.83 ± 5.32
A. Engagement (5-25 points)	17.33 ± 2.50
B. Functionality (4-20 points)	15.58 ± 1.88
C. Aesthetics (3-15 points)	10.00 ± 2.00
D. Information (4-20 points)	16.92 ± 1.44
2) Subjective quality (4-20 points)	14.58 ± 2.64
3) Perceived impact (6-30 points)	20.17 ± 5.20
Total score (26-130 points)	94.58 ± 10.69

[a] SD = standard deviation (+/- 1 SD); uMARS = user version of the Mobile Application Rating Scale

[b] More information on the uMARS scoring can be found in *3.4.2. User experience variables*.

5. Discussion

The aim of this study was to evaluate the user experience of patients with chronic dizziness with WeBaVeR, a web-based home VRT programme. The results of this study show that WeBaVeR is a useful, acceptable, satisfactory and quality telemedicine method.

The peculiarity of WeBaVeR compared to other VRT methods is twofold. On the one hand, WeBaVeR allows exercises to be selected and tailored to the individual patient. Indeed, research shows that it is more effective to perform exercises that provoke the patient's dizziness [5, 41] and that are focused on his/her daily life [42]. The effectiveness and possibilities for exercise progression have been described in the literature [18, 19, 41], and became possible in WeBaVeR thanks in part to the different adjustable parameters on the web application. A second special feature of WeBaVeR is the visual desensitisation therapy, the relevance of which in chronic dizziness has already been sufficiently confirmed in the literature [25, 43, 44]. Through the web application, there is a wide choice of both realistic and abstract images/videos. The many adjustable parameters also result here in a patient-specific approach, without getting too complex for both the patient and the therapist.

The remarks on WeBaVeR were mainly about the user interface and interactive capabilities of the web application, and the lack of improvement in health awareness, or accessibility of the patient to health care providers. The comments about the web application are explainable given that the web application focused primarily on being functional and complete, and to a lesser extent aesthetically outstanding. Also, the interactive features are indeed limited. The web application does not remember any data of the users, which on the other hand is conducive to privacy and appreciated by the patients. In terms of accessibility and health awareness, the brochure contains information on the general importance of VRT, and in which symptoms contacting a physician is recommended. Further optimisation of the web application and providing additional information in the brochure should therefore be considered.

Other comments mentioned were that it took some learning before they could get started with WeBaVeR. It is true that in the beginning the patient needs a word of explanation about the different parts of WeBaVeR. This can be a little difficult for patients because concentration problems are common in chronic dizziness [45]. The comment that the exercise period could be longer, that it may provoke uncomfortable feelings, and that it can disrupt the daily routine, is inherent to the pathology of chronic dizziness which requires a long-term and daily approach [5, 46]. Finally, it was reported that WeBaVeR may not be able to serve as a substitute for physical consultations. This could indicate that although exercise therapy at home is useful, the patient might needs adequate supervision to achieve a better therapy result [47].

Thus, telemedicine - with the recent covid-19 pandemic - is getting more attention than ever before [48-50]. The benefits include making healthcare more accessible and reducing patient costs. The potential of telemedicine for vestibular rehabilitation is evidenced by the fact that VRT is still too often difficult to access [7], and that VRT needs to be performed on a daily basis and thus requires high patient commitment [8]. However, there are also concerns about the use of telemedicine in terms of patient safety, ease of use, accessibility and data security, among others [49]. By developing WeBaVeR and evaluating its user experience, we sought to address both these needs from the literature. With the results of this study, WeBaVeR can be further refined to meet the standards of evidence.

Both study strengths and weaknesses need to be mentioned. A strength is that not only usability but also acceptability, satisfaction and quality were surveyed [30]. Another strength is that the user experience was evaluated after 6 weeks so that patients had enough time to get acquainted with WeBaVeR. There are also some limitations to the study. Patient recruitment was complicated by the covid-19 pandemic, although the number of patients collected in this study could already be sufficient to obtain reliable information [35]. Another disadvantage is that although all types of chronic dizziness were allowed to be included, it ended up being only patients with PPPD. Nevertheless, patients with PPPD are those who report visually induced dizziness, and thus are a relevant group. A final limitation is that potential influencing factors on user experience (e.g., degree of Internet access, age, duration of dizziness symptoms) were not taken into account.

6. Conclusion

The results show that WeBaVeR is considered a useful, acceptable, satisfactory and quality therapy method for chronic dizziness. However, there are still optimisation points, especially regarding the user interface and the interactive capabilities of the web application. Next, a randomised trial will be conducted to study its effectiveness on dizziness and imbalance before implementation in practice is possible.

7. Appendix

Appendix A

Patient A - with mild visually induced dizziness

1. Baseline assessment

It was determined that **(1)** a mild degree of visually induced dizziness was present (based on the Visual Vertigo Analogue Scale, VVAS, which had a score of 19.6%), **(2)** fast head movements and stooping were important triggers for dizziness (based on the Dizziness Handicap Inventory scale, DHI), **(3)** fast body rotations in stance provoked dizziness (based on the Functional Gait Assessment, FGA), and finally, **(4)** with eyes closed, static balance on a foam required a lot of concentration but succeeds (30s), while Tandem Romberg (17s) and standing on one leg (11s) were more difficult (based on the Static Balance tests, SBS). Mild neck pain was present secondary to the dizziness symptoms.

2. Example of the exercise programme for this patient [a]

Week 1-2	*Category Balance* · Static standing with feet together, eyes open, on uneven surface (e.g., slope, cushion) and/or with arm movements (e.g., ball bouncing against wall) · Static standing with the heel of one foot against the side of the caput metatarsale 1 of the other foot (semitandem), eyes open, on flat/uneven surface *Category Habituation* · Slalom between 2 cones at self-selected speed · Sitting upright and quickly picking up an object on the ground right in front of you *Category Gaze Stabilisation* · VOR x1 in seated position with target on white background, both horizontal and vertical head movements. Speed of head movements is increased by 8bpm every 2-4 days as dizziness subsides, until 240bpm is reached. *Category Neck* · Training position sense of the neck with laser light with eyes open/closed (more information, see [51])
Week 3-4	*Category Balance* · Static standing with feet together, eyes closed, on uneven surface (e.g., slope, cushion) and/or with arm movements (e.g., clapping your hands)

	· Static standing with the heel of one foot against the toes of the other (tandem Romberg), eyes open, on flat/uneven surface *Category Habituation* · Figure 8 stepping between 2 cones at increased speed · Sitting upright, turning the head 45 degrees left/right, then quickly bending the head forward to the knees *Category Gaze Stabilisation* combined with *Category Visual Desensitisation* · VOR x1 in seated position with target on busy background (e.g., patterned floor, stripes), both horizontal, vertical and oblique head movements *Category Neck* · Training motion sense of the neck with laser light (more information, see [51])
Week 5-6	*Category Balance* combined with *Category Visual Desensitisation* · Static standing with feet together/semitandem/tandem on an even surface while looking at a busy image (e.g., checkerboard) or video (e.g., supermarket, passing train, moving water) · Static standing with heel of one foot against toes of the other (tandem Romberg) with eyes open on uneven surface *Category Habituation* · Stepping, quickly turning 180 degrees or 360 degrees, and stepping further · In standing position grasping an object on the ground straight/angled in front of you *Category Gaze Stabilisation* · VOR x2 in sitting position with moving target on white background, both horizontal and vertical head movements *Category Neck* · Neck – Craniocervical flexion training (more information, see [51])

[a] VOR = vestibulo-ocular reflex

Patient B - with high visually induced dizziness

1. Baseline assessment

It was determined that **(1)** a high degree of visually induced dizziness was present (based on the VVAS which had a score of 83.9%), **(2)** looking up, quick head movements, turning over in bed, walking in the dark, and stooping were important triggers for dizziness (based on the DHI), **(3)** with eyes closed, tandem standing (19s) and standing on one leg (9s) were difficult to perform (based on the SBS), and finally **(4)** horizontal and vertical head movements while stepping, and fast body rotations in stance also trigger dizziness (based on the FGA). There was no neck pain present.

2. Example of the exercise programme for this patient

Week 1-2

Category Balance

- Static standing with feet together, eyes closed, on uneven surface (e.g., slope, cushion) and/or with arm movements (e.g., moving the arms quickly sideways)
- Static standing with the heel of one foot against the side of the caput metatarsale 1 of the other foot (semitandem), eyes open, on flat/uneven ground

Category Habituation

- From supine position turning quickly to left/right side position
- Standing upright and throwing a soft ball straight up and catch it, with the head following the movement of the soft ball

Category Gaze Stabilisation

- VOR x1 in seated position with target on white background, with both horizontal and vertical head movements. Speed of head movements is increased by 8bpm every 2-4 days as dizziness subsides, until 240bpm is reached.

Category Visual Desensitisation

- Sitting (chair with arm and/or backrest, or stool) or standing upright and looking at realistic images (e.g., patterned floor, fruit basket, bowling alley)

Week 3-4

Category Balance

- Static standing with the heel of one foot against the toes of the other (tandem Romberg) with eyes open, on flat/uneven surface
- Static standing with nodding/shaking head movements with eyes open/closed

Category Habituation

- From side lying right quickly turning to side lying left, and vice versa
- Throwing and catching a soft ball in an arc in front of you with both hands, with the head following the movement of the soft ball

Category Gaze Stabilisation

- VOR x1 in seated position with target on white background, both horizontal, vertical and oblique head movements. Speed of head movements is increased by 8bpm every 2-4 days as dizziness subsides, until 240bpm is reached.

