Aus dem Institut für medizinische Informationsverarbeitung, Biometrie und Epidemiologie (IBE)
Institut der Ludwig-Maximilians-Universität München
Direktor: Univ. Prof. Dr. Urlich Mansmann

Dissertation

zum Erwerb des Doctor of Philosophy (Ph.D.)

an der Medizinischen Fakultät der

Ludwig-Maximilians-Universität zu München

The impact of episodic and chronic vestibular disorders and their specific vs. unspecific diagnosis on Health-related quality of life

vorgelegt von:

Saly Harajli

aus:

Bent Jbeil, Lebanon

Jahr: 2023

_____

Mit Genehmigung der Medizinischen Fakultät der

Ludwig-Maximilians-Universität zu München

First evaluator (1. TAC member):	Univ. Prof. Dr. Eva Grill, MPH
Second evaluator (2. TAC member):	Univ. Prof. Dr. Ulrich Mansmann
Third evaluator:	Priv. Doz. Dr. Max Wühr
Fourth evaluator:	Priv. Doz. Dr. Vera Zingler

Dean: **Prof. Dr. med. Thomas Gudermann**

date of the defense:

24.10.2023

_____

Table of content

Abstract

Vertigo and dizziness are relatively frequent complaints at primary, secondary and tertiary health-care settings. They tend to occur more often with increasing age and to negatively influence Health-related-quality of life (HRQoL) and functioning. Vestibular disorders are of episodic or chronic nature with a broad range of possible underlying causes. Episodic vestibular syndromes (EVS) present with unpredictable short attacks of vertigo and dizziness while chronic vestibular syndromes (CVS) present with long lasting episodes of vertigo and dizziness. Although they are manageable, vertigo and dizziness are often under- and misdiagnosed especially in primary care. It is not yet fully understood how EVS and CVS affect HRQoL and functioning. This far, little is known how an unspecific versus specific diagnosis of vertigo and dizziness is associated with HRQoL and its trajectories.

Therefore, this doctoral thesis aims to study how EVS and CVS affect HRQoL and functioning. in addition to how an unspecific versus specific diagnosis of vertigo and dizziness is associated with HRQoL and its trajectories. The first analysis compares the effect of episodic and chronic vestibular diseases on HRQoL and functioning in a tertiary care setting, and the impact of lifestyle and sociodemographic factors. The second analysis assesses the different effects of specific and unspecific diagnoses of vertigo and dizziness on HRQoL in a primary care setting. The change in HRQoL over one year is also assessed among specific and unspecific diagnoses.

Data of study one originates from the “DizzyReg” database. The latter is an ongoing prospective registry for vertigo and dizziness patients. Patients showing up at the interdisciplinary outpatient clinic of the German Center for Vertigo and Balance (DSGZ) at the Ludwig Maximilian University Hospital (LMU Klinikum) were included between December 2015 and July 2019. The main outcomes are HRQoL and functioning scores which were measured by self-report using the 3-level version of the Euro-Qol five-dimensional (EQ5D3L) and the dizziness handicap inventory (DHI) questionnaires respectively. CVS and EVS classifications were based on a comprehensive thorough neuro-

otological examination by the clinical experts at the DSGZ following diagnostic guidelines of the international classification of vestibular disorders. The impact of CVS and EVS on HRQoL and functioning was assessed using multivariable linear regression models adjusting for possible confounders.

Data of study two derives from the longitudinal MobilE-TRA which was collected between 2017 and 2019. The latter is a multicenter observational practice-based prospective cohort study among general practitioners (GPs) who have recruited patients with acute episode of vertigo and dizziness in the last quarter. Diagnosis was given by the GP at baseline and was classified as “Specific” if a clear underlying mechanism of vertigo and dizziness could be given, or “unspecific” otherwise. The main outcome was HRQoL score that had been measured also through EQ5D3L at 3- time points over one year (baseline, follow-up after 6 months and follow-up after 12 months). The association between the diagnosis and HRQoL over time was examined through mixed-effects regression models adjusting for possible confounders.

The first analysis involved 548 participants with a mean age at the date of admission 51.35 years, among which 57% were women. Seventy-four percent had EVS while 26% had CVS. Compared to CVS, EVS patients had a female predominance (60% > 49%), younger age (48.5 < 59.6 years), and significantly higher HRQoL (63.87 > 58.08) and functioning (42.1 < 47.8) even after adjusting for confounders.

The second analysis included 158 vestibular patients with a mean age at baseline 77.1 years (69% female, 42% had a specific diagnosis, 40% unspecific diagnosis and 18% left undecided). Compared to specific diagnosis, patients with unspecific diagnosis reported significantly lower HRQoL. No differential change in HRQoL over time could be shown, while being one year older was inversely associated with HRQoL.

This thesis is leading in reporting: 1- lower HRQoL among CVS patients in comparison to EVS and 2- worse HRQoL among patients with unspecific diagnosis of vertigo and dizziness compared to specific. The findings enhance the knowledge on the impact of both the nature of vestibular syndrome and the specificity of diagnosis on HRQoL of

the patients. This knowledge might help to maintain better HRQoL among vestibular patients as they age. This could be done by shedding the light on mobility and balance in CVS patients on one hand, and referring patients with unspecific diagnosis for a more solid diagnosis (when possible) and better management of symptoms on the other hand. The findings of this thesis form a start for future research aiming to illuminate the above relationships and fill in the gaps to help preserve HRQoL of patients with vestibular disorders as they age.

List of Figures

List of Tables

List of abbreviations

AIC	Akaike Information Criterion
BIC	Bayesian Information Criteria
BPPV	Benign Paroxysmal Positional Vertigo
CCI	Charlson Comorbidity Index
CVS	Chronic Vestibular Syndromes
DAGs	Directed Acyclic Graphs
DHI	Dizziness Handicap Inventory
DSGZ	German Center for Vertigo and Balance (Deutsches Schwindel- und Gleichgewichtszentrum)
EQ5D3L	EuroQol Five-Dimensional Three-Level questionnaire
ER	Emergency Room
EVS	Episodic Vestibular Syndromes
FU	Follow-Up
GPs	General Practitioners
GVIF	Generalized Variance Inflation Factor
HRQoL	Health-Related Quality of Life
ICD-10	International Classification of Diseases - tenth revision
LMU	Ludwig-Maximilians-Universität München
M	Model
SD	Standard Deviation
SE	Standard Error
VAS	Visual Analog Scale

1. Introduction

Vestibular disorders present with a dysfunction in the vestibular system which is responsible for the body's balance. They usually present with acute and chronic symptoms with the most common being vertigo and dizziness [1]. Regardless of their origin, vertigo and dizziness are highly encountered in the medical practice and are considered daily life limiting by interrupting everyday activities [2] and reducing social participation [3]. While dizziness is a general term used to describe disequilibrium, vertigo is a subcategory of dizziness characterized with a sensation of movement caused by asymmetry in the vestibular system [4]. The lifetime prevalence of moderate to severe vertigo and dizziness in a general adult population living in Germany is around 30% [5] while the yearly incidence among adult Americans is approximately 11% [6]. The most prevalent vestibular syndrome is Benign Paroxysmal Positional Vertigo (BPPV). The onset of BPPV is between 50 and 70 years of age [7] with higher prevalence among women [8], increasing their risk of fractures due to falls compared to women without BPPV [9]. Giving examples of common complaints from daily life, patients with BPPV experience discrete brief and rotatory vertigo when bending over to lace their shoes or looking up [10].

Health-related quality of life (HRQoL) of patients with vestibular disorders was shown to be significantly low compared to that in the general population. Moreover, their lifestyle and social behavior may be influenced where 41% of the affected individuals have difficulties to work, 40% face interruption in daily activities, and 19% avoid leaving the house [5]. Vertigo and dizziness are not only a burden on the patient, but also on the healthcare system which is loaded with substantial costs. This could be due to mismanaged treatment plans and both underdiagnosis and overuse of diagnostic tests. It has been shown that patients can go through a long diagnostic journey before they get a specific and definite diagnosis [11].

Vestibular disorders have episodic or chronic symptoms, and their diagnoses can be either specific with a clear underlying cause, or unspecific (i.e., the specific cause of vertigo and dizziness remains unspecific).

In episodic vestibular syndromes (EVS), patients experience repeated vertigo and dizziness episodes followed by asymptomatic periods. For instance, patients with vestibular migraine and Menière's disease have increased risk of developing depression and anxiety caused by the random episodes [12]. This unpredictability and uncontrollability of the vertigo and dizziness attacks in Menière's disease patients appear to be a significant factor for reporting higher level of dysfunction compared to patients with BPPV where attacks are more controllable [13].

Unlike short attacks of EVS, chronic vestibular syndromes (CVS) such as in the case of chronic unilateral and bilateral vestibulopathy are characterized by longer periods of dizziness [14, 15].

HRQoL of CVS patients is significantly impaired which leads to substantial economic and social overload [16]. However, CVS patients show significantly less anxiety and depression compared to EVS patients that are characterized by more anxiety disorders. This could be due to the loss of functional vestibular system in CVS patients where the vestibular-autonomic interaction is reduced due to the lack of vestibular input [17, 18]. On the other hand, CVS patients show higher rates of falling compared to EVS patients [19].

HRQoL and health-related functioning in both EVS and CVS patients seem to be affected by some sociodemographic factors. It was shown that being female and younger were associated with lower HRQoL and functioning in both EVS [20, 21] and CVS patients [5]. It is still not clear how the episodicity or chronicity of a vestibular disease affects the HRQoL and functioning. This dissertation aims therefore to study this relationship.