Category Visual Desensitisation

- Sitting (chair with arm and/or backrest, or stool) or standing upright and looking at abstract images (e.g., checkerboard, horizontal or vertical stripes)

Week 5-6 *Category Balance*

- Static standing on one leg with eyes open, on flat/uneven surface
- Walking with nodding/shaking head movements

Category Habituation

- Quickly turning 180 or 270 degrees
- Sitting upright and quickly picking up an object on the ground right in front of you

Category Gaze Stabilisation

- VOR x2 in sitting position with moving target on white background, both horizontal and vertical head movements

Category Visual Desensitisation

- Sitting (chair with arm and/or backrest, or stool) or standing upright and looking at realistic/abstract videos (e.g., supermarket, moving water, turning dots, moving stripes, tunnel)

Appendix B

Table 7. Overview of the scores given to each question of the SUS. [a]

Questions	Mean ± SD
1. I think I would like to use WeBaVeR frequently.	3.83 ± 0.72
1 2 3 4 5 6 7 8 9 10 11 12	
2. I found WeBaVeR unnecessarily complex.	1.92 ± 0,67
1 2 3 4 5 6 7 8 9 10 11 12	
3. I thought WeBaVeR was easy to use.	4.08 ± 0.90
1 2 3 4 5 6 7 8 9 10 11 12	
4. I think that I would need the support of a technical person to be able to use WeBaVeR.	1.33 ± 0.65
1 2 3 4 5 6 7 8 9 10 11 12	
5. I found the various parts in WeBaVeR were well integrated.	4.08 ± 0.51
1 2 3 4 5 6 7 8 9 10 11 12	
6. I thought there was too much inconsistency in WeBaVeR.	1.58 ± 0.79
1 2 3 4 5 6 7 8 9 10 11 12	
7. I would imagine that most people would learn to use WeBaVeR very quickly.	3.92 ± 0.90
1 2 3 4 5 6 7 8 9 10 11 12	
8. I found WeBaVeR very awkward to use.	1.92 ± 0.51
1 2 3 4 5 6 7 8 9 10 11 12	
9. I felt very confident using WeBaVeR.	4.58 ± 0.51
1 2 3 4 5 6 7 8 9 10 11 12	
10. I needed to learn a lot of things before I could get going with WeBaVeR.	2.25 ± 1.36
1 2 3 4 5 6 7 8 9 10 11 12	
Total score	78.75 ± 8.95

[a] Legend:
strongly agree; moderately agree; neutral; moderately disagree; strongly disagree

Table 8. *Overview of the scores given to each question of the CSQ.* [a]

Questions	1	2	3	4	5	6	7	8	9	10	11	12	Mean ± SD
1. How do you find the quality of WeBaVeR?	strongly agree	strongly agree	strongly agree	strongly agree	moderately agree	moderately agree	moderately agree	moderately agree	moderately agree	moderately agree	moderately agree	moderately disagree	3.25 ± 0.62
2. Was this the kind of help you were hoping to get?	strongly agree	strongly agree	strongly agree	strongly agree	strongly agree	moderately agree	moderately agree	moderately agree	moderately agree	moderately agree	moderately agree	moderately disagree	3.33 ± 0.65
3. To what extent has WeBaVeR met your needs?	strongly agree	strongly agree	strongly agree	moderately agree	moderately agree	moderately agree	moderately agree	moderately agree	moderately agree	moderately agree	moderately disagree	moderately disagree	3.08 ± 0.67
4. If an acquaintance needed the same help, would you recommend our WeBaVeR?	strongly agree	strongly agree	strongly agree	strongly agree	strongly agree	strongly agree	strongly agree	moderately agree	moderately agree	moderately agree	moderately agree	moderately disagree	3.50 ± 0.67
5. Overall, did you find the length of the exercise period sufficient?	strongly agree	strongly agree	strongly agree	strongly agree	strongly agree	strongly agree	strongly agree	moderately agree	moderately agree	moderately disagree	moderately disagree	strongly disagree	3.25 ± 1.06
6. Did you feel you were able to practice adequately?	strongly agree	strongly agree	strongly agree	strongly agree	moderately agree	moderately agree	moderately agree	moderately agree	moderately agree	moderately agree	moderately agree	moderately agree	3.33 ± 0.49
7. Did WeBaVeR help you cope better with your problems?	strongly agree	strongly agree	strongly agree	strongly agree	moderately agree	moderately agree	moderately agree	moderately agree	moderately agree	moderately agree	moderately agree	moderately disagree	3.25 ± 0.62
8. Overall, how satisfied are you with WeBaVeR you received?	strongly agree	strongly agree	strongly agree	strongly agree	strongly agree	strongly agree	moderately agree	moderately agree	moderately agree	moderately agree	moderately agree	moderately disagree	3.42 ± 0.67
9. To what extent was the conclusion of treatment a joint decision between you and the caregiver?	strongly agree	strongly agree	strongly agree	strongly agree	moderately agree	moderately agree	moderately agree	moderately agree	moderately agree	moderately agree	moderately disagree	moderately disagree	3.17 ± 0.72
10. Suppose you ever seek help again, would you come back to us?	strongly agree	strongly agree	strongly agree	strongly agree	strongly agree	strongly agree	strongly agree	moderately agree	moderately agree	moderately agree	moderately agree	moderately disagree	3.50 ± 0.67
Total score													33.08 ± 3.37

[a] Legend:
strongly agree (dark green) moderately agree (light green) moderately disagree (orange) strongly disagree (red)

Table 10. *Overview of the scores given to each question of the SUTAQ.* [a]

Questions	**Mean ± SD**
Enhanced care (score ranges between 5-30)	*24.58 ± 3.23*
1. WeBaVeR has made me more actively involved in my health	5.00 ± 0.95
1 2 3 4 5 6 7 8 9 10 11 12	
2. WeBaVeR allows the people looking after me, to better monitor me and my condition	4.58 ± 1.08
1 2 3 4 5 6 7 8 9 10 11 12	
3. WeBaVeR can be/should be recommended to people in a similar condition to mine	5.67 ± 0.49
1 2 3 4 5 6 7 8 9 10 11 12	
4. WeBaVeR can certainly be a good addition to my regular health or social care	4.83 ± 1.03
1 2 3 4 5 6 7 8 9 10 11 12	
5. WeBaVeR has allowed me to be less concerned about my health and/or social care	4.50 ± 1.45
1 2 3 4 5 6 7 8 9 10 11 12	
Increased accessibility (score ranges between 4-24)	*17.00 ± 5.44*
6. WeBaVeR I received has saved me time in that I did not have to visit my GP clinic	4.50 ± 1.83
1 2 3 4 5 6 7 8 9 10 11 12	
7. WeBaVeR I received has increased my access to care (health and/or social care professionals)	3.83 ± 1.70
1 2 3 4 5 6 7 8 9 10 11 12	
8. WeBaVeR I received has helped me to improve my health	5.17 ± 0.84
1 2 3 4 5 6 7 8 9 10 11 12	
9. WeBaVeR has made it easier to get in touch with health and social care professionals	3.50 ± 1.83
1 2 3 4 5 6 7 8 9 10 11 12	
Privacy and discomfort (score ranges between 4-24)	*7.33 ± 3.00*
10. WeBaVeR has made me feel uncomfortable, e.g., physically or emotionally	2.17 ± 1.80
1 2 3 4 5 6 7 8 9 10 11 12	
11. WeBaVeR I received has invaded my privacy	1.00 ± 0.00
1 2 3 4 5 6 7 8 9 10 11 12	

Item	1	2	3	4	5	6	7	8	9	10	11	12	Mean ± SD
12. WeBaVeR I received has interfered with my everyday routine	strongly agree	moderately agree	moderately agree	slightly agree	slightly agree	slightly disagree	moderately disagree	moderately disagree	moderately disagree	moderately disagree	moderately disagree	strongly disagree	3.17 ± 1.59
13. WeBaVeR makes me worried about the confidentiality of the private information being exchanged through it	strongly disagree	strongly disagree	strongly disagree	strongly disagree	strongly disagree	strongly disagree	strongly disagree	strongly disagree	strongly disagree	strongly disagree	strongly disagree	strongly disagree	1.00 ± 0.00
Care personnel concerns (score ranges between 3-18)													*4.67 ± 1.78*
14. I am concerned that the person who monitors my status through WeBaVeR, does not know my personal health/social care history	strongly disagree	strongly disagree	strongly disagree	strongly disagree	strongly disagree	strongly disagree	strongly disagree	strongly disagree	strongly disagree	strongly disagree	strongly disagree	strongly disagree	1.00 ± 0.00
15. WeBaVeR interferes with the continuity of the care I receive (i.e., I do not see the same care professional each time)	moderately agree	slightly agree	slightly agree	moderately disagree	moderately disagree	moderately disagree	strongly disagree	strongly disagree	strongly disagree	strongly disagree	strongly disagree	strongly disagree	2.08 ± 1.44
16. I am concerned about the level of expertise of the individuals who monitor my status via WeBaVeR	slightly disagree	moderately disagree	moderately disagree	moderately disagree	moderately disagree	moderately disagree	strongly disagree	strongly disagree	strongly disagree	strongly disagree	strongly disagree	strongly disagree	1.58 ± 0.67
Satisfaction (score ranges between 3-18)													*16.50 ± 2.02*
17. WeBaVeR has been explained to me sufficiently	strongly agree	strongly agree	strongly agree	strongly agree	strongly agree	strongly agree	strongly agree	strongly agree	strongly agree	strongly agree	moderately agree	moderately agree	5.83 ± 0.39
18. WeBaVeR can be trusted to work appropriately	strongly agree	strongly agree	strongly agree	strongly agree	strongly agree	strongly agree	strongly agree	moderately agree	moderately agree	moderately agree	slightly agree	slightly agree	5.42 ± 0.79
19. I am satisfied with WeBaVeR I received	strongly agree	strongly agree	strongly agree	strongly agree	strongly agree	strongly agree	moderately agree	moderately agree	moderately agree	moderately agree	slightly agree	slightly disagree	5.25 ± 0.97
WEBAVER as substitution (score ranges between 3-18)													*11.08 ± 3.34*
20. WeBaVeR is not as suitable as regular face to face consultations with the people looking after me	strongly agree	moderately agree	moderately agree	moderately agree	slightly agree	slightly agree	slightly agree	slightly disagree	moderately disagree	moderately disagree	strongly disagree	strongly disagree	3.50 ± 1.68
21. WeBaVeR can be a replacement for my regular health or social care	moderately agree	moderately agree	moderately agree	slightly agree	slightly agree	slightly agree	slightly disagree	slightly disagree	slightly disagree	slightly disagree	strongly disagree	strongly disagree	3.42 ± 1.38
22. WeBaVeR has allowed me to be less concerned about my health status	strongly agree	moderately agree	moderately agree	moderately agree	slightly agree	slightly agree	slightly agree	slightly agree	slightly agree	slightly agree	slightly agree	strongly disagree	4.17 ± 1.19
Total score (score ranges between 22-132) (scores inverted for 'privacy and discomfort' and 'care personnel concerns')													105.67 ± 13.40

[a] Legend: strongly agree; moderately agree; slightly agree; slightly disagree; moderately disagree; strongly disagree

Table 4. Overview of the scores given to each question of the uMARS. [a]