Vertigo and dizziness can have numerous causes ranging from the benign to the health-threatening [22, 23]. This makes the diagnostic procedure more challenging and consequently leads to unspecific diagnoses [24, 25]. Even from their own perspective, general practitioners (GPs) find dizziness a challenging condition due to self-reported symptoms that are vulnerable to different interpretations by both patients as well as phy-

sicians [26-29]. When it comes to vertigo and dizziness, a physician is challenged between assuming a harmless underlying cause and following a traditional treatment, or offering an advanced and pricey treatment to seek the possible serious cause even if that was rare [30]. It was shown in a German retrospective study of 475 patients admitted to the emergency room (ER) due to dizziness, that the initial ER diagnosis was corrected in 44% of the cases after reassessment [31]. Serious causes of dizziness were more prevalent than can be expected where a re-evaluation of the cases revealed that 7% of the patients had a more serious diagnosis that was incorrectly diagnosed as harmless. Additionally, 23% were re-labeled as benign after they had been diagnosed with a serious underlying cause [31]. This was in accordance with data at a tertiary care setting, where it was shown in a retrospective study at an academic vertigo center that a specialized reassessment by neurologists lead to significant correction of diagnoses. Nearly all neuro-otological disorders were underdiagnosed, where “unclear dizziness” decreased from 70 to 10% [32]. Unlike specialists, GPs at the primary healthcare do not always pursue the fundamental cause to make an exact and solid diagnosis. However, they tend to ease the symptoms without overlooking potential serious diseases that would need further investigations [33].

It is even more complicated when it comes to the elderly population where it gets more challenging to specifically describe and report symptoms from the serious to the rather harmless making diagnosis more complex [30].

Given that vertigo and dizziness can have many possible reasons [22, 23], the difficulty of communicating and explaining symptoms could lead to unspecific diagnoses [25]. It is not yet completely understood how the impact of an unspecific diagnosis of vertigo and dizziness on HRQoL and its trajectories differs in comparison to that of specific diagnosis. Therefore, in addition to the impact of EVS vs. CVS on HRQoL and functioning, I also aim in this dissertation to study the effect of the diagnosis.

This PhD dissertation addresses two research questions. First, it studies how episodic and chronic vestibular syndromes differently affect HRQoL and functioning of patients in a tertiary care setting by comparing the burden of symptoms. It also focuses on some lifestyle and sociodemographic factors and analyzes how they influence this relationship in a cross-sectional study. Second, this dissertation investigates in a primary care setting how a specific vs. unspecific diagnosis of vertigo and dizziness affect the HRQoL of the patients based on a survey-based cohort study. The initial hypothesis was that HRQoL of patients who have received a specific diagnosis of their vertigo and dizziness to be higher than those who received an unspecific diagnosis. We also hypothesized that HRQoL over time would change. We aim to describe, compare and analyze 3-time measurements HRQoL and its trajectories in vertigo and dizziness patients given specific vs. unspecific diagnosis for their symptoms over a period of one year.

1.1 Study objectives

This dissertation aims to assess and compare HRQoL in patients with vestibular disorders based on the nature of their symptoms (episodic vs. chronic) on one hand and the diagnosis on the other hand (specific vs. unspecific).

The first study intends to reveal the influence of episodic vs. chronic vestibular syndromes on HRQoL and functioning of the affected individuals. This would be done by assessing and comparing functioning and HRQoL in episodic vs. chronic vestibular patients and, identifying the lifestyle and sociodemographic factors affecting the HRQoL.

Study two intends to show the impact of specific versus unspecific diagnosis of vertigo and dizziness on HRQoL. This would be accomplished by describing and comparing HRQoL of vertigo and dizziness patients given specific vs. unspecific diagnosis and, analyzing the effect of unspecific diagnosis on HRQoL and its trajectories over a period of 1 year.

The work presented aims to better understand and add to the knowledge of what is known about the impact of vestibular syndromes and their symptoms on HRQoL and to

help maintain HRQoL in vestibular patients as they age. This could provide a fundamental knowledge for researchers in this field to be used as a base for their further investigations on this topic. Doing so would help maintain HRQoL and functioning of the affected persons in a more customized way and shed the light on what is essential to be considered when targeting mobility and balance in vestibular patients at older age.

2. Material and Methods

2.1 Study design and data source

To be able to answer the first question, we followed a cross-sectional design and used data from the “DizzyReg” database [34]. DizzyReg is a continuing prospective registry at the Ludwig Maximilian University Hospital (LMU Klinikum). It serves patients with vertigo and dizziness, visiting the interdisciplinary outpatient clinic of the German Center for Vertigo and Balance (DSGZ). It centralizes all information present in electronic health record or medical discharge reports and then generates a comprehensive database of patients with vertigo and dizziness including their characteristics, symptoms, diagnoses, therapeutic procedures and outcomes. DizzyReg aims to examine factors of quality of life and functioning of vestibular patients, to interpret the outcome of therapeutic procedures on those patients and to recruit participants in upcoming case-control studies.

The registry was authorized by the local institutional review board and the regional data protection officer has consulted on data protection issues. All participants or their surrogate have signed a consent for willing to join the study [34].

To answer the second question, we followed a longitudinal prospective cohort design, and used data from the longitudinal study MobilE-TRA [35]. The latter is an observational multicenter practice-based prospective cohort study. It involves general practitioners (GPs) and their patients with acute vertigo and dizziness, and symptomatic hip or knee osteoarthritis [35]. The current analysis is based only on patients with vertigo and dizziness of the MobilE-TRA and does not include the osteoarthritis group. The original MobilE-TRA study was approved by the Ethics Committee of the Ludwig-Maximilians-Universität München (no. 17-443) as well as the Ethics Committee of the Technische Universität Dresden (no. E365092017). All participating patients have given their written and signed informed consent and the study was carried out following the Declaration of Helsinki principles [35].

Data collection of study one started during the patient initial visit to the DSGZ. Questions covered sociological and demographic characteristics, lifestyle and subjective manifestation of symptoms [34]. Recruitment of participants started in December 2015 at the DSGZ. In the current study, participants were recruited between December 2015 and July 2019 with the following inclusion criteria: 1) patient has a certified diagnosis of: Menière's disease, vestibular migraine, vestibular paroxysmia, bilateral vestibulopathy, or chronic unilateral vestibulopathy, 2) patient is at least 18 years old, 3) patient provides an informed consent and 4) patient has sufficient German language. Figure 1 shows the flowchart for the study sample.

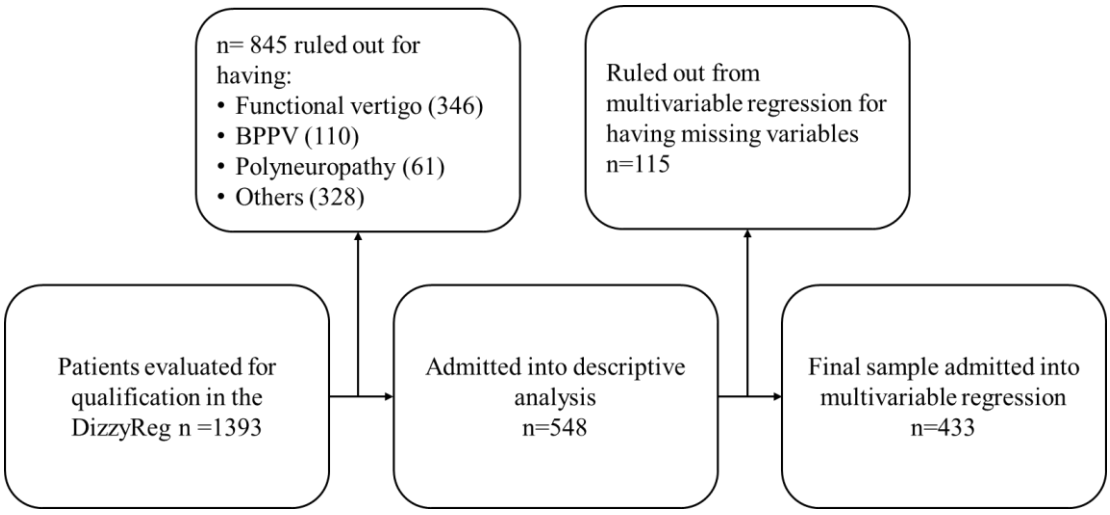


Figure 1 - Flowchart - Study Sample 1: participants recruited in the study and included in the analysis of dataset 1

Data of study two was collected between 2017 and 2019 through GPs clinics in two German cities and their surroundings: Munich and Dresden. Over 250 GP practices associated with the Institute of Primary Care and Family Practice of the LMU Hospital) and over a hundred GP clinics affiliated with the Department of General Practice of the University Hospital Carl Gustav Carus of the Technische Universität Dresden were contacted. GPs were invited by mail. Participating GPs were asked to search their patient database for some international classification of diseases (ICD-10) codes specialized for the diagnosis of vertigo, dizziness and balance disorders or osteoarthritis: R42, A88.1, E53.8, F45.8, G11.8, G43.1, G45.0, G62, G63, H55, H83.0–2, I95.1, N95.1, R26. GPs were then asked to invite their eligible patients via mail by sending out invitation letters along with paper-based consent forms, study information sheet, baseline questionnaires and a postage prepaid envelope to send back the answered surveys. After receiving the signed consents, patients were then contacted by the study team for further follow-ups. Participants received two follow-up surveys, six months (FU1) and twelve months (FU2) after baseline. The follow-up surveys consisted of self-administered health questionnaires. Inclusion criteria consisted of patients who: 1) are 65 years or older 2) have consulted their GP due to vertigo and dizziness in the last three months, 3) have public health insurance 4) can read and speak good German language. Further details on methodology can be found in the original study protocol by Kisch and colleagues [35]. One-hundred fifty-eight (158) eligible patients with vertigo or dizziness (64 from Dresden and 94 from Munich) were included in the analysis of study two. Recruitment was done through seven GP clinics in Munich and 12 in Dresden (Figure 2).

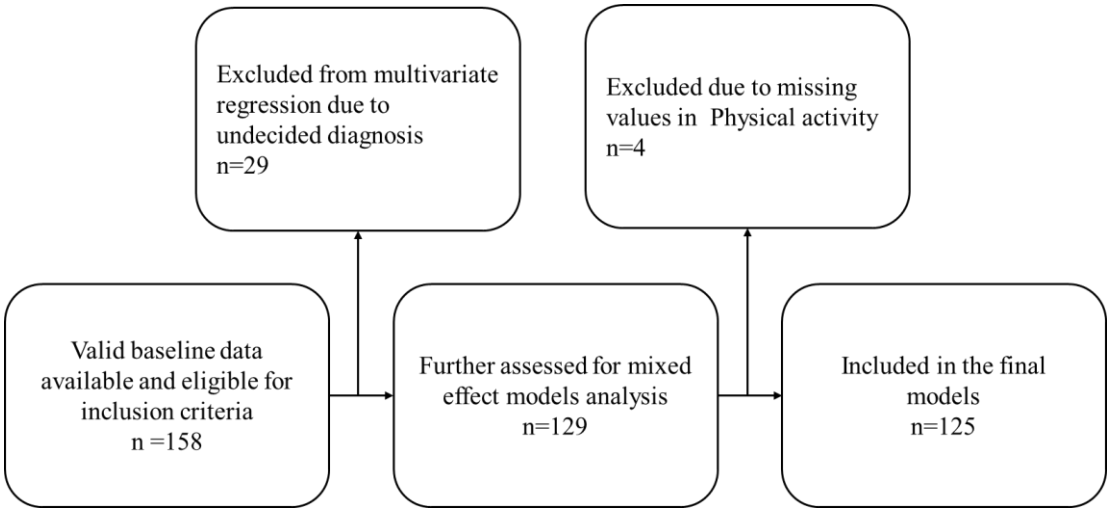


Figure 2 - Flowchart - Study Sample 2: Participants recruited in the study and included in the analysis of dataset 2

2.1.1 Assessments and instruments

2.1.1.1 EVS Vs. CVS

Vestibular diagnoses at the DizzyReg were done through a thorough neuro-otological examination by the clinical experts at the DSGZ. This was done following diagnostic guidelines of the international categorization of vestibular disorders: the Bárány Society founded in 1960 [36]. Participants were classified as EVS if they had possible or certain vestibular migraine, Menière's disease, or vestibular paroxysmia [37-39]. Patients who had certain bilateral vestibulopathy [15] or unilateral vestibulopathy with persistent vestibular symptoms [14, 40] were classified as CVS.

2.1.1.2 Specific vs. unspecific

Patients were initially diagnosed with vertigo and dizziness by their GP at the initial assessment, to be further classified by the study team as having "specific" or "unspecific" diagnosis. The diagnoses classification of vertigo and dizziness as "specific", "unspecific "or undecided" was based on the following: The term "specific" refers to a known underlying mechanism of the vertigo and dizziness. The term "unspecific" was set if there was no known underlying mechanism and where the physician ticked "yes" for "unspecific diagnosis". If neither specific nor unspecific diagnosis was given by the physician for vertigo or dizziness then the study team labeled the diagnosis as "undecided" (no entry) [35].

2.1.1.3 Health-Related-Quality of Life (HRQoL)

Assessment of HRQoL was completed through the EuroQoL 5-Dimentional 3-Level questionnaire (EQ5D3L), the visual analog scale (VAS) and the utility index values [41]. The EQ-5D-3L index contains 2 core parts: the descriptive system and the VAS with brief demographic questions. The EQ-5D-5L is a new version with 5 answer options [42] and has been validated for improving sensitivity to change in unselected vertigo and dizziness patients at a primary care setting [41, 43]. It comprises the following five dimensions indicating five health states: mobility, self-care, usual activities, pain/discomfort and

anxiety/depression. Every dimension consists of three levels: no problems, some problems, and extreme problems. The health-state index score was then calculated following the German time trade-off scoring algorithm [44]. The participants rate their health status by ticking the most appropriate statement in each dimension that best describes them. Each choice results in a one-digit number to eventually produce five-digit number that ranges from 0 to 1 to describe the participant's health state. VAS is a straight vertical line where the patient marks their health between 0 and 100 with highest score indicating best imaginable health state. For the analysis of study 2, VAS was measured 3 times over the course of one year: Baseline, FU1 (six months after baseline) and FU2 (twelve months after baseline).

2.1.1.4 The Dizziness Handicap Inventory (DHI)

The Dizziness Handicap Inventory (DHI) was completed to evaluate patients' functioning level. It is a validated self-report questionnaire, that is widely used to measure the impact of vertigo and dizziness on individual's everyday life. DHI comprises 25 questions that tackle nine-item functional subscale, seven-item physical subscale and nine-item emotional subscale to measure the disability resulting from dizziness and imbalance [45]. A "yes" response generates 4 points, "sometimes" generates 2 points and a "no" response gives no points. The outcome of DHI questionnaire is a total score between zero (indicating zero impairment) and 100 (indicating severe impairment). The internal consistency of DHI was checked by estimating Cronbach's alpha coefficients which was set as acceptable if higher than 0.8 [46].

2.2 Statistical Analysis

2.2.1 Covariates

2.2.1.1 Covariates of study one

Age and gender were defined on admission day. Lifestyle and other sociodemographic variables were assessed using standard questionnaires. Family status and educational level were assessed and categorized as shown in

Table 1. Quality of sleep was evaluated by asking about satisfaction with different aspects of the patient's sleep experience such as hours of sleep and time needed to fall asleep. Furthers questions on quality of sleep followed in order to assess the severity and frequency of those problems. Physical activity was assessed separately in winter and summer and was classified as Active (if it is "Moderate activity" or "High activity") and Inactive (if it is "No activity" or "Low activity"). Alcohol consumption was treated as binary where a "Yes" indicates that the participant has had alcohol in the past seven days and "No" otherwise. Smoking was evaluated based on being a regular or occasional smoker and on the approximate number of cigarettes smoked per day. Year of quitting was noted for former smokers.

Three psychiatric indicators were documented from patients records and those are: a comorbid functional component of vertigo [47], anxiety or depression, and ongoing psychiatric or psychological treatment. "Psychiatric disorder" was defined as "Yes" in case one of those indicators is present, otherwise as "No". In order to assess disease-related emotional stress, some DHI questions about heights, frustration, depression, leaving the house without a companion, and staying home alone were covered. A "Yes" response indicated that a problem exists and "No" otherwise; however, these were not part of the regression analysis as they do not contribute to the outcome [48].

2.2.1.2 Covariates of study two

Age was defined at baseline by years as a continuous variable. Gender (female/male) and location (Munich/Dresden) were treated as binary variables.

Smoking was set as “Yes” for currently smoking and “No” otherwise. Alcohol consumption was assessed by the type and average quantity of alcohol consumed in the last seven days to be set as “Low”, “High” or “No” alcohol consumption. Physical activity was assessed separately in winter and summer in leisure time and was classified as “Active” if the patient performed medium to high physical activity, and “Inactive” if they were low to not al all physically active. Education was measured by years completed and was categorized based on the German system where “No graduation” means the participant has completed a maximum of nine years of school, “Lower secondary education” means the participant has completed a maximum of 10 years, “upper secondary education” means the participant has completed a maximum of 12 or 13 years of school, and “Tertiary education” means the participant has graduated from the university. Job training was identified as the highest professional qualification attained and was classified as “Low” (no qualification, other), “Middle” (vocational school, technician, master school) and “High” (engineering school, college, university). Multimorbidity was defined as having at least two or more health conditions other than vertigo and dizziness diagnosed by the physicians during the baseline assessment based on the Charlson Comorbidity Index (CCI) [49]. Comorbidities included: pulmonary diseases, joint disease, cancer, diabetes, gastrointestinal diseases, cardiovascular diseases, renal diseases, liver diseases, stroke, neurologic diseases, eye diseases (excluding hyperopia and myopia), and blood pressure diseases.

2.2.2 Analysis

We calculated mean and standard deviation for continuous variables. Absolute frequencies, relative frequencies and percentages were generated for categorical data.

2.2.2.1 Impact of EVS vs. CVS vestibular disorders on HRQoL and DHI

In order to identify variables influencing HRQoL and functioning in dataset one (study one), we ran multiple linear regression models covering exclusively complete cases.

Cramér's V was reported for categorical variables. It examines the association between two categories where zero signifies no association and one signifies very strong association. For continuous variables, the standardized effect size (Cohen's d) was reported consequently for the difference between two group means where the association gets stronger as the number increases. Overspecification of the model was minimized with as few predictors as possible using the directed acyclic graphs (DAGs) [48, 50, 51]. These predictors are summarized in Figure 3 in Appendix A . Multi-collinearity among predicting variables was assessed by the generalized variance inflation factor (GVIF). GVIF ranges between 1 and 5 as the correlation increases, and indicates a high correlation if more than 5 [52].

2.2.2.2 Impact of specific vs. unspecific diagnosis of vertigo and dizziness on HRQoL

In order to analyze the effect of specific and unspecific diagnosis on HRQoL and its trajectories, we ran mixed-effects regression models. To compare groups, Kruskal Wallis non-parametric test for continuous variables, and X^2 test and Fischer exact test were used.

We started with a univariate regression for each variable to check if it is significantly associated with the outcome. Variables with significant association with the outcome were then included in the mixed-effects regression models. In order to keep the same cohort and for a more accurate estimate across the models, the category of "undecided" diagnosis was excluded from the multivariate analyses which were based on cases with no missing data (cases that have full sets of variables used in the models), hence the new N= 125. We start with the crude model and then gradually started to add variables that have previously tested significant in the univariate regression step. Akaike Information Criterion (AIC) was used across models to select the best model fit (a lower AIC signifying better model fit). P-values across models were generated through ANOVA.