Questions	Mean ± SD
Objective quality (score ranges between 16-80)	*59.83 ± 5.32*
A. Engagement	*17.33 ± 2.50*
1. Entertainment: Is the app fun/entertaining to use? Does it have components that make it more fun than other similar apps?	3.33 ± 0.78
1 2 3 4 5 6 7 8 9 10 11 12	
2. Interest: Is the app interesting to use? Does it present its information in an interesting way compared to other similar apps?	4.25 ± 0.62
1 2 3 4 5 6 7 8 9 10 11 12	
3. Customisation: Does it allow you to customise the settings and preferences that you would like to (e.g., sound, content and notifications)?	3.50 ± 1.38
1 2 3 4 5 6 7 8 9 10 11 12	
4. Interactivity: Does it allow user input, provide feedback, contain prompts (reminders, sharing options, notifications, etc.)?	2.17 ± 0.84
1 2 3 4 5 6 7 8 9 10 11 12	
5. Target group: Is the app content (visuals, language, design) appropriate for the target audience?	4.08 ± 0.67
1 2 3 4 5 6 7 8 9 10 11 12	
B. Functionality	*15.58 ± 1.88*
6. Performance: How accurately/fast do the app features (functions) and components (buttons/menus) work?	4.00 ± 0.74
1 2 3 4 5 6 7 8 9 10 11 12	
7. Ease of use: How easy is it to learn how to use the app; how clear are the menu labels, icons and instructions?	3.92 ± 0.52
1 2 3 4 5 6 7 8 9 10 11 12	
8. Navigation: Does moving between screens make sense; Does app have all necessary links between screens?	3.58 ± 0.67
1 2 3 4 5 6 7 8 9 10 11 12	
9. Gestural design: Do taps/swipes/pinches/scrolls make sense? Are they consistent across all components/screens?	4.08 ± 0.67
1 2 3 4 5 6 7 8 9 10 11 12	

C. Aesthetics	*10.00 ± 2.00*
10. Layout: Is arrangement and size of buttons, icons, menus and content on the screen appropriate?	3.42 ± 1.0

1	2	3	4	5	6	7	8	9	10	11	12

11. Graphics: How high is the quality/resolution of graphics used for buttons, icons, menus and content?	3.50 ± 0.67

1	2	3	4	5	6	7	8	9	10	11	12

12. Visual appeal: How good does the app look?	3.08 ± 0.67

1	2	3	4	5	6	7	8	9	10	11	12

D. Information	*16.92 ± 1.44*
13. Quality of information: Is app content correct, well written, and relevant to the goal/topic of the app?	4.00 ± *0.60*

1	2	3	4	5	6	7	8	9	10	11	12

14. Quantity of information: Is the information within the app comprehensive but concise?	4.00 ± 0.43

1	2	3	4	5	6	7	8	9	10	11	12

15. Visual information: Is visual explanation of concepts – through charts/graphs/images/videos, etc. – clear, logical, correct?	4.17 ± 0.58

1	2	3	4	5	6	7	8	9	10	11	12

16. Credibility of source: does the information within the app seem to come from a credible source?	4.75 ± 0.45

1	2	3	4	5	6	7	8	9	10	11	12

Subjective quality (score ranges between -)	*14.58 ± 2.64*
17. Would you recommend this app to people who might benefit from it?	4.25 ± 0.62

1	2	3	4	5	6	7	8	9	10	11	12

18. How many times do you think you would use this app in the next 12 months if it was relevant to you?	3.83 ± 1.47

1	2	3	4	5	6	7	8	9	10	11	12

19. Would you pay for this app?	2.92 ± 1.24

1	2	3	4	5	6	7	8	9	10	11	12

20. What is your overall (star) rating of the app?	3.58 ± 0.52

1	2	3	4	5	6	7	8	9	10	11	12

Perceived impact (score ranges between -)	*20.17 ± 5.20*
21. Awareness – This app has increased my awareness of the importance of addressing the health behaviour	3.17 ± 1.53

1	2	3	4	5	6	7	8	9	10	11	12
strongly agree	strongly agree	strongly agree	moderately agree	moderately agree	moderately agree	neutral	moderately disagree	moderately disagree	moderately disagree	strongly disagree	strongly disagree

22. Knowledge – This app has increased my knowledge/understanding of the health behaviour	3.25 ± 1.22

1	2	3	4	5	6	7	8	9	10	11	12
strongly agree	strongly agree	moderately agree	moderately agree	moderately agree	neutral	neutral	neutral	neutral	moderately disagree	moderately disagree	strongly disagree

23. Attitudes – The app has changed my attitudes toward improving this health behaviour	3.17 ± 0.94

1	2	3	4	5	6	7	8	9	10	11	12
strongly agree	moderately agree	moderately agree	moderately agree	neutral	neutral	neutral	neutral	neutral	moderately disagree	moderately disagree	moderately disagree

24. Intention to change – The app has increased my intentions/motivation to address this health behaviour	3.58 ± 0.79

1	2	3	4	5	6	7	8	9	10	11	12
strongly agree	moderately agree	moderately agree	moderately agree	moderately agree	moderately agree	moderately agree	neutral	neutral	neutral	neutral	moderately disagree

25. Help seeking – This app would encourage me to seek further help to address the health behaviour (if I needed it)	3.75 ± 0.97

1	2	3	4	5	6	7	8	9	10	11	12
strongly agree	strongly agree	strongly agree	moderately agree	moderately agree	moderately agree	moderately agree	neutral	neutral	neutral	neutral	moderately disagree

26. Behaviour change – Use of this app will increase/decrease the health behaviour	3.25 ± 0.97

1	2	3	4	5	6	7	8	9	10	11	12
strongly agree	moderately agree	moderately agree	moderately agree	moderately agree	neutral	neutral	neutral	neutral	moderately disagree	moderately disagree	moderately disagree

[a] Legend:
strongly agree, moderately agree, neutral, moderately disagree, strongly disagree