Two-tailed p-values less than 0.05 were treated as statistically significant. Our data analyses were performed using language R 3.6.1 [53].

2.2.2.3 Sensitivity analysis

When asked about impairments and how chronic they are, “sometimes” is more often expected from EVS patients, while “yes” is more often expected from CVS patients. In order to compare this incidence between EVS and CVS groups, we ran a Poisson regression analysis and reported an incidence rate ratio (IRR). this was done using two scales: the first one responsible for the “sometimes” responses and the second for the “yes”. An IRR <1 indicates that the incident rate is lower in one group than the other, while an IRR >1 indicates otherwise.

3. Results

Dataset 1

Baseline characteristics

Out of the 548 vestibular patients who participated in study one, 406 (74%) had EVS while 142 (26%) had CVS with a mean age 51.35 years (SD ±15.58) and 57% were female (Table 1). Thirty-nine percent were diagnosed with Vestibular migraine, 25.9% had Menière's disease, 15.7% had unilateral vestibulopathy, 10.2% had bilateral vestibulopathy and 8.9% had vestibular paroxysmia. Forty-two percent of the patients experienced vertigo or dizziness for less than two years whereas only 15% experienced it for longer than ten years (Table 2) [48].

EVS vs. CVS

Compared to CVS, the EVS group had higher female predominance (60% > 49%, p-value=0.0367) and younger patients (48.47 < 59.61 years, p-value<0.0001).

Rotational vertigo was more often reported by the EVS group than the CVS (67% > 44%, p-value<0.0001). The same applies for nausea (64% >37%, p-value<0.0001), hearing problems (29% > 16%, p-value=0.0050), ear pressure (38% > 23%, p-value=0.0009), and headache (43% > 29%, p-value=0.0039). The CVS group reported more oscillopsia (35% > 24% p-value=0.0258), and walking problems (79% > 69%, p-value=0.0364) (Table 1 and Table 2). Compared to CVS, significant differences in psychological indicators can be summarized by EVS group feeling more frustrated (82% > 72%, p-value=0.0126), having less heights anxiety (52% < 65%, p-value=0.0101), and less feeling of being perceived as intoxicated (39% < 57%, p-value=0.0007). Further symptoms and accompanying complaints are presented in detail in Table 3 [48].

Health related quality of life and functioning

The total sample of study 1 showed a total mean VAS=62.4 (SD±20.47). The overall mean EQ-5D score=0.85 (SD±0.20), and the overall mean DHI total score=43.52 (SD±20.97). A Cronbach's alpha test for internal consistency came back with 0.90 (95%

CI [0.88; 0.92]) indicating that DHI is consistent and reliable. Compared to CVS, EVS group reported significantly better HRQoL with mean VAS score (63.87>58.08, p-value=0.0049) and better functioning with mean score of DHI (42.07<47.8, p-value=0.0092) (Table 1). EQ5D score did not differ significantly between the two groups. Compared to EVS, CVS patients showed significantly more impairment (better functioning) in two DHI domains. They scored higher for the physical (13.86<10.43) as well as for the functional (19.33 > 16.42) domains (Table 1). CVS patients reported also more walking problems than that of the EVS patients (79% > 69%) (Table 2) [48].

Both better functioning and HRQoL persisted to be significant among the EVS group compared to the CVS group (lower DHI and higher VAS scores; p-value=0.0043 and 0.0011 respectively) even after adjusting for possible confounders, and no noticeable GVIF was perceived. Age did not show any significant association with HRQoL (p-value=0.8094) or DHI (p-value=0.5752). Gender was not significantly associated with HRQoL (p-value=0.4955) unlike DHI, where being a female had on average 6.41 higher (worse) DHI score in comparison to males accounting for confounders (p-value<0.0019). Except the problem of falling asleep, adding sleeping variables to the model had no effect on the results and were eventually eliminated from the linear regression model. Worse HRQoL and functioning were significantly reported by patients who had problems falling asleep. The presence of a psychiatric disorder showed a significant association with worse HRQoL (p-value=0.0014) but not with functioning (p-value=0.0609) (Table 3). The best attenuated model fit was $R^2 = 0.13$.

Sensitivity analysis

After running a sensitivity analysis, and compared to CVS patients, the “sometimes” answer was more common among EVS patients with IRR=1.11 and p-value <0.0001. The “yes” answer had an IRR=0.776 and a p-value < .0001. Details of sensitivity analysis are shown in Table 7 in Appendix A [48].

All tables of study 1, as well as the Appendix tables have been taken from the published manuscript [48] as indicated in the citations under the tables.

Table 1: Baseline characteristics, Symptoms and VAS scores of 548 vestibular patients

Variable	All (548)	EVS (406)	CVS (142)	*p*-value
Mean Age (±SD)	51.35 (SD=15.58)	48.47 (SD=14.37)	59.61 (SD=16.01)	<0.0001
Gender = female	313 (57%)	243 (60%)	70 (49%)	0.0367
VAS Score	62.2 (SD±20.56)	63.55 (SD±20.25)	58.49 (SD±20.99)	0.0060
EQ5D score	0.85 (SD±0.20)	0.85 (SD±0.20)	0.83 (SD±0.21)	0.3612
DHI Score				
-Total	43.52 (SD=20.97)	42.07 (SD=20.88)	47.8 (SD=20.74)	0.0092
-Physical	11.29 (SD=6.88)	10.43 (SD=6.77)	13.86 (SD=6.58)	< 0.0001
-Functional	17.17 (SD=9.34)	16.42 (SD=9.29)	19.33 (SD=9.18)	0.0020
-Emotional	15.31 (SD=8.37)	15.39 (SD=8.47)	15.09 (SD=8.1)	0.7247
Problems falling asleep				0.1344
- Almost never	209 (39%)	147 (37%)	62 (45%)	
-Sometimes	217 (41%)	163 (41%)	54 (39%)	
-Often	108 (20%)	87 (22%)	21 (15%)	
Psychological Indicators				
Functional component	126 (23%)	98 (24%)	28 (20%)	0.3363
Anxiety / Depression	12 (2%)	10 (2%)	2 (1%)	0.6847
Psychological treatment	51 (9%)	41 (10%)	10 (7%)	0.3622
DHI: Feeling frustated	425 (80%)	328 (83%)	97 (72%)	0.0126
DHI: Leaving home	225 (42%)	171 (43%)	54 (39%)	0.5062
DHI: Height	293 (55%)	204 (52%)	89 (65%)	0.0101
DHI: Intoxicated	232 (44%)	155 (39%)	77 (57%)	0.0007
DHI: Being alone	123 (23%)	99 (25%)	24 (18%)	0.0962
DHI: Feeling depressed	366 (69%)	276 (70%)	90 (66%)	0.4386
Physical Activity (Active)	301 (57%)	232 (59%)	69 (51%)	0.1353
Education				0.2744
-Low	174 (38%)	122 (36%)	52 (44%)	
-Medium	158 (35%)	123 (37%)	35 (30%)	
-High	121 (27%)	90 (27%)	31 (26%)	
Marital Status				0.3141
- Single	127 (24%)	101 (26%)	26 (19%)	
-Married	323 (61%)	233 (59%)	90 (65%)	
-Divorced	62 (12%)	47 (12%)	15 (11%)	
-Widowed	20 (4%)	13 (3%)	7 (5%)	
Smoking				0.4356
-Never	218 (42%)	163 (42%)	55 (42%)	
-Former	213 (41%)	154 (40%)	59 (45%)	
-Current occasionally	8 (2%)	7 (2%)	1 (1%)	
-Current regular	77 (15%)	62 (16%)	15 (12%)	
Alcohol consumption (Yes)	265 (49%)	186 (46%)	79 (57%)	0.0355

Strobl, R., S. Harajli, D. Huppert, A. Zwergal and E. Grill (2023). "Impact of episodic and chronic vestibular disorders on health-related quality of life and functioning-results from the DizzyReg patient registry." Qual Life Res.

Table 2: Symptoms, symptoms duration, attacks duration and health problems of 548 patients with episodic and chronic vestibular syndromes

Variable	All (548)	EVS (406)	CVS (142)	*p*-value
Falls	161 (31%)	111 (29%)	50 (37%)	0.0957
Disease duration				0.0026
<3 months	67 (13%)	49 (13%)	18 (13%)	
3 months to 2 years	152 (29%)	96 (25%)	56 (42%)	
2–5 years	134 (26%)	105 (27%)	29 (22%)	
5–10 years	85 (16%)	66 (17%)	19 (14%)	
>10 years	80 (15%)	68 (18%)	12 (9%)	
Attack duration*				
<2 min	113 (21%)	90 (22%)	23 (16%)	0.1636
2–20 min	88 (16%)	72 (18%)	16 (11%)	0.0942
20–60 min	81 (15%)	71 (17%)	10 (7%)	0.0040
Several hours	190 (35%)	170 (42%)	20 (14%)	< 0.0001
>12h	41 (7%)	31 (8%)	10 (7%)	0.9633
Several days	138 (25%)	94 (23%)	44 (31%)	0.0821
Symptoms				
Rotational	333 (61%)	271 (67%)	62 (44%)	< 0.0001
Staggering	304 (55%)	220 (54%)	84 (59%)	0.3538
Dizziness	254 (46%)	197 (49%)	57 (40%)	0.1039
Turning or shaking pictures	77 (14%)	51 (13%)	26 (18%)	0.1196
Sickness	219 (40%)	170 (42%)	49 (35%)	0.1491
Permanent vertigo	128 (23%)	85 (21%)	43 (30%)	0.0315
Double vision	57 (10%)	39 (10%)	18 (13%)	0.3833
Imbalance	311 (57%)	227 (56%)	84 (59%)	0.5665
Oscillopsia	148 (27%)	99 (24%)	49 (35%)	0.0258
Nausea	312 (57%)	260 (64%)	52 (37%)	< 0.0001
Walking problems	393 (72%)	281 (69%)	112 (79%)	0.0364
Impaired vision	151 (28%)	115 (28%)	36 (25%)	0.5664
Blurred vision	165 (30%)	127 (31%)	38 (27%)	0.3658
Complaints				
Headache	216 (39%)	175 (43%)	41 (29%)	0.0039
Feeling lightheaded	169 (31%)	135 (33%)	34 (24%)	0.0498
Prickling	91 (17%)	74 (18%)	17 (12%)	0.1112
Hearing problems	139 (25%)	116 (29%)	23 (16%)	0.0050
Vision problems	192 (35%)	137 (34%)	55 (39%)	0.3319
Neck pain	157 (29%)	124 (31%)	33 (23%)	0.1214
Head pressure	193 (35%)	145 (36%)	48 (34%)	0.7578
Ear pressure	188 (34%)	156 (38%)	32 (23%)	0.0009
Ear noise (Tinnitus)	176 (32%)	147 (36%)	29 (20%)	0.0008

Strobl, R., S. Harajli, D. Huppert, A. Zwergal and E. Grill (2023). "Impact of episodic and chronic vestibular disorders on health-related quality of life and functioning-results from the DizzyReg patient registry." Qual Life Res.

Table 3: Linear regression models of the impact of vestibular syndromes (episodic versus chronic) on HRQoL and functioning

Variables	**VAS**		**DHI**	
	coefficient [CI]	***p*-value**	**coefficient [CI]**	***p*-value**
(Intercept)	68.03 [51.68; 84.39]	< 0.0001	32.93 [16.41; 49.45]	< 0.0001
EVS (reference: CVS)	7.56 [3.04; 12.09]	0.0011	-6.86 [-11.56; -2.17]	0.0043
Problems falling asleep (reference: never)				
Sometimes	-2.83 [-6.92; 1.27]	0.1755	4.22 [-0.054; 8.49]	0.0530
Often	-11.24 [-16.40; -6.08]	< 0.0001	10.10 [4.72; 15.49]	0.0003
Psychiatric disorder (reference: no)				
Yes	-6.85 [-11.03; -2.66]	0.0014	4.10 [-0.19; 8.39]	0.0609
Age	0.02 [-0.14; 0.18]	0.8094	0.046 [-0.12; 0.21]	0.5752
Gender (reference: female)				
Male	1.34 [-2.52; 5.2]	0.4955	-6.41 [-10.44; -2.37]	0.0019

Strobl, R., S. Harajli, D. Huppert, A. Zwergal and E. Grill (2023). "Impact of episodic and chronic vestibular disorders on health-related quality of life and functioning-results from the DizzyReg patient registry." Qual Life Res.

Dataset 2

This study included 158 patients with a mean age at baseline 77.1 years, SD ± 6.2. Sixty nine percent (69%) were females, 42% had a specific diagnosis of vertigo and dizziness, 40% had unspecific diagnosis, and 18% were not specified. Baseline characteristics are presented in Table 4 and show that 60.5% of the participants were married, 65.8% had middle educational level, 59.7% had middle job training level, >60% were physically active and 3% smoked at all times (baseline, FU1, FU2). Compared to patients from Dresden, patients from Munich were more likely to receive an unspecific diagnosis 75.8% vs. 24.2% (p-value=0.004).

HRQoL scores

The mean HRQoL score (VAS) for all 158 patients was 62.8 (SD ± 20.7) at baseline, 65 (SD ±20.9) at FU1 and 62.9 (SD ±22.9) at FU2. Compared to patients of unspecific diagnosis, patients wiyh specific diagnosis reported significantly higher mean HRQoL score at FU1 (VAS= 70 vs. 59.5, p-value=0.020) and FU2 (VAS= 67.6 vs. 56.4, p-value=0.040) however this significant difference was not present at baseline (VAS= 67.2 vs. 59.5, p-value=0.098 (Table 4).

Univariate analysis

The univariate analysis did not show any change in HRQoL over time (p-value=0.52) (Table 5).

Multivariable Analysis

Starting with an empty model (M0) and gradually adding variables that resulted in a significant p-value<0.05 from the univariate analyses, the final set consisted of 5 models.

We adjusted for “diagnosis” in model one (M1), which resulted in lower HRQoL mean score among patients with unspecific diagnosis by 8.89 (p-value=0.011) compared to patients with specific diagnosis. Adjusting for “time” in M2 did not change the HRQoL mean score (coefficient=-8.90, p-value=0.011). However; further adding the “interaction”

term between time and diagnosis in M3 has decreased it to 8.05 (coefficient -8.05, p-value=0.033). The change of the HRQoL over time in the group with specific diagnosis did not differ from that with unspecific diagnosis (M3: coefficient =0.89, p-value=0.56). The association between diagnosis and HRQoL remained significant in M4 even upon further adjustments for “age” and “gender” (coefficient =-7.32, p-value=0.032). Being one year older seemed to be significantly associated with lower level of HRQoL by 0.87 (coefficient =0.87, p-value=0.001).

The interaction term was removed at this step since it inhibited the effect of diagnosis after M3. The model fit got improved in M5 after adding “physical activity” (AIC=2853.5) which has maintained the significant association between diagnosis and HRQoL (M5, coefficient = -7.10, p-value=0.031). The association between diagnosis and HRQoL persisted to be significant even with the adjustment for “multimorbidity”, but with greater AIC than M5 (M6, coefficient = -7.07, p-value=0.036). This suggests that the model with the best fit is M5 (Table 6).

Table 4: Baseline characteristics of 158 patients with vertigo and dizziness

Variable	All (158)	undecided (29)	Specific (67)	Unspecific (62)	*p*-value
Continuous			**Mean±SD**		
HRQoL at t0	62.8±20.7	59.8±20.6	67.2±19.7	59.5±21.4	0.098
HRQoL at t1	65±20.9	65±18.1	70±19.4	59.5±22.4	0.023*
HRQoL at t2	62.9±22.9	66±22.2	67.6±20.4	56.4±24.6	0.048*
Age (years)	77.1±6.21	77.1±6.28	76.4±6.14	78±6.14	0.426
Categorical			**N (%)**		
City					0.004*
Munich	94 (59.5%)	14 (48.3%)	33 (49.3%)	47 (75.8%)	
Dresden	64 (40.5%)	15 (51.7%)	34 (50.7%)	15 (24.2%)	
Gender					0.126
M	48 (30.4%)	6 (20.7%)	26 (38.8%)	16 (25.8%)	
F	110 (69.6%)	23 (79.3%)	41 (61.2%)	46 (74.2%)	
Education					0.281
None or lower secondary	71 (47.4%)	15 (53.6%)	231 (35.4%)	33 (57.9%)	
Lower secondary	33 (22%)	6 (21.4%)	26 (24.6%)	11 (19.3%)	
Upper secondary	11 (7.2%)	1 (3.6%)	7 (10.8%)	3 (5.3%)	
Tertiary	35 (23.4%)	6 (21.4%)	19 (29.2%)	10 (17.5%)	
Job training					0.305
Low	11 (8.1%)	2 (7.7%)	2 (3.3%)	7 (14%)	
Middle	89 (65.4%)	18 (69.2%)	39 (65%)	32 (64%)	
High	36 (26.5%)	6 (23.1%)	19 (31.7%)	11 (22%)	
Multimorbidity					0.006*
No	30 (19%)	10 (34.5%)	15 (22.4%)	5 (8.1%)	
Yes	128 (81%)	19 (65.5%)	52 (77.6%)	57 (91.9%)	
Physical activity at t0					0.146
Inactive	52 (34.9%)	14 (48.3%)	17 (27.4%)	21 (36.2%)	
Active	97 (65.1%)	15 (51.7%)	45 (72.6%)	37 (63.8%)	
Physical activity at t1					0.391
Inactive	52 (38%)	11 (47.8%)	19 (32.2%)	22 (40%)	
Active	85 (62%)	12 (52.2%)	40 (67.8%)	33 (60%)	
Physical activity at t2					0.0717
Inactive	47 (36.2%)	11 (57.9%)	17 (28.8%)	19 (36.5%)	
Active	83 (63.8%)	8 (42.1%)	42 (71.2%)	33 (63.5%)	
Alcohol consumption at t0					0.994
No	68 (44.7%)	12 (42.9%)	29 (45.3%)	27 (45%)	
Low	77 (50.7%)	15 (53.6%)	32 (50%)	30 (50%)	
High	7 (4.6%)	1 (3.6%)	3 (4.7%)	3 (5%)	
Alcohol consumption at t1					0.821
No	65 (46.1%)	9 (39.1%)	26 (44.1%)	30 (50.8%)	
Low	63 (44.7%)	11 (47.8%)	28 (47.5%)	24 (40.7%)	
High	13 (9.2%)	3 (13%)	5 (8.5%)	5 (8.5%)	
Alcohol consumption at t2					0.181
No	71 (53.8%)	10 (50%)	27 (45%)	34 (65.4%)	
Low	50 (37.9%)	7 (35%)	28 (46.7%)	15 (28.8%)	
High	11 (8.3%)	3 (15%)	5 (8.3%)	3 (5.8%)	
Smoking at t0					0.126
No	145 (96.7%)	25 (92.6%)	61 (95.3%)	59 (100%)	
Yes	5 (3.3%)	2 (7.4%)	3 (4.7%)	0 (0.0%)	
Smoking at t1					0.236
No	127 (96.9%)	22 (95.7%)	52 (94.5%)	53 (100%)	
Yes	4 (3.1%)	1 (4.3%)	3 (5.5%)	0 (0.0%)	
Smoking at t2					0.237
No	120 (96.8%)	15 (93.8%)	54 (94.7%)	51 (100%)	
Yes	4 (3.2%)	1 (6.2%)	3 (5.3%)	0 (0.0%)	