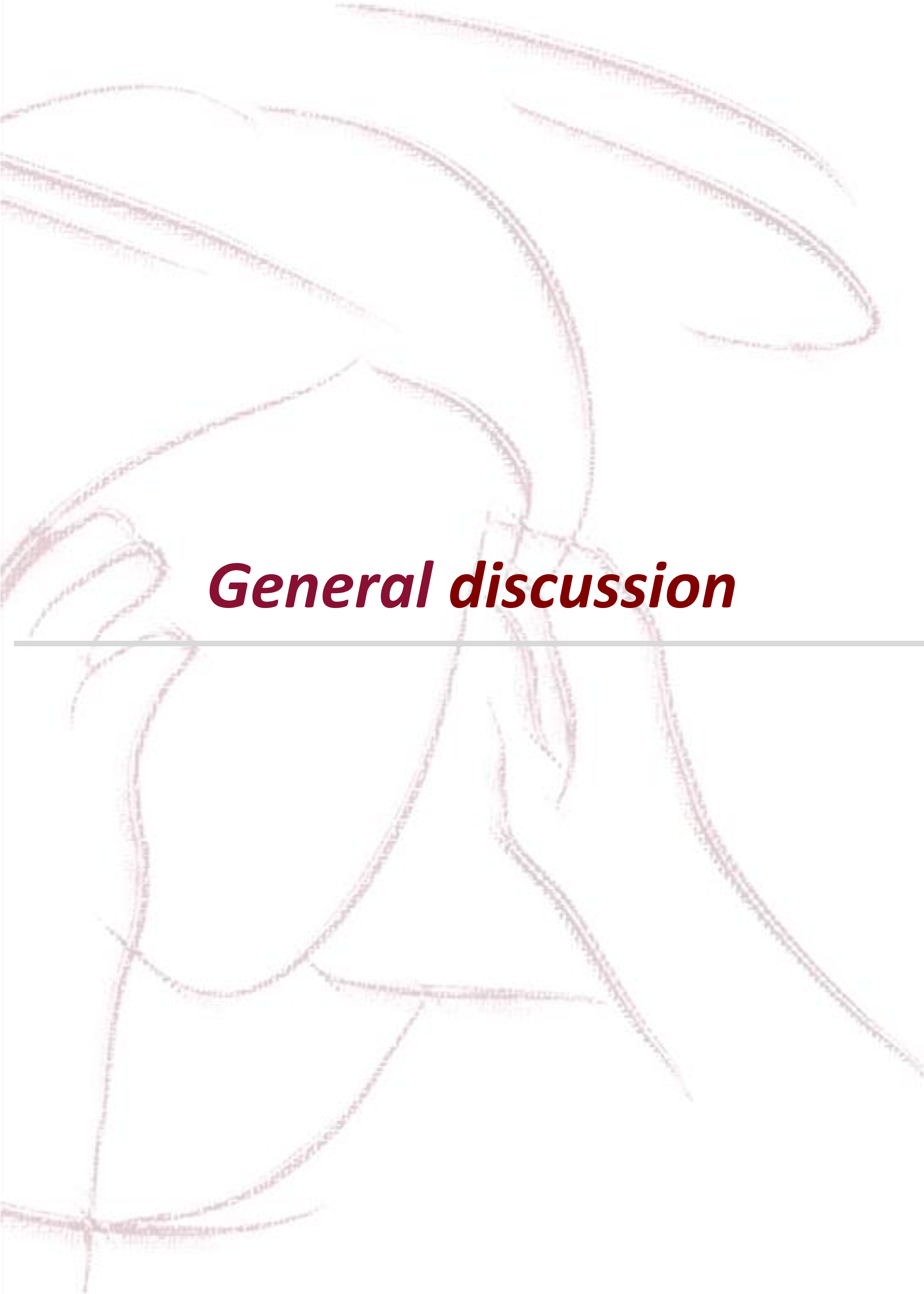
8. References

1. Dros, J., et al., *Impact of dizziness on everyday life in older primary care patients: a cross-sectional study.* Health Qual Life Outcomes, 2011. **9**: p. 44.
2. Dunlap, P.M., et al., *Fear Avoidance Beliefs Are Associated With Perceived Disability in Persons With Vestibular Disorders.* Phys Ther, 2021. **101**(9).
3. Kao, C.L., et al., *Vestibular rehabilitation ameliorates chronic dizziness through the SIRT1 axis.* Front Aging Neurosci, 2014. **6**: p. 27.
4. van Vugt, V.A., et al., *Chronic vertigo: treat with exercise, not drugs.* BMJ, 2017. **358**: p. j3727.
5. Kundakci, B., *The effectiveness of exercise-based vestibular rehabilitation in adult patients with chronic dizziness: A systematic review.* F1000Research, 2018. **7**.
6. Foster, C.A., *Vestibular rehabilitation.* Baillieres Clin Neurol, 1994. **3**(3): p. 577-92.
7. Meldrum, D., et al., *Vestibular rehabilitation in Europe: a survey of clinical and research practice.* Journal of Neurology, 2020. **267**(SUPPL 1): p. 24-35.
8. Han, B.I., H.S. Song, and J.S. Kim, *Vestibular rehabilitation therapy: review of indications, mechanisms, and key exercises.* J Clin Neurol, 2011. **7**(4): p. 184-96.
9. Geraghty, A.W.A., et al., *Internet-Based Vestibular Rehabilitation for Older Adults With Chronic Dizziness: A Randomized Controlled Trial in Primary Care.* Annals of Family Medicine, 2017. **15**(3): p. 209-216.
10. van Vugt, V.A., et al., *Internet based vestibular rehabilitation with and without physiotherapy support for adults aged 50 and older with a chronic vestibular syndrome in general practice: three armed randomised controlled trial.* Bmj, 2019. **367**: p. l5922.
11. Yardley, L., et al., *Effectiveness of primary care-based vestibular rehabilitation for chronic dizziness.* Annals of Internal Medicine, 2004. **141**(8): p. 598-605.
12. Eldoen, G., et al., *Web-based vestibular rehabilitation in persistent postural-perceptual dizziness.* Brain Behav, 2021. **11**(10): p. e2346.
13. Yardley, L., et al., *Clinical and cost effectiveness of booklet based vestibular rehabilitation for chronic dizziness in primary care: single blind, parallel group, pragmatic, randomised controlled trial.* Bmj, 2012. **344**: p. e2237.
14. van Vugt, V.A., et al., *Cost-effectiveness of internet-based vestibular rehabilitation with and without physiotherapy support for adults aged 50 and older with a chronic vestibular syndrome in general practice.* BMJ Open, 2020. **10**(10): p. e035583.

15. Shepard, N.T. and S.A. Telian, *Programmatic vestibular rehabilitation.* Otolaryngol Head Neck Surg, 1995. **112**(1): p. 173-82.
16. Cohen, H., et al., *Vestibular rehabilitation with graded occupations.* Am J Occup Ther, 1995. **49**(4): p. 362-7.
17. Cohen, H., et al., *Occupation and visual/vestibular interaction in vestibular rehabilitation.* Otolaryngol Head Neck Surg, 1995. **112**(4): p. 526-32.
18. Roller, R.A. and C.D. Hall, *A speed-based approach to vestibular rehabilitation for peripheral vestibular hypofunction: A retrospective chart review.* J Vestib Res, 2018. **28**(3-4): p. 349-357.
19. Klatt, B.N., et al., *A Conceptual Framework for the Progression of Balance Exercises in Persons with Balance and Vestibular Disorders.* Phys Med Rehabil Int, 2015. **2**(4).
20. Telian, S.A., et al., *Habituation therapy for chronic vestibular dysfunction: preliminary results.* Otolaryngol Head Neck Surg, 1990. **103**(1): p. 89-95.
21. Norre, M.E. and A.M. Beckers, *Vestibular habituation training. Specificity of adequate exercise.* Arch Otolaryngol Head Neck Surg, 1988. **114**(8): p. 883-6.
22. Pavlou, M., *The use of optokinetic stimulation in vestibular rehabilitation.* J Neurol Phys Ther, 2010. **34**(2): p. 105-10.
23. Guerraz, M., et al., *Visual vertigo: symptom assessment, spatial orientation and postural control.* Brain, 2001. **124**(Pt 8): p. 1646-56.
24. Bronstein, A.M., *Visual vertigo syndrome: clinical and posturography findings.* J Neurol Neurosurg Psychiatry, 1995. **59**(5): p. 472-6.
25. Pavlou, M., R.A. Davies, and A.M. Bronstein, *The assessment of increased sensitivity to visual stimuli in patients with chronic dizziness.* J Vestib Res, 2006. **16**(4-5): p. 223-31.
26. Ertunc Gulcelik, G., et al., *Research on the Effects of a Web-Based System With Oculomotor and Optokinetic Stimuli on Vestibular Rehabilitation.* Am J Phys Med Rehabil, 2021. **100**(6): p. 555-562.
27. Ding, C.R., et al., *Advantages of Short-term Personalized Vestibular Rehabilitation at Home Guided by Professional Therapist for Treatment of Decompensated Vestibular Vertigo.* Current Medical Science, 2021. **41**(4): p. 687-694.
28. Smolka, W., et al., *The efficacy of vestibular rehabilitation in patients with chronic unilateral vestibular dysfunction.* International Journal of Occupational Medicine and Environmental Health 2020 Apr 30;33(3):273-282, 2020.
29. Hurtado, J.E., et al., *Technology-enhanced visual desensitization home exercise program for post-concussive visually induced dizziness: a case series.* Physiotherapy theory and practice, 2020: p. 1-10.

30. Hajesmaeel-Gohari, S. and K. Bahaadinbeigy, *The most used questionnaires for evaluating telemedicine services.* Bmc Medical Informatics and Decision Making, 2021. **21**(1).
31. Cuschieri, S., *The STROBE guidelines.* Saudi J Anaesth, 2019. **13**(Suppl 1): p. S31-S34.
32. Wuyts, F.L., V. Van Rompaey, and L.K. Maes, *"SO STONED": Common Sense Approach of the Dizzy Patient.* Frontiers in surgery, 2016. **3**: p. 32-32.
33. De Vestel, C., et al., *Comparison of Clinical Balance and Visual Dependence Tests in Patients With Chronic Dizziness With and Without Persistent Postural-Perceptual Dizziness: A Cross-Sectional Study.* Frontiers in Neurology, 2022. **13**.
34. Brooke, J., *SUS: A quick and dirty usability scale.* Usability Eval. Ind., 1995. **189**.
35. Sauro, J. *Measuring Usability with the System Usability Scale (SUS)*. 2011; Available from: https://measuringu.com/sus/.
36. De Brey, H., *A cross-national validation of the Client Satisfaction Questionnaire: The Dutch experience.* Evaluation and Program Planning, 1983. **6**(3-4): p. 395-400.
37. Hirani, S.P., et al., *Quantifying beliefs regarding telehealth: Development of the Whole Systems Demonstrator Service User Technology Acceptability Questionnaire.* J Telemed Telecare, 2017. **23**(4): p. 460-469.
38. Stoyanov, S.R., et al., *Development and Validation of the User Version of the Mobile Application Rating Scale (uMARS).* JMIR Mhealth Uhealth, 2016. **4**(2): p. e72.
39. Beaton, D.E., et al., *Guidelines for the process of cross-cultural adaptation of self-report measures.* Spine (Phila Pa 1976), 2000. **25**(24): p. 3186-91.
40. *IBM Corp. Released 2020. IBM SPSS Statistics for Windows; Version 27.0* Armonk, NY.
41. Akin, F.W. and M.J. Davenport, *Validity and reliability of the Motion Sensitivity Test.* J Rehabil Res Dev, 2003. **40**(5): p. 415-21.
42. Dal, B.T., et al., *Comparison of Activity-Based Home Program and Cawthorne-Cooksey Exercises in Patients with Chronic Unilateral Peripheral Vestibular Disorders.* Arch Phys Med Rehabil, 2021.
43. Bronstein, A.M., *Vision and vertigo - Some visual aspects of vestibular disorders.* Journal of Neurology, 2004. **251**(4): p. 381-387.
44. Powell, G., et al., *Visually-induced dizziness is associated with sensitivity and avoidance across all senses.* Journal of Neurology, 2020. **267**(8): p. 2260-2271.
45. Gresty, M.A. and J.F. Golding, *Impact of vertigo and spatial disorientation on concurrent cognitive tasks.* Ann N Y Acad Sci, 2009. **1164**: p. 263-7.

46. Schaaf, H. and G. Hesse, *Patients with long-lasting dizziness: a follow-up after neurotological and psychotherapeutic inpatient treatment after a period of at least 1 year.* Eur Arch Otorhinolaryngol, 2015. **272**(6): p. 1529-35.
47. Pavlou, M., A.M. Bronstein, and R.A. Davies, *Randomized trial of supervised versus unsupervised optokinetic exercise in persons with peripheral vestibular disorders.* Neurorehabil Neural Repair, 2013. **27**(3): p. 208-18.
48. Meldrum, D., et al., *Toward a Digital Health Intervention for Vestibular Rehabilitation: Usability and Subjective Outcomes of a Novel Platform.* Front Neurol, 2022. **13**: p. 836796.
49. Sharma, A., et al., *Using Digital Health Technology to Better Generate Evidence and Deliver Evidence-Based Care.* J Am Coll Cardiol, 2018. **71**(23): p. 2680-2690.
50. Cottrell, M.A. and T.G. Russell, *Telehealth for musculoskeletal physiotherapy.* Musculoskelet Sci Pract, 2020. **48**: p. 102193.
51. Jull, G., et al., *Retraining cervical joint position sense: The effect of two exercise regimes.* Journal of Orthopaedic Research, 2007. **25**(3): p. 404-412.



General discussion

This doctoral thesis sought to add knowledge to the research on the identification and treatment of patients with cervicogenic dizziness (CGD) and persistent postural-perceptual dizziness (PPPD).

Our main findings from Part 1, on how to identify CGD and PPPD, are that both patients with CGD and PPPD generally differed little clinically from patients with other causes of chronic dizziness on clinical cervical and visual dependence tests, respectively. Consequently, the differential diagnostic value of these clinical tests for CGD and PPPD was limited [1, 2].

Our main findings from Part 2, on how to treat CGD and PPPD, show the potential added value of combined manual and exercise therapy in the treatment of CGD [3], and the good user experience of patients with PPPD with WeBaVeR (i.e., our self-developed customised web-based home VRT programme containing visual desensitisation exercises).

Hereafter, these main findings of the doctoral thesis (**TABLE 1**) are discussed in detail in the light of the currently available literature. Clinical implications and suggestions for further research are formulated.

Furthermore, recommendations are given for the design of an intervention study on the therapeutic effectiveness of WeBaVeR. Due to the COVID-19 pandemic, an intervention study could not be conducted and published within the expected duration of this doctoral mandate. Hopefully, the information provided here can be an impetus to continue research on this topic.

Lastly, we summarise this doctoral thesis in the final conclusion.

Table 1. *Main findings of this doctoral thesis.*

Main findings of part 1 – Identifying CGD and PPPD

- Clinical overlap exists between patients with CGD, PPPD and other causes of chronic dizziness.
- Cervical and visual dependency tests have limited differential diagnostic value for CGD and PPPD.

Main findings of part 2 – Treatment of CGD and PPPD

- Combined manual and exercise therapy may be even more effective in the treatment of CGD than manual therapy alone.
- WeBaVeR is a web-based home VRT programme with visual desensitisation therapy that shows good user experience.