HRQoL: Health related quality of life; SD: standard deviation; t0: baseline; t1: follow-up 1; t2: Follow-up 2

Table 5: Univariate regression analysis of specific vs. unspecific diagnosis of vertigo and dizziness in relation to HRQoL

Variables	**Univariate Coefficient (SE)**	***p*-value**
Time	-0.47 (0.73)	0.52
City (reference = Munich)		
Dresden	8.18(3.12)	0.009*
Age	-0.92 (0.24)	<0.0001*
Gender (reference = M)		
F	–3.34 (3.38)	0.324
Education (reference = Low)		
Middle	8.34 (7.55)	0.27
High	15.34 (7.84)	0.052
Education 2 (reference = None or lower secondary**)**		
Lower secondary	5.92 (2.32)	0.155
Upper secondary	12.61 (6.31)	0.047*
Tertiary education	8.5 (4.03)	0.037*
Job (reference = Low)		
Middle	18.95 (6.30)	0.032*
High	25.06 (6.78)	0.0003*
Comorbidity number	-2.03 (0.78)	0.01*
Multi-comorbidity (reference = No)		
Yes	-0.66 (4.03)	0.868
Diagnosis (reference = Specific)		
Unspecific	–9.14 (3.39)	0.008*
Physical activity (reference = Inactive)		
Active	6.12 (2.16)	0.007*
Alcohol consumption (reference = No)		
Low	2.83 (1.87)	0.132
High	1.16 (3.84)	0.762
Smoking (reference = No)		
Yes	4.54 (9.36)	0.654

HRQoL: Health related quality of life; SE: Standard Error; ref: reference

Table 6: Multivariate analysis: Mixed-effects models of the impact of diagnosis (specific vs. unspecific) of vertigo and dizziness on HRQoL over time

	HRQoL - N= 125 Coefficient (SE) – P [95% CI]						
Variables	**M0** **AIC = 2864.3** **BIC = 2875.8**	**M1** **AIC = 2859.9** **BIC = 2875.2** **p = 0.011**	**M2** **AIC = 2861.0** **BIC = 2880.1** **p = 0.329**	**M3** **AIC = 2862.6** **BIC = 2885.6** **p = 0.559**	**M4** **AIC = 2854.7** **BIC = 2881.4** **p = 0.001**	**M5** **AIC = 2853.5** **BIC = 2884.0** **p = 0.072**	**M6** **AIC = 2855.5** **BIC = 2889.9** **p = 0.962**
Fixed Effects							
Intercept	63.26 (1.77) - <0.0001* [59.75; 66.77]	67.48 (2.38) - <0.0001* [62.76; 72.19]	68.19 (2.49) - <0.0001* [63.26; 73.11]	67.78 (2.59) - <0.0001* [62.68; 72.89]	137.22 (21.28) - <0.0001* [95.13; 179.24]	125.64 (21.50) - <0.0001* [83.37; 168.58]	125.69 (21.53) - <0.0001* [83.36; 168.70]
Diagnosis *(reference = specific)*		-8.89 (3.47) - 0.011* [-15.75; -2.04]	-8.90 (3.47) - 0.011* [-15.76; -2.05]	-8.05 (3.76) - 0.033* [-15.47; -0.64]	-7.32 (3.37) - 0.032* [-13.99; -0.66]	-7.10 (3.26) - 0.031* [-13.57; -0.66]	-7.07 (3.33) - 0.036* [-13.68; -0.48]
Time			-0.75 (0.77) - 0.329 [-2.27; 0.76]	-0.32 (1.06) - 0.76 [-2.41; 1.77]	-0.77 (0.77) - 0.318 [-2.29 ; 0.75]	-0.76 (0.77) - 0.327 [-2.30; 0.77]	-0.76 (0.77) - 0.327 [-2.30; 0.77]
Diagnosis * Time				-0.89 (1.54) - 0.56 [-3.93; 2.14]			
Age*(years)*					-0.87 (0.27) - 0.001* [-1.41; -0.34]	-0.76 (0.26) - 0.005* [-1.30; -0.24]	-0.76 (0.27) - 0.005* [-1.31; -0.23]
Gender *(reference = M)*					-3.65 (3.57) - 0.307 [-10.72; 3.39]	-3.20 (3.46) - 0.356 [-10.06; 3.62]	-3.20 (3.46) - 0.356 [-10.08; 3.62]
Physical Activity *(reference = Inactive)*						4.52 (2.39) - 0.059 [-0.41; 9.48]	4.52 (2.39) - 0.060 [-0.42; 9.48]
Multimorbidity *(reference = No)*							0.22 (4.63) - 0.962 [-9.41; 8.93]
Random Effects							
Variance of Intercept	344.4	324.6	324.9	325.3	294	270.6	270.6

Model 0: crude model
Model 1: adjusted for diagnosis
Model 2: adjusted for diagnosis, time
Model 3: adjusted for interaction of diagnosis with time
Model 4: adjusted for diagnosis, time, age and gender
Model 5: adjusted for diagnosis, time, age, gender and Physical activity
Model 6: adjusted for diagnosis, time, age, gender, Physical activity and multimorbidity

SE: Standard Error; AIC: Akaike's Information Criteria; BIC: Bayesian Information Criteria; M: model
Interaction was removed after M3 since it hindered the significance of Diagnosis.
P of the models comes from ANOVA

4. Discussion

This dissertation aims to examine the effect of episodic vs. chronic vestibular disorders on HRQoL and functioning; as well as to evaluate the impact of specific vs. unspecific diagnosis of vertigo and dizziness on HRQoL. Therefore, I ran two observational studies based on data from the “DizzyReg” and the “MobileTRA”, in the period from 2015 and 2019.

The first analysis showed that CVS patients reported significantly worse HRQoL and functioning than EVS patients. While the second analysis showed that having an unspecific diagnosis of vertigo and dizziness is associated with poorer HRQoL compared to having specific diagnosis.

It is already well established that vestibular disorders are common and limit patients’ life by interrupting their functioning and their ability to partake in their daily activities [2, 3, 5]. It is also known that diagnosis can be difficult and misdiagnoses are common [24]. However, the nature of episodes (episodic versus chronic) of vestibular disorders and the diagnosis of vertigo and dizziness (specific versus unspecific), may have a significant effect on patient’s HRQoL. To elucidate these potential associations, this doctoral thesis aims to accomplish two research questions. First, it addresses the association between vestibular diseases and their nature with Health-related quality of life (HRQoL) and functioning. Second, it studies how the diagnosis of the symptoms affect the HRQoL.

To the knowledge of our research team, this is the first time that different impact of episodic vs. chronic vestibular disorders and specific vs. unspecific diagnoses of vertigo and dizziness disorders on HRQoL are studied.

In the first study of this dissertation, data from a tertiary setting were used to evaluate the difference of the impact of episodic versus chronic vestibular syndromes on HRQoL and functioning in a cross-sectional design [48]. In the second study, and using a different dataset from a primary setting, it was possible to study the association between the

type of diagnosis of vertigo and dizziness and HRQoL. This was done following a longitudinal prospective cohort design.

As demonstrated in study 1, the main finding was that CVS patients reported significantly worse HRQoL and functioning than EVS patients. Moreover, it was also demonstrated that CVS patients had more mobility-related problems while EVS patients reported more emotional problems. This suggests that the nature of the vestibular syndromes i.e episodic vs. chronic seems to have an effect on HRQoL and functioning. The possible reason behind the higher functional impairment and poorer HRQoL among the CVS group is the longer duration of illness than that of EVS. This finding agrees with the literature where it was shown that chronic migraineurs who suffer from migraine for more than 15 days a month, reported more severe disability and poorer HRQoL than episodic migraineurs [54-56]. As for mobility-related problems that were expressed more among CVS patients in our results, this finding is in accordance with previous findings. It was shown that patients with Bilateral vestibulopathy (a chronic vestibular disorder) complain from physical and cognitive symptoms mainly imbalance and oscillopsia, negatively affecting their quality of life [57]. Vestibulo-spinal and -ocular reflex deficits in patients with bilateral vestibulopathy were associated with instable gait and poor visual acuity respectively [58]. In addition, high gait variability at slow-speed walking due to impaired sensory control [59] and the impaired vestibular cortical projections result in cognitive problems related to orientation, memory and attention [15, 60-62] consequently increasing the risk of falls [19]. It has been previously reported that the risk of fall is higher among CVS (bilateral and unilateral) than EVS patients [19, 63]. However, the literature shows that CVS patients report less anxiety to fall compared to EVS patients [64]. An explanation to that could be due to an impaired peripheral vestibular system that keeps the vertigo-related anxiety low among the CVS group [63, 64]. Whereas the higher anxiety among EVS patients could be related to the unpredictability of their episodes. For instance, vestibular migraineurs that fall under the EVS group, show higher rates of psychiatric disorders compared to patients with other vestibular syndromes [12, 65]. This in turn could

contribute to interrupted daily activities such as not being eligible to drive/hold a driving license which contributes to more impaired functioning and hence poorer HRQoL [66].

This study shows that CVS patients have more physical and mobility-related impairment, while EVS patients reported more emotional deficits. Emotional DHI scores were similar in the two groups. However, “Feeling frustrated” and “Being alone” were common among EVS patients, while “Walking problems” was frequent among CVS patients. These higher mobility-related deficits in the CVS group and the higher emotional deficits in the EVS group have exerted an overall impact on HRQoL and functioning favoring EVS. This suggests that the mobility-related deficits were more powerful and have been taken more seriously by CVS patients than that of emotional deficits by EVS patients. On the other hand, our linear regression analysis showed significant impact of both psychiatric disorders and sleeping problems, not only on HRQoL but also on functioning. We believe that this effect could be overvalued in our analyses due to the fact that anxiety and depressive symptoms overlap with HRQoL measures as stated by Hays and colleagues [67, 68].

Our analyses showed that among all lifestyle factors, only alcohol consumption was significantly higher among the CVS group than the EVS. This could be due to the avoidance of alcohol which could provoke episodes among the EVS patients especially those with migraine.

Compared to the German general population, HRQoL in our sample was low (VAS 62.39 < 71.59 and 73.2) which calls for therapeutic programs tackling HRQoL in both episodic and chronic vestibular patients. Therapeutic options should focus on mobility and falls among CVS patients which has been proven to be effective in maintaining HRQoL in clinical practice [69, 70]. Online rehabilitation was also shown to have a great clinical effectiveness on HRQoL perceived symptoms among chronic vestibular patients. This makes it a reliable and safe option especially for older individuals who might prefer to train from the comfort of their home [71]. As for EVS patients, especially those suffering from vestibular migraine and Meniere’s disease, psychological interventions would be more efficient in minimizing symptoms than physical rehabilitation [72, 73]. Relaxation

techniques and possibly pharmacotherapy seem to be more helpful for EVS patients [65, 74].

The major finding of our second analysis was that having an unspecific diagnosis of vertigo and dizziness is associated with poorer HRQoL as compared to having specific diagnosis. We could not show differential change in HRQoL between specific and unspecific diagnosis over time. Moreover, we could not show a significant interaction of the diagnosis with time. However, the study shows that a one-year increase in age is associated with lower mean score HRQoL.

To the knowledge of our research team, this investigation is leading the assessment of the impact of specific and unspecific diagnoses of vertigo and dizziness on HRQoL and its trajectories in a primary care setting. Therefore, it was not easy to compare our findings to other research work.

It was not surprising that receiving an unspecific diagnosis of vertigo and dizziness is associated with lower HRQoL. It has been reported repeatedly that vertigo and dizziness at older age can have numerous possible reasons [22, 23] and that it becomes challenging to describe the symptoms leading to unspecific diagnoses [25] and hence making treatment less effective [32]. Moreover, it was previously shown by our research group that GPs lack certainty and routine in diagnosing and treating vertigo, dizziness and balance disorders (VDB) [75]. Our current finding is in line with what was recently reported by our research group that VDB patients that had and unspecific diagnosis, had a higher risk of poorer HRQoL [76]. Interestingly, Katzenberger et al. showed that referring a VDB patient to a specialist has improved their HRQoL over time compared to their baseline assessment. This suggests that a specialist provides a more effective management and treatment of the real underlying condition and thus helps maintaining HRQoL [76]. In a study at a tertiary care setting, Obermann and colleagues found that 2/3 of patients (N= 1272) with vertigo and dizziness reported an improved quality of life after receiving a specific diagnosis for their symptoms [77]. This suggests that receiving a specific diag-

nosis and being treated by a specialist improve the patient's HRQoL. However, our results cannot provide direct comparison with the data of Obermann et al which comes from a tertiary care setting [77] while the data analyzed in our study are primary care data.

Regarding age in relation to HRQoL, our multivariate results show that being one year older is significantly associated with a lower mean HRQoL score. This finding is in accordance with two studies done on German populations as well where HRQoL was also measured by VAS score of the EQ-5D-5L [78, 79]. In both investigations, the overall VAS-score significantly decreases with age. In our study, having a mean age greater than that of Huber's (47.3) but close to that of Marten's (73.1) suggests that chronic diseases that develop later in life could be inversely associated with HRQoL [78, 79].

As for gender in relation to HRQoL, our results showed that women tend to report significantly poorer HRQoL than men. We realized that this gender-specific trend had been there in the German populations while comparing HRQoL between males and females. Our comparison was based on population studies that aimed to analyze the HRQoL of the Germans [78], the geriatric community [79], and an analysis of population surveys from 20 countries [80]. The poorer score of HRQoL among women could be due to differences in health perception between sexes [81].

This dissertation has some limitations. First, the cross-sectional design in study one did not allow us to eliminate the likelihood of simultaneous causality. Second, the exact size of the impact of vertigo and dizziness on HRQoL and functioning could be overestimated because our study population is limited to tertiary care setting. Third, recall bias could not be ruled out because the data was based on patient's self-report of health status. Fourth, although it increases statistical power, combining different vestibular disorders under two categories CVS and EVS could induce heterogeneity due to different underlying mechanisms and causes. However, our classification was done by expert specialists based on international gold-standard diagnostic criterium. Moreover, although observations with incomplete data on HRQoL or DHI were eliminated from the analysis,

this did not result in substantial bias as there was no difference between included and excluded data. Details are shown in Table 8 and Table 9 in Appendix A [48]. Fifth, the small sample size in the second study may be doubtful. However, this size is still valid to the primary care since it comes from a real-life scenario and not an interventional one. Lastly, the misclassification of the diagnoses is possible which could in turn confuse the association between the diagnosis and HRQoL. However, the GPs in this study base their classification on the ICD-10 [35] which makes the previous assumption less likely.

It is recommended for future research to investigate functioning and HRQoL in a community-based group of patients with episodic and chronic vestibular syndromes and to compare them to a healthy control group considering life style and sociodemographic covariates. Moreover, it would be interesting to provide a direct comparison with specific and unspecific diagnoses from tertiary care settings in order to confirm whether the latter is more effective than standard care in maintaining HRQoL over time.

5. Conclusion

This doctoral thesis is the first to present worse HRQoL among CVS patients in comparison to EVS; and worse HRQoL among patients with unspecific diagnosis of vertigo and dizziness compared to specific. The relationship between vestibular disorders and HRQoL is complex and is in continuous need for research. While trying to discuss our results in the loop of previous literature, we realized there was a lack of information especially regarding chronicity on one hand and specificity of the diagnoses on the other hand, and how they differently affect HRQoL. Further research work should comprehensively study the impact of vestibular disorders on HRQoL and functioning from a broader perspective and different settings. Evidence-based referrals of vertigo and dizziness patients to specialists might provide a solution for this problem.

References

[1] Strupp M, Dlug`zyk J, Ertl-Wagner BB, Rujescu D, Westhofen M, Dieterich M. Vestibular Disorders. Dtsch Arztebl Int. 2020;117(17):300-10.

[2] Mueller M, Schuster E, Strobl R, Grill E. Identification of aspects of functioning, disability and health relevant to patients experiencing vertigo: a qualitative study using the international classification of functioning, disability and health. Health Qual Life Outcomes. 2012;10:75.

[3] Bronstein AM, Golding JF, Gresty MA, Mandala M, Nuti D, Shetye A, et al. The social impact of dizziness in London and Siena. J Neurol. 2010;257(2):183-90.

[4] Karatas M. Central vertigo and dizziness: epidemiology, differential diagnosis, and common causes. Neurologist. 2008;14(6):355-64.

[5] Neuhauser HK, Radtke A, von Brevern M, Lezius F, Feldmann M, Lempert T. Burden of dizziness and vertigo in the community. Arch Intern Med. 2008;168(19):2118-24.

[6] Corrales CE, Bhattacharyya N. Dizziness and death: An imbalance in mortality. Laryngoscope. 2016;126(9):2134-6.

[7] von Brevern M, Radtke A, Lezius F, Feldmann M, Ziese T, Lempert T, et al. Epidemiology of benign paroxysmal positional vertigo: a population based study. J Neurol Neurosurg Psychiatry. 2007;78(7):710-5.

[8] Kim HJ, Park J, Kim JS. Update on benign paroxysmal positional vertigo. J Neurol. 2021;268(5):1995-2000.

[9] Liao WL, Chang TP, Chen HJ, Kao CH. Benign paroxysmal positional vertigo is associated with an increased risk of fracture: a population-based cohort study. J Orthop Sports Phys Ther. 2015;45(5):406-12.

[10] Brandt T, Dieterich M, Strupp M. Vertigo and dizziness: common complaints. London: Springer; 2005.

[11] Grill E, Strupp M, Muller M, Jahn K. Health services utilization of patients with vertigo in primary care: a retrospective cohort study. J Neurol. 2014;261(8):1492-8.

[12] Best C, Eckhardt-Henn A, Tschan R, Dieterich M. Psychiatric morbidity and comorbidity in different vestibular vertigo syndromes. Results of a prospective longitudinal study over one year. J Neurol. 2009;256(1):58-65.

[13] Ten Voorde M, van der Zaag-Loonen HJ, van Leeuwen RB. Dizziness impairs health-related quality of life. Qual Life Res. 2012;21(6):961-6.

[14] Bronstein AM, Dieterich M. Long-term clinical outcome in vestibular neuritis. Curr Opin Neurol. 2019;32(1):174-80.

[15] Strupp M, Kim JS, Murofushi T, Straumann D, Jen JC, Rosengren SM, et al. Bilateral vestibulopathy: Diagnostic criteria Consensus document of the Classification Committee of the Barany Society. J Vestib Res. 2017;27(4):177-89.

[16] Sun DQ, Ward BK, Semenov YR, Carey JP, Della Santina CC. Bilateral Vestibular Deficiency: Quality of Life and Economic Implications. JAMA Otolaryngol Head Neck Surg. 2014;140(6):527-34.

[17] Brandt T, Dieterich M. 'Excess anxiety' and 'less anxiety': both depend on vestibular function. Curr Opin Neurol. 2020;33(1):136-41.

[18] Brandt T, Grill E, Strupp M, Huppert D. Susceptibility to Fear of Heights in Bilateral Vestibulopathy and Other Disorders of Vertigo and Balance. Front Neurol. 2018;9:406.

[19] Schlick C, Schniepp R, Loidl V, Wuehr M, Hesselbarth K, Jahn K. Falls and fear of falling in vertigo and balance disorders: A controlled cross-sectional study. J Vestib Res. 2016;25(5-6):241-51.