1. Clinical overlap between CGD, PPPD and other causes for chronic dizziness

The first main finding from our studies [1, 2] is that neck complaints, increased visual dependence, and postural imbalance are significantly more common in patients with chronic dizziness than in healthy non-dizzy persons. However, there is little difference in outcomes on clinical tests within the group of chronic dizzy patients, regardless of the cause.

Studies show that neck complaints are frequently reported in the general population [4], so coincidental presence of neck complaints in patients with dizziness is possible. However, if there is a link between the neck complaints and the dizziness, the neck complaints may be a primary or secondary contributor to the dizziness. An example of where it is a primary contributor is in the case of CGD, where altered cervical afferents are supposed to cause the dizziness. Secondary can be when the neck complaints occur only as a result of a head-on-trunk stiffness reaction to the dizziness present [5]. In the latter case, the avoidance of head movements impedes vestibular compensation, thus maintaining dizziness [5].

A similar scenario is present in PPPD: visual dizziness, implying increased visual dependence, is an important diagnostic criterion for PPPD [6]. However, increased visual dependence may also be present in patients with chronic dizziness who do not otherwise meet the criteria for PPPD. In contrast to neck complaints, increased visual dependence always contributes primarily to the dizziness symptoms in environments with excessive and/or disturbing visual stimuli [7].

The clinical implication of our first main finding is that it is important to pay attention to the presence of neck complaints and increased visual dependence, even if they are not a symptom of the presumed underlying cause. They very frequently occur in chronic dizziness in general, and can always (indirectly) contribute to the dizziness symptoms.

Further research is needed to investigate all other (primary and secondary) contributing factors to the maintenance of dizziness, such as anxiety, depression, and reduced physical activity. This list can then be used by the clinician to screen the (chronic) patient, and propose a (preventive) treatment approach tailored to the patient.

A summary of our first main finding is presented in **TABLE 2**.

Table 2. *First main finding (on clinical overlap): clinical implications and further research*

Clinical implications • Attention to neck complaints and increased visual dependence is necessary in all patients with (chronic) dizziness. *Further research* • An overview of all contributing factors to the maintenance of dizziness is needed. • The development of an algorithm that allows the clinician to screen the patient for contributing factors to the dizziness may be helpful.

2. Differential diagnostic value of clinical tests for CGD and PPPD

A second main finding arising from our studies is that clinical cervical and visual dependence tests have limited differential diagnostic value for CGD and PPPD [1, 2].

In this doctoral thesis, we evaluated whether clinical cervical and visual dependence tests can detect CGD and PPPD, respectively. The results show that high visual dependence measured by the VVAS (AUC = 0.72, 95% CI [0.57; 0.86]) had the highest discriminant ability for PPPD [2], and the combination of high neck complaints measured by the NBQ and good dynamic balance measured by the Tandem Gait (AUC = 0.74, 95% CI [0.61; 0.87]) had the highest discriminant ability for CGD [1]. The reason for the addition of the Tandem Gait is that this balance test does not require head movements, and thus would not cause balance disturbance in patients with CGD as it would in patients with a vestibular disease. The sensitivity for the tests is fair but the specificity is low. This means that these tests can exclude the presence of PPPD or CGD adequately, but are not specific enough to make the diagnosis of PPPD or CGD with certainty. This conclusion is also in line with our previous main finding that the presence of neck complaints or increased visual dependence is not in itself sufficiently suggestive of CGD and PPPD, respectively.

The diagnostic difficulties for CGD and PPPD are also confirmed in the literature. For CGD, these difficulties are partly due to the multisensory mismatch: CGD is best evaluated in a dynamic manner, but this makes it difficult to evaluate the contribution of proprioception to dizziness [8]. Moreover, head movements/positions are not only a trigger for dizziness in CGD, but also for dizziness caused by, for example, vestibular disorders (e.g., BPPV), cervical arterial occlusion (e.g., vertebrobasilar insufficiency) and migraine. Therefore, some say that in many patients diagnosed with CGD, another cause for the dizziness may eventually be found [9]. Finally, the diagnosis of CGD is also complicated by the lack of clear diagnostic criteria, let alone the availability of a diagnostic gold standard. Thus, due to the many diagnostic uncertainties, the existence of CGD is still disputed [10, 11].

In contrast, PPPD is less controversial and has been included in the International Classification of Vestibular Diseases (ICVD) [6]. The diagnostic gold standard for PPPD is currently medical imaging [12]. Since this is a cumbersome method, in clinical practice the diagnosis of PPPD is based on questionnaires during the medical history taking [6]. However, this is a subjective method, so the risk of misdiagnosis is real.

The clinical implication of our second main finding is that the NBQ and VVAS are meaningful and easy-to-use tests for clinical practice to detect the presence of neck complaints and increased visual dependence, respectively. Evaluation of the clinical presentation of the patient is most important, and should be the starting point for therapy. The many diagnostic problems make the exact diagnosis a discussion that can be further considered academically, but should not get in the way of patient-tailored treatment.

Further research is needed to find a diagnostic gold standard for the objective detection of altered proprioceptive afferents in CGD, against which the diagnostic value of tests can be measured. For PPPD, medical imaging should be used to assess the diagnostic value of tests. For practicality, simple clinical test materials are preferred for both CGD and PPPD.

A summary of our second main finding is presented in **TABLE 3**.

Table 3. *Second main finding (on diagnosing CGD and PPPD): clinical implications and further research*

Clinical implications

- NBQ and VVAS are easy-to-use tests for clinical practice to detect the presence of neck complaints and increased visual dependence, respectively.

Further research

- Research into a diagnostic gold standard for the objective detection of altered proprioceptive afferents in CGD is needed .
- Medical imaging should be used as the diagnostic gold standard in PPPD against which the diagnostic value of clinical tests can be measured.

3. Exercise therapy for CGD

A third main finding of this doctoral thesis, based on our meta-analysis of the available literature, is that exercise therapy can be a valuable addition to manual therapy for the treatment of dizziness, neck complaints and postural imbalance in patients with CGD [3]. This includes techniques such as deep cervical flexor endurance, scapular retraction and postural education. Effectiveness of manual therapy for CGD was already known in the literature [13, 14]. The possible reason for the additional effectiveness of exercise therapy may be its multisensory nature that allows central adaptation to the changed proprioceptive information.

However, our finding should be interpreted with caution. First, the included studies were of rather low methodological quality. Second, due to the diagnostic uncertainties in CGD, there was variation in the chosen diagnostic criteria between studies. Third, given the recent new recommendations to exclude migraine and head/neck trauma from the diagnosis of CGD, it is possible that some patients were incorrectly assigned the diagnosis of CGD [8].

The clinical implication of our third main finding - taking into account the proposed ex juvantibus principle in the literature [15] - is that, unless contraindicated (e.g., cervical instability), cervical manual and exercise therapy can certainly be applied in the possible presence of CGD. Even if the therapy does not help, it cannot do any harm.

Further research is needed to determine the most optimal therapy protocol. In the case of CGD in combination with a vestibular disorder, a well-integrated approach is needed that includes a feasible total exercise load while ensuring continued compliance by the patient.

A summary of our third main finding is presented in **TABLE 4**.

Table 4. *Third main finding (on treatment of CGD): clinical implications and further research*

Clinical implications • Unless contraindicated (e.g., cervical instability), cervical manual and exercise therapy can certainly be applied in the presence of neck pain (following the ex juvantibus principle).
Further research • Research into the most optimal therapy protocol for CGD is needed.

4. User experience of WeBaVeR in PPPD

Our last main finding was the good user experience of WeBaVeR in patients with PPPD.

WeBaVeR includes an information brochure, diary, booklet with customised vestibular exercises (i.e., gaze stabilisation, balance, movement habituation, visual desensitisation and neck exercises) and a supporting web application. More detailed information about WeBaVeR can be found in *Part 2 - Chapter 2*.

WeBaVeR responds to the demand in the literature for customised vestibular therapy in the home environment [16-19]. Indeed, since vestibular therapy requires a daily effort from the patient, it is desirable to provide a low-threshold method (both financially and in terms of convenience) for performing the exercises [20].

The uniqueness of WeBaVeR is that it also provides materials for customisable visual desensitisation and neck exercises. Our results (*main findings of part 1 of this doctoral thesis*) show that increased visual dependence and neck complaints are common in patients with chronic dizziness, regardless of the specific underlying cause. WeBaVeR may therefore be suitable not only for PPPD or CGD, but for a wide range of patients with chronic dizziness.

The clinical implication of our fourth main finding is that WeBaVeR is a good concept for the application of vestibular therapy in the home environment, that includes customisable visual desensitisation and neck exercises.

Further research is needed to evaluate the therapeutic effectiveness of WeBaVeR for chronic dizziness in different patient groups (e.g., visually induced dizziness, neck complaints). Below, we provide recommendations on how an intervention study could be designed (5. Recommendations for an intervention study).

A summary of our fourth main finding is presented in **TABLE 5**.

Table 5. Fourth main finding (on treatment of PPPD): clinical implications and further research

Clinical implications
• WeBaVeR is a good concept for the application of vestibular therapy that includes customisable visual desensitisation and neck exercises.
Further research
• Evaluation of the therapeutic effectiveness of WeBaVeR for chronic dizziness in different patient groups (e.g., visually induced dizziness, neck complaints) is needed.

5. Recommendations for an intervention study

Now that our study (*part 2 - chapter 2*) shows that WeBaVeR - provided some improvements are made - is a user-friendly instrument, the next step can be taken: evaluation of its therapeutic effectiveness. WeBaVeR could be used for a broad spectrum of patients with chronic dizziness, as the tool allows therapy to be set up according to the patient's specific needs (tailored vestibular, visual desensitisation and/or neck exercises). However, the question of the effectiveness of WeBaVeR for the treatment of visually induced dizziness is currently the most pressing.

Creating a visually challenging environment in a clinical setting that is also tailored to the patient is quite a challenge, let alone creating such an exercise situation in the patient's home environment. Recent literature evaluates the possibility of an optokinetic DVD for in the home environment [21, 22]. WeBaVeR improves on this idea by providing individually adjustable parameters for the various exercises. An additional advantage of WeBaVeR is that it allows for a complete vestibular home exercise programme to be set up immediately for the patient with chronic dizziness.

Below, we provide some recommendations for an intervention study evaluating the *effectiveness of WeBaVeR for visually induced dizziness*. Successively, we discuss the design, the patient selection, the interventions, the primary outcome measure, and the sample size calculation. Finally, we provide some additional comments.

5.1. Design

The study design should fit the preconceived research aim. This study, in which the researcher evaluates the effect of WeBaVeR ('intervention') on visually induced dizziness ('outcome'), is an intervention study (also called a 'clinical trial').

A randomised controlled trial (RCT) is the most often recommended, strong research design for this type of study. This procedure compares an experimental therapy (WeBaVeR) with a control therapy (the current treatment approach) for the therapy aim under investigation, in our case treating visually induced dizziness. The major goal may not be to assess whether WeBaVeR is better, but at least equivalent to the current treatment approach. This can be done by setting up a non-inferiority study, with the null hypothesis that WeBaVeR is inferior to the current treatment approach.

Accurate randomisation and stratification in this RCT is important to make sure any differences in outcome measures between groups are maximally related to

differences between experimental and control therapy, and not to differences in participants' characteristics between the two groups ("confounding variables").
The randomisation of subjects to the intervention or control therapy can be done via concealed envelopes or via, for example, a web-based computer-generated block randomisation. By also varying the block size, randomisation is further strengthened.
Stratification could, for example, be considered in terms of the duration of chronic dizziness (e.g., less than 1 year versus more than 1 year). The disadvantage is that the more stratification is used, the larger the overall sample size of the trial will have to be. Therefore, we suggest to make the eligibility criteria sufficiently stringent when recruiting participants (see 5.3. Patient selection) to ensure more homogeneity in study participants.

Additional note: a crossover design is less appropriate. The design does have advantages: fewer participants needed, and solving the problem of interindividual variability in patients with chronic dizziness (because participants act as their own control). However, considering that the therapy effect of visual desensitisation is expected only after 6 weeks on average, and a wash-out period is needed before starting another therapy, the crossover method is less time-efficient.

5.3. Patient selection

For patient recruitment, we suggest to include all patients with chronic, non-vertiginous visually triggered dizziness. Our study results (*main findings part 1 of this doctoral thesis*) show that we should not only focus on patients with PPPD, as visually triggered dizziness also occurs in other forms of chronic dizziness. To increase the homogeneity of the study participants, and thus the reliability of the study results, some additional inclusion criteria should be considered, such as:

- having a significant increase in dizziness in situations with intense visual stimuli and/or visuo-vestibular conflicts (Visual Vertigo Analogue Scale (VVAS) score of ≥40%)
- adults (≥ 18 years)
- no psychological comorbidities (Hospital Anxiety and Depression Scale (HADS)-anxiety ≤ 7/14; HADS-depression ≤ 7/14)
- absence of neck complaints
- absence of severe visual impairment that cannot be corrected by, for example, wearing glasses

- absence of balance problems unrelated to the dizziness (e.g., orthopaedic or neurological conditions)
- absence of dizziness due to untreated cardiovascular, pulmonary, hormonal, metabolic or mental problems or substance abuse
- absence of medical contraindication for treatment (e.g., epilepsy, serious comorbidities)
- adequate access to the Internet and having an e-mail account

5.4. Interventions

The experimental and control therapy should differ only in that which we want to investigate the therapeutic effect of. A relevant research question may be whether WeBaVeR is as effective as an optokinetic DVD for the treatment of visually induced dizziness in the home setting. Another relevant research question may be whether visual desensitisation therapy with WeBaVeR offered in the clinical setting is as effective as when WeBaVeR is used independently by the patient in the home setting. The former compares two types of therapy content, and the latter two types of administration method.

Additional note: Since both the experimental and the control therapy are tailor-made for the patient and adjusted during the intervention period, a detailed clinical treatment decision model should be drawn up in advance, indicating for each therapy component, via well-defined cut-off values on assessments, which exercises will be given at what intensity.

5.5. Primary outcome measure

Visually induced dizziness can be measured with the Situational Characteristics Questionnaire (SCQ) [or also called Situational Vertigo Questionnaire (SVQ)] and the Visual Vertigo Analogue Scale (VVAS). Originally, the SCQ was a 36-item questionnaire [23]. More recently, the SCQ was shortened to a 19-item version [7], but almost no studies have been conducted with it. In contrast, the VVAS, a 9-item questionnaire (based on an earlier 5-item version [24]) has already been evaluated for its clinimetric properties. Studies show that the VVAS is a valid and reliable instrument, and sensitive to changes in patient behaviour [25, 26]. The latter makes VVAS the most appropriate primary outcome measure for the intervention study.

Additional note: The effect of WeBaVeR can additionally be examined on secondary outcome measures, such as visual dependence, postural balance, and level of activity and participation.

5.6. Sample size calculation

The intervention study should have sufficient power, or sufficient probability to detect a true positive effect of WeBaVeR on visually-induced dizziness. Therefore, it is important to calculate the required sample size.

One method of calculating the required sample size is based on the minimum clinically important difference (MCID) of VVAS, in other words the minimum required change in VVAS at which the patient actually notices improvement in visual dizziness. However, the MCID is not known in the literature for VVAS. VVAS is only described as sensitive to change [25].

We therefore propose to conduct a pilot study, recruiting a minimum of 12 participants per study arm to estimate the effect sizes we can expect in the full study [27]. To account for possible drop-outs, we recommend increasing the number of participants per study arm obtained from the sample size calculation by 30%.

5.7. Additional comments

Finally, we would like to mention the importance of paying sufficient attention to the following points: sources of bias, publication of the study protocol, medical ethics committee and valorisation.

5.7.1. Sources of bias

Several precautions should be taken to minimise possible sources of bias. The most important are:

Allocation concealment: We recommend that the random group allocation be communicated to the participant by an independent person (i.e. not otherwise involved in any part of the RCT, and not aware of the content of the treatments).

Blinding: We recommend keeping patients and the outcome assessor blinded. Furthermore, we suggest not informing the administering clinicians about what the other therapy entails so that they do not know whether they are giving the intervention or the control therapy.

Avoiding missing data: We recommend carefully considering in advance how to maximise data collection. In this study, this can be done by sending a reminder to complete the VVAS questionnaire, and always keeping a good record of why data are missing.

Intention-to-treat analysis: This approach is preferable to on-treatment analysis, so that, whatever happens afterwards, the patients continue to be followed up and assessed according to the group to which they originally belonged.

Balance in baseline prognostic variables: Patient characteristics that may affect the outcome of therapy (e.g., duration of dizziness present, previous therapies received) should be balanced between the two therapy groups. Hence, it is important to establish narrow patient eligibility criteria (see above, *5.3. Patient selection*).

Modification or discontinuation: Any change to the originally proposed protocol should be recorded along with the reason for it.

Concomitant care: Other care that does not affect dizziness can be continued. Therapies that may affect dizziness (e.g., cervical manual therapy) are best not allowed for the duration of the study. If the latter therapies cannot be discontinued, e.g., for medical reasons, it is better to exclude those patients from the study.

5.7.2. Publishing the study protocol

It is advisable to publish the intervention protocol (e.g., in BMC trials). This will result in immediate feedback via peer-reviewing from a wider scientific community, helping to firmly shape the intervention study from the start. It also prevents publication bias, and discourages others from starting the same study. Because peer-reviewing took place at the beginning, the results of the study will also be more easily published afterwards.

5.7.3. Medical ethics committee

Studies involving human participants must be approved by the Medical ethics committee. This must detail the purpose and methods of the study, and how the data will be collected and stored.

As WeBaVeR falls under the definition of a medical device as indicated by the European Regulation (EU) 2017/745, the Medical ethics committee should check with the Federal Agency for Medicines and Health Products (FAMHP) whether regulation for WeBaVeR is needed before starting the intervention study. However, it is expected that regulation will be limited or even unnecessary because WeBaVeR does not collect patient data and poses virtually no risks.

5.7.4. Valorisation

We suggest making WeBaVeR available only to study participants (e.g., via an access code). If WeBaVeR proves effective, it could be made publicly available afterwards (e.g., paid access, free access under certain conditions). If there are plans for commercialisation, it would be best to ask patients to sign a confidentiality agreement during the study.

6. Conclusion

It is difficult to diagnose a patient with persistent dizziness. We focussed on two causes: altered cervical proprioceptive afferents in cervicogenic dizziness (CGD), and altered functional brain connectivity in persistent postural-perceptual dizziness (PPPD). Unfortunately, no clinical tests are available that can detect the pathophysiological mechanisms of CGD or PPPD, nor can we rely on their clinical symptoms [mainly neck complaints (for CGD) or increased visual dependence (for PPPD)] for detection, as these symptoms are also common in other forms of chronic dizziness.

From a clinical perspective, we believe that the ex juvantibus principle is the appropriate approach in patients with chronic dizziness. In other words, in the presence of neck complaints and increased visual dependence, regardless of whether it is related to CGD or PPPD, the discussed therapies of combined exercise and manual therapy and/or visual desensitisation therapy (delivered through WeBaVeR) should be considered.

6. References

1. De Vestel, C., et al., *Clinical characteristics and diagnostic aspects of cervicogenic dizziness in patients with chronic dizziness: A cross-sectional study.* Musculoskelet Sci Pract, 2022. **60**: p. 102559.
2. De Vestel, C., et al., *Comparison of Clinical Balance and Visual Dependence Tests in Patients With Chronic Dizziness With and Without Persistent Postural-Perceptual Dizziness: A Cross-Sectional Study.* Frontiers in Neurology, 2022. **13**.
3. De Vestel, C., et al., *Systematic review and meta-analysis of the therapeutic management of patients with cervicogenic dizziness.* J Man Manip Ther, 2022: p. 1-11.
4. Hoy, D.G., et al., *The epidemiology of neck pain.* Best Pract Res Clin Rheumatol, 2010. **24**(6): p. 783-92.
5. Balaban, C.D., M.E. Hoffer, and K.R. Gottshall, *Top-down approach to vestibular compensation: Translational lessons from vestibular rehabilitation.* Brain Research, 2012. **1482**: p. 101-111.
6. Staab, J.P., et al., *Diagnostic criteria for persistent postural-perceptual dizziness (PPPD): Consensus document of the committee for the Classification of Vestibular Disorders of the Barany Society.* J Vestib Res, 2017. **27**(4): p. 191-208.
7. Guerraz, M., et al., *Visual vertigo: symptom assessment, spatial orientation and postural control.* Brain, 2001. **124**(Pt 8): p. 1646-56.
8. Cherchi, M., et al., *The Enduring Controversy of Cervicogenic Vertigo, and Its Place among Positional Vertigo Syndromes.* Audiol Res, 2021. **11**(4): p. 491-507.
9. Yacovino, D.A. and T.C. Hain, *Clinical characteristics of cervicogenic-related dizziness and vertigo.* Seminars in Neurology, 2013. **33**(3): p. 244-255.
10. Brandt, T., *Cervical vertigo--reality or fiction?* Audiol Neurootol, 1996. **1**(4): p. 187-96.
11. Li, Y.C. and B.G. Peng, *Pathogenesis, Diagnosis, and Treatment of Cervical Vertigo.* Pain Physician, 2015. **18**(4): p. E583-E595.
12. Teh, C.S., et al., *Neuroimaging Systematic Review in Persistent Postural-Perceptual Dizziness: The Elaborate Alterations in the Delicate Network to Remain Balanced.* Otol Neurotol, 2022. **43**(1): p. 12-22.
13. Lystad, R.P., et al., *Manual therapy with and without vestibular rehabilitation for cervicogenic dizziness: a systematic review.* Chiropr Man Therap, 2011. **19**(1): p. 21.