[20] Carrillo Munoz R, Ballve Moreno JL, Villar Balboa I, Rando Matos Y, Cunillera Puertolas O, Almeda Ortega J, et al. Disability perceived by primary care patients with posterior canal benign paroxysmal positional vertigo. BMC Fam Pract. 2019;20(1):156.

[21] Yardley L, Dibb B, Osborne G. Factors associated with quality of life in Meniere's disease. Clin Otolaryngol Allied Sci. 2003;28(5):436-41.

[22] Fernandez L, Breinbauer HA, Delano PH. Vertigo and Dizziness in the Elderly. Front Neurol. 2015;6:144.

[23] Maarsingh OR, Dros J, Schellevis FG, van Weert HC, van der Windt DA, ter Riet G, et al. Causes of persistent dizziness in elderly patients in primary care. Ann Fam Med. 2010;8(3):196-205.

[24] Edlow JA, Gurley KL, Newman-Toker DE. A New Diagnostic Approach to the Adult Patient with Acute Dizziness. J Emerg Med. 2018;54(4):469-83.

[25] Maarsingh OR, Dros J, Schellevis FG, van Weert HC, Bindels PJ, Horst HE. Dizziness reported by elderly patients in family practice: prevalence, incidence, and clinical characteristics. BMC Fam Pract. 2010;11:2.

[26] Kwong EC, Pimlott NJ. Assessment of dizziness among older patients at a family practice clinic: a chart audit study. BMC Fam Pract. 2005;6(1):2.

[27] Newman-Toker DE, Cannon LM, Stofferahn ME, Rothman RE, Hsieh YH, Zee DS. Imprecision in patient reports of dizziness symptom quality: a cross-sectional study conducted in an acute care setting. Mayo Clin Proc. 2007;82(11):1329-40.

[28] Sloane PD, Coeytaux RR, Beck RS, Dallara J. Dizziness: state of the science. Ann Intern Med. 2001;134(9 Pt 2):823-32.

[29] Stanton VA, Hsieh YH, Camargo CA, Jr., Edlow JA, Lovett PB, Goldstein JN, et al. Overreliance on symptom quality in diagnosing dizziness: results of a multicenter survey of emergency physicians. Mayo Clin Proc. 2007;82(11):1319-28.

[30] Lo AX, Harada CN. Geriatric dizziness: evolving diagnostic and therapeutic approaches for the emergency department. Clin Geriatr Med. 2013;29(1):181-204.

[31] Royl G, Ploner CJ, Leithner C. Dizziness in the emergency room: diagnoses and misdiagnoses. Eur Neurol. 2011;66(5):256-63.

[32] Geser R, Straumann D. Referral and final diagnoses of patients assessed in an academic vertigo center. Front Neurol. 2012;3:169.

[33] Bosner S, Schwarm S, Grevenrath P, Schmidt L, Horner K, Beidatsch D, et al. Prevalence, aetiologies and prognosis of the symptom dizziness in primary care - a systematic review. BMC Fam Pract. 2018;19(1):33.

[34] Grill E, Muller T, Becker-Bense S, Gurkov R, Heinen F, Huppert D, et al. DizzyReg: the prospective patient registry of the German Center for Vertigo and Balance Disorders. J Neurol. 2017;264(Suppl 1):34-6.

[35] Kisch R, Bergmann A, Koller D, Leidl R, Mansmann U, Mueller M, et al. Patient trajectories and their impact on mobility, social participation and quality of life in patients with vertigo/dizziness/balance disorders and osteoarthritis (MobilE-TRA): study protocol of an observational, practice-based cohort study. BMJ Open. 2018;8(4):e022970.

[36] Bisdorff A, Von Brevern M, Lempert T, Newman-Toker DE. Classification of vestibular symptoms: towards an international classification of vestibular disorders. J Vestib Res. 2009;19(1-2):1-13.

[37] Lempert T, Olesen J, Furman J, Waterston J, Seemungal B, Carey J, et al. Vestibular migraine: diagnostic criteria. J Vestib Res. 2012;22(4):167-72.

[38] Lopez-Escamez JA, Carey J, Chung WH, Goebel JA, Magnusson M, Mandala M, et al. Diagnostic criteria for Meniere's disease. J Vestib Res. 2015;25(1):1-7.

[39] Strupp M, Lopez-Escamez JA, Kim JS, Straumann D, Jen JC, Carey J, et al. Vestibular paroxysmia: Diagnostic criteria. J Vestib Res. 2016;26(5-6):409-15.

[40] Strupp M, Magnusson M. Acute Unilateral Vestibulopathy. Neurol Clin. 2015;33(3):669-85, x.

[41] EuroQol G. EuroQol--a new facility for the measurement of health-related quality of life. Health Policy. 1990;16(3):199-208.

[42] Greene ME, Rader KA, Garellick G, Malchau H, Freiberg AA, Rolfson O. The EQ-5D-5L Improves on the EQ-5D-3L for Health-related Quality-of-life Assessment in Patients Undergoing Total Hip Arthroplasty. Clin Orthop Relat Res. 2015;473(11):3383-90.

[43] Yardley L, Barker F, Muller I, Turner D, Kirby S, Mullee M, 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:e2237.

[44] Greiner W, Weijnen T, Nieuwenhuizen M, Oppe S, Badia X, Busschbach J, et al. A single European currency for EQ-5D health states. Results from a six-country study. Eur J Health Econ. 2003;4(3):222-31.

[45] Kurre A, Bastiaenen CH, van Gool CJ, Gloor-Juzi T, de Bruin ED, Straumann D. Exploratory factor analysis of the Dizziness Handicap Inventory (German version). BMC Ear Nose Throat Disord. 2010;10:3.

[46] Cronbach LJ. Coefficient alpha and the internal structure of tests. Psychometrika. 1951;16(3):297-334.

[47] Staab JP, Eckhardt-Henn A, Horii A, Jacob R, Strupp M, Brandt T, 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):191-208.

[48] Strobl R, Harajli S, Huppert D, Zwergal A, Grill E. Impact of episodic and chronic vestibular disorders on health-related quality of life and functioning-results from the DizzyReg patient registry. Qual Life Res. 2023.

[49] Chaudhry S, Jin L, Meltzer D. Use of a self-report-generated Charlson Comorbidity Index for predicting mortality. Med Care. 2005;43(6):607-15.

[50] Shrier I, Platt RW. Reducing bias through directed acyclic graphs. BMC Med Res Methodol. 2008;8:70.

[51] Textor J, van der Zander B, Gilthorpe MS, Liskiewicz M, Ellison GT. Robust causal inference using directed acyclic graphs: the R package 'dagitty'. Int J Epidemiol. 2016;45(6):1887-94.

[52] Fox J, Monette G. Generalized Collinearity Diagnostics. Journal of the American Statistical Association. 1992;87(417):178-83.

[53] R Development Core Team. A language and environment for statistical computing.: R Foundation for Statistical Computing. Vienna, Austria.2019.

[54] Bigal ME, Ashina S, Burstein R, Reed ML, Buse D, Serrano D, et al. Prevalence and characteristics of allodynia in headache sufferers: a population study. Neurology. 2008;70(17):1525-33.

[55] Blumenfeld AM, Varon SF, Wilcox TK, Buse DC, Kawata AK, Manack A, et al. Disability, HRQoL and resource use among chronic and episodic migraineurs: results from the International Burden of Migraine Study (IBMS). Cephalalgia. 2011;31(3):301-15.

[56] Buse D, Manack A, Serrano D, Reed M, Varon S, Turkel C, et al. Headache impact of chronic and episodic migraine: results from the American Migraine Prevalence and Prevention study. Headache. 2012;52(1):3-17.

[57] Lucieer FMP, Van Hecke R, van Stiphout L, Duijn S, Perez-Fornos A, Guinand N, et al. Bilateral vestibulopathy: beyond imbalance and oscillopsia. J Neurol. 2020;267(Suppl 1):241-55.

[58] Schniepp R, Boerner JC, Decker J, Jahn K, Brandt T, Wuehr M. Noisy vestibular stimulation improves vestibulospinal function in patients with bilateral vestibulopathy. J Neurol. 2018;265(Suppl 1):57-62.

[59] Schniepp R, Wuehr M, Neuhaeusser M, Kamenova M, Dimitriadis K, Klopstock T, et al. Locomotion speed determines gait variability in cerebellar ataxia and vestibular failure. Mov Disord. 2012;27(1):125-31.

[60] Bronstein A. Visual symptoms and vertigo. Neurol Clin. 2005;23(3):705-13, v-vi.

[61] Dobbels B, Mertens G, Gilles A, Claes A, Moyaert J, van de Berg R, et al. Cognitive Function in Acquired Bilateral Vestibulopathy: A Cross-Sectional Study on Cognition, Hearing, and Vestibular Loss. Front Neurosci. 2019;13:340.

[62] Schoberl F, Pradhan C, Grosch M, Brendel M, Jostes F, Obermaier K, et al. Bilateral vestibulopathy causes selective deficits in recombining novel routes in real space. Sci Rep. 2021;11(1):2695.

[63] Dobbels B, Lucieer F, Mertens G, Gilles A, Moyaert J, van de Heyning P, et al. Prospective cohort study on the predictors of fall risk in 119 patients with bilateral vestibulopathy. PLoS One. 2020;15(3):e0228768.

[64] Decker J, Limburg K, Henningsen P, Lahmann C, Brandt T, Dieterich M. Intact vestibular function is relevant for anxiety related to vertigo. J Neurol. 2019;266(Suppl 1):89-92.

[65] Lahmann C, Henningsen P, Brandt T, Strupp M, Jahn K, Dieterich M, et al. Psychiatric comorbidity and psychosocial impairment among patients with vertigo and dizziness. J Neurol Neurosurg Psychiatry