14. Yaseen, K., et al., *The effectiveness of manual therapy in treating cervicogenic dizziness: a systematic review.* J Phys Ther Sci, 2018. **30**(1): p. 96-102.
15. Magnusson, M. and E.M. Malmström, *The conundrum of cervicogenic dizziness.* Handbook of clinical neurology, 2016. **137**: p. 365-369.
16. Eldoen, G., et al., *Web-based vestibular rehabilitation in persistent postural-perceptual dizziness.* Brain Behav, 2021. **11**(10): p. e2346.
17. Ertunc Gulcelik, G., et al., *Research on the Effects of a Web-Based System With Oculomotor and Optokinetic Stimuli on Vestibular Rehabilitation.* Am J Phys Med Rehabil, 2021. **100**(6): p. 555-562.
18. Ding, C.R., et al., *Advantages of Short-term Personalized Vestibular Rehabilitation at Home Guided by Professional Therapist for Treatment of Decompensated Vestibular Vertigo.* Current Medical Science, 2021. **41**(4): p. 687-694.
19. Smolka, W., et al., *The efficacy of vestibular rehabilitation in patients with chronic unilateral vestibular dysfunction.* International Journal of Occupational Medicine and Environmental Health 2020 Apr 30;33(3):273-282, 2020.
20. Han, B.I., H.S. Song, and J.S. Kim, *Vestibular rehabilitation therapy: review of indications, mechanisms, and key exercises.* J Clin Neurol, 2011. **7**(4): p. 184-96.
21. Pavlou, M., *The use of optokinetic stimulation in vestibular rehabilitation.* J Neurol Phys Ther, 2010. **34**(2): p. 105-10.
22. Manso, A., M.M. Gananca, and H.H. Caovilla, *Vestibular rehabilitation with visual stimuli in peripheral vestibular disorders.* Braz J Otorhinolaryngol, 2016. **82**(2): p. 232-41.
23. Jacob, R.G., et al., *Panic disorder with vestibular dysfunction: Further clinical observations and description of space and motion phobic stimuli.* Journal of Anxiety Disorders, 1989. **3**(2): p. 117-130.
24. Longridge, N.S. and A.I. Mallinson, *Visual vestibular mismatch in work-related vestibular injury.* Otol Neurotol, 2005. **26**(4): p. 691-4.
25. Dannenbaum, E., G. Chilingarian, and J. Fung, *Validity and Responsiveness of the Visual Vertigo Analogue Scale.* J Neurol Phys Ther, 2019. **43**(2): p. 117-121.
26. Verdecchia, D.H., et al., *Validated argentine version of the visual vertigo analogue scale.* J Vestib Res, 2022. **32**(3): p. 235-243.
27. Julious, S.A., *Sample size of 12 per group rule of thumb for a pilot study.* Pharmaceutical Statistics, 2005. **4**(4): p. 287-291.

Appendix

Overview of the assessment questionnaires used in this doctoral thesis

1. Dizziness Handicap Inventory (DHI)

Reference: Jacobson, G.P. and C.W. Newman, *The development of the Dizziness Handicap Inventory.* Arch Otolaryngol Head Neck Surg, 1990. **116**(4): p. 424-7.

2. Hospital Anxiety and Depression Scale (HADS)

Reference: Pritchard, M.J., *Using the hospital anxiety and depression scale in surgical patients.* Nurs Stand, 2011. **25**(34): p. 35-41.

3. Neck Bournemouth Questionnaire (NBQ)

Reference: Bolton, J.E. and A.C. Breen, *The Bournemouth Questionnaire: A short-form comprehensive outcome measure. I. Psychometric properties in back pain patients.* Journal of Manipulative and Physiological Therapeutics, 1999. **22**(8): p. 503-510.

7. Visual Vertigo Analogue Scale (VVAS)

Reference: Dannenbaum, E., G. Chilingaryan, and J. Fung, *Visual vertigo analogue scale: an assessment questionnaire for visual vertigo.* J Vestib Res, 2011. **21**(3): p. 153-9.

1. Dizziness Handicap Inventory (DHI)

Instructions: The purpose of this scale is to identify difficulties that you may be experiencing because of your dizziness or unsteadiness. Please answer "yes," "no," or "sometimes" to each question. Answer each question as it pertains to your dizziness or unsteadiness problem only. [a]

Domain	Questions	Yes	Some-times	No
P1	Does looking up increase your problem?			
E2	Because of your problem, do you feel frustrated?			
F3	Because of your problem, do you restrict your travel for business or recreation?			
P4	Does walking down the aisle of a supermarket increase your problem?			
F5	Because of your problem, do you have difficulty getting into or out of bed?			
F6	Does your problem significantly restrict your participation in social activities such as going out to dinner, going to movies, dancing, or to parties?			
F7	Because of your problem, do you have difficulty reading?			
P8	Does performing more ambitious activities like sports, dancing, household chores such as sweeping or putting dishes away increase your problem?			
E9	Because of your problem, are you afraid to leave your home without having someone accompany you?			
E10	Because of your problem, have you been embarrassed in front of others?			
P11	Do quick movements of your head increase your problem?			
F12	Because of your problem, do you avoid heights?			
P13	Does turning over in bed increase your problem?			
F14	Because of your problem, is it difficult for you to do strenuous housework or yardwork?			
E15	Because of your problem, are you afraid people may think you are intoxicated?			
F16	Because of your problem, is it difficult for you to go for a walk by yourself?			
P17	Does walking down a sidewalk increase your problem?			
E18	Because of your problem, is it difficult for you to concentrate?			
F19	Because of your problem, is it difficult for you to walk around your house in the dark?			
E20	Because of your problem, are you afraid to stay home alone?			
E21	Because of your problem, do you feel handicapped?			
E22	Has your problem placed stress on your relationships with members of your family or friends?			
E23	Because of your problem, are you depressed?			
F24	Does your problem interfere with your job or household responsibilities?			
P25	Does bending over increase your problem?			

[a] Domains: E = Emotional, F = Functional, P = Physical

2. Hospital Anxiety and Depression Scale (HADS)

Instructions: Tick the box beside the reply that is closest to how you have been feeling in the past week. Don't take too long over you replies: your immediate is best. [a]

A	**I feel tense or wound up**		**D**	**I still enjoy the things I used to enjoy**	
	Most of the time	☐		Definitely as much	☐
	A lot of the time	☐		Not quite so much	☐
	From time to time, occasionally	☐		Only a little	☐
	Not at all	☐		Hardly at all	☐
A	**I get a sort of frightened feeling as if something awful is about to happen**		**D**	**I can laugh and see the funny side of things**	
	Very definitely and quite badly	☐		As much as I always could	☐
	Yes, but not too badly	☐		Not quite so much now	☐
	A little, but it doesn't worry me	☐		Definitely not so much now	☐
	Not at all	☐		Not at all	☐
A	**Worrying thoughts go through my mind**		**D**	**I feel cheerful**	
	A great deal of the time	☐		Not at all	☐
	A lot of the time	☐		Not often	☐
	From time to time, but not too often	☐		Sometimes	☐
	Not at all	☐		Most of the time	☐
A	**I can sit at ease and feel relaxed**		**D**	**I feel as if I am slowed down**	
	Definitely	☐		Nearly all the time	☐
	Usually	☐		Very often	☐
	Not often	☐		Sometime	☐
	Not at all	☐		Not at all	☐
A	**I get sudden feelings of panic**		**D**	**I have lost interest in my appearance**	
	Very often indeed	☐		Definitely	☐
	Quite often	☐		I don't take as much care as I should	☐
	Not very often	☐		I may not take quite as much care	☐
	Not at all	☐		I take just as much care as ever	☐
A	**I feel restless as if I have to be on the move**		**D**	**I look forward with enjoyment to things**	
	Very much indeed	☐		As much as I ever did	☐
	Quite a lot	☐		Rather less than I used to	☐
	Not very much	☐		Definitely less than I used to	☐
	Not at all	☐		Hardly at all	☐
A	**I get a sort of frightened feeling like butterflies in the stomach**		**D**	**I can enjoy a good book, radio or television programme**	
	Not at all	☐		Often	☐
	Occasionally	☐		Sometimes	☐
	Quite often	☐		Not often	☐
	Very often	☐		Very seldom	☐

[a] Domains: A = Anxiety; D = Depression

3. Neck Bournemouth Questionnaire (NBQ)

Instructions: The following scales have been designed to find out about your neck pain and how it is affecting you. Please answer all the scales by circling one number on each scale that best describes how you feel.

1. Over the past week, on average, how would you rate your neck pain?

No pain	1	2	3	4	5	6	7	8	9	10	Worst pain possible

2. Over the past week, how much has your neck pain interfered with your daily activities (housework, washing, dressing, walking, climbing stairs, getting in/out of bed/chair)?

No interference	1	2	3	4	5	6	7	8	9	10	Unable to carry out activity

3. Over the past week, how much has your neck pain interfered with your ability to take part in recreational, social, and family activities?

No interference	1	2	3	4	5	6	7	8	9	10	Unable to carry out activity

4. Over the past week, how anxious (tense, uptight, irritable, difficulty in concentrating/relaxing) have you been feeling?

Not at all anxious	1	2	3	4	5	6	7	8	9	10	Extremely anxious

5. Over the past week, how depressed (down-in-the-dumps, sad, in low spirits, pessimistic, unhappy) have you been feeling?

Not at all depressed	1	2	3	4	5	6	7	8	9	10	Extremely depressed

6. Over the past week, how have you felt your work (both inside and outside the home) has affected (or would affect) your neck pain?

Have made it no worse	1	2	3	4	5	6	7	8	9	10	Have made it much worse

7. Over the past week, how much have you been able to control (reduce/help) your neck pain on your own?

Completely control it	1	2	3	4	5	6	7	8	9	10	No control whatsoever

4. Visual Vertigo Analogue Scale (VVAS)

Instructions: Indicate the amount of dizziness you experience in the following situations by marking off the scales below. 0 represents no dizziness and 10 represents the most dizziness .

1. Walking through a supermarket aisle

Not applicable ☐ 0 |————————————| 10

2. Being a passenger in a car

Not applicable ☐ 0 |————————————| 10

3. Being under fluorescent lights

Not applicable ☐ 0 |————————————| 10

4. Watching traffic at a busy intersection

Not applicable ☐ 0 |————————————| 10

5. Walking through a shopping mail

Not applicable ☐ 0 |————————————| 10

6. Going down an escalator

Not applicable ☐ 0 |————————————| 10

7. Watching a movie at the movie theatre

Not applicable ☐ 0 |————————————| 10

8. Walking over a patterned floor

Not applicable ☐ 0 |————————————| 10

9. Watching action television

Not applicable ☐ 0 |————————————|

Summary // samenvatting

1. Summary

Dizziness is a frequent disorder with a prevalence of up to 40% in the general population. Although it is almost always non-life-threatening, dizziness can have a significant impact on personal and social functioning. This is particularly the case when the symptoms persist, i.e., in chronic dizziness.

Patients with chronic dizziness present a particular challenge to the clinician. Diagnosing is complicated by the subjectivity of the symptoms, the often-present multicausality, and the lack of abnormalities on clinical/laboratory tests. The absence of a diagnosis makes the patient feel misunderstood, and all too often no (appropriate) treatment is administered.

This doctoral thesis focuses on Cervicogenic Dizziness (CGD) and Persistent Postural-Perceptual Dizziness (PPPD). These two forms of chronic dizziness are frequently mentioned in the literature, but there is still some uncertainty how these disorders can be reliably detected and adequately treated. For CGD, the dizziness is said - according to the most common theory - to be caused by altered cervical proprioceptive afferents. In PPPD cases, dizziness is thought to be caused by altered functional brain connectivity.

Our results show that the combination of low scores on the Neck Bournemouth Questionnaire and low scores on the Tandem Gait is sufficiently reliable to exclude the diagnosis of CGD, and that low scores on the Visual Vertigo Analogue Scale can be used to exclude the diagnosis of PPPD. However, clinical tests that can reliably identify CGD or PPPD are lacking: the existing ones cannot detect the pathophysiological mechanism sufficiently and what the tests do detect is also frequently seen in other causes of chronic dizziness than CGD and PPPD.

The results also demonstrate the increased effectiveness of combined manual and exercise therapy for the treatment of CGD, and the good user experience of WeBaVeR in patients with PPPD. Further research into the therapeutic effect of WeBaVeR is still needed. However, given the clinical overlap, we suggest that every patient with chronic dizziness should be screened for the presence of neck complaints and increased visual dependence, and if present, these treatments should be applied regardless of the diagnosis.

In other words, we advocate a patient-tailored, symptom-based approach for patients with chronic dizziness, including manual and exercise therapy and/or WeBaVeR. The diagnostic discussion can be continued academically, but should not get in the way of the clinical approach.

2. Samenvatting

Duizeligheid is een frequent voorkomende aandoening met een prevalentie tot 40% in de algemene bevolking. Hoewel duizeligheid bijna altijd niet levensbedreigend is, kan het een aanzienlijke invloed hebben op het persoonlijk en sociaal functioneren. Dit is vooral het geval wanneer de symptomen aanhouden, d.w.z. bij chronische duizeligheid.

Patiënten met chronische duizeligheid vormen een bijzondere uitdaging voor de clinicus. Het stellen van de diagnose wordt bemoeilijkt door de subjectiviteit van de symptomen, de vaak aanwezige multicausaliteit, en het ontbreken van afwijkingen bij klinisch/laboratorium onderzoek. Het ontbreken van een diagnose maakt dat de patiënt zich onbegrepen voelt, en er vaak geen (passende) behandeling wordt gegeven.

Dit proefschrift richt zich op Cervicogene Duizeligheid (CGD) en Persisterende Positionele-Perceptie Duizeligheid (PPPD). Deze twee vormen van chronische duizeligheid worden vaak genoemd in de literatuur, maar er bestaat nog steeds onduidelijkheid over hoe deze aandoeningen betrouwbaar kunnen worden opgespoord en adequaat behandeld. Bij CGD zou de duizeligheid - volgens de meest gangbare theorie - veroorzaakt worden door veranderde cervicale proprioceptieve afferentie. Bij PPPD zou de duizeligheid veroorzaakt worden door een veranderde functionele hersenconnectiviteit.

Onze resultaten tonen aan dat de combinatie van lage scores op de Neck Bournemouth Questionnaire en lage scores op de Tandem Gait voldoende betrouwbaar is om de diagnose CGD uit te sluiten, en dat lage scores op de Visual Vertigo Analogue Scale kunnen worden gebruikt om de diagnose PPPD uit te sluiten. Klinische tests die CGD of PPPD op betrouwbare wijze kunnen identificeren, ontbreken echter: de bestaande tests kunnen het pathofysiologische mechanisme onvoldoende opsporen en wat de tests wel opsporen, wordt ook vaak gezien bij andere oorzaken van chronische duizeligheid dan CGD en PPPD.

De resultaten tonen ook de verhoogde effectiviteit aan van de combinatie van manuele therapie met oefentherapie voor de behandeling van CGD, en de goede gebruikerservaring van WeBaVeR bij PPPD-patiënten. Verder onderzoek naar het therapeutisch effect van WeBaVeR is nog nodig. Echter, gezien de klinische overlap, suggereren wij dat elke patiënt met chronische duizeligheid gescreend zou moeten worden op de aanwezigheid van nekklachten en verhoogde visuele afhankelijkheid, en indien aanwezig, zouden deze behandelingen toegepast moeten worden, ongeacht de diagnose

Met andere woorden, wij pleiten voor een op de patiënt afgestemde, symptoomgerichte aanpak voor patiënten met chronische duizeligheid, inclusief manuele en oefentherapie en/of WeBaVeR. De diagnostische discussie kan academisch worden voortgezet, maar mag de klinische benadering niet in de weg staan.

About the research team

Charlotte De Vestel, MSc, graduated as Master in Rehabilitation sciences and Physiotherapy in the major Musculoskeletal Disorders (University of Ghent, 2017), and the major Neurological Disorders (Catholic University of Leuven, 2018), both 'cum laude'. She then became a researcher at the Department of Rehabilitation sciences and Physiotherapy of the University of Antwerp. With her PhD thesis "Identification and Treatment of Cervicogenic Dizziness and Persistent Postural-Perceptual Dizziness" she aims to obtain the title of Doctor of Medical Sciences at the University of Antwerp.

Luc Vereeck, PhD, is Professor at the Department of Rehabilitation Sciences and Physiotherapy of the University of Antwerp. His clinical and research interests include the assessment and treatment of patients with peripheral, functional, and central vestibular disorders, and patients with multiple sensory deficits.

Willem De Hertogh, PhD, is Associate Professor at the Department of Rehabilitation Sciences and Physiotherapy of the University of Antwerp, and is musculoskeletal physical therapist with over 20 years of clinical expertise. His research interests include head and neck complaints, headaches (cervicogenic headache, tension-type headache, migraine), tinnitus, and dizziness.

Vincent Van Rompaey, PhD, is Professor at the Department of Otorhinolaryngology and the Department of Translational Neurosciences of the University of Antwerp, and Consultant at the Maastricht University Medical Centre. His research interests include hearing implants, ear surgery, skull base surgery, tinnitus, balance disorders, and DFNA9.

Acknowledgements

This doctoral thesis is the result of an intense four years of research, but fortunately I could count on the support of many people.

First, I would like to thank my supervisors – Prof. Dr. Luc Vereeck, Prof. Dr. Willem De Hertogh and Prof. Dr. Vincent Van Rompaey - for giving me the opportunity to start this adventure, and for their continued support. Their expertise and insights were very valuable in the realisation of this doctoral thesis. I would also like to thank them for all the improvements of my personal development by encouraging me to attend various (inter)national courses and conferences, and organising (extra-) university activities.

Furthermore, a special word of thanks goes to Prof. Dr. Ann Hallemans and Lab Coordinator Patrick De Bock, not only for introducing me to our Movement analysis lab 'M^2OCEAN' (Multidisciplinary Motor Centre Antwerp), but also for their close involvement in my doctoral project. They were always ready to help, which I greatly appreciate. Special thanks also go to Prof. Dr. Nick Gebruers for all his support and pointers, Prof. Dr. Erik Fransen for his statistical advice, Lies Peeters for all her help in arranging the finances, and my colleague Lien Van Laer for the pleasant collaboration.

Actually, I could mention each of my colleagues by name (doctoral students, teaching assistants, professors, administrative staff, etc.). Each of you brought so much warmth and enthusiasm to the workplace. I could always turn to you for a nice chat or support. I am going to miss you enormously!

Last, but definitely not least, I would like to thank my family - especially my parents and my brother – and friends who put up with my frequent absences or many hours of writing this doctoral thesis. Thank you for your continued support, trust and patience with me.

Charlotte De Vestel
31 augustus 2022

Our body is an ingenious construction which enables us to perform complex functions in an often subconscious way. Some of these complex functions are provided by the **balance system**, which allows us to navigate in space, focus our gaze and maintain our balance.

Disturbances in the balance system can cause dizziness. It is not hard to imagine that dizziness can have a **major impact on an individual's functioning**, especially when it persists over a long period of time.

This doctoral thesis concentrates on two specific forms: **cervicogenic dizziness** and **persistent postural-perceptual dizziness**. Our goal is to provide clinicians with tools to recognise and effectively treat these two forms in patients with chronic dizziness.

Charlotte De Vestel graduated as Master in Rehabilitation sciences and Physiotherapy in the major Musculoskeletal Disorders (University of Ghent, 2017), and the major Neurological Disorders (Catholic University of Leuven, 2018). With her doctoral thesis “Identification and Treatment of Cervicogenic Dizziness and Persistent Postural-Perceptual Dizziness” she aims to obtain the title of Doctor of Medical Sciences at the University of Antwerp.

Faculty of Medicine and Health Sciences
Department of Rehabilitation Sciences and Physiotherapy
University of Antwerp

Antwerp, 2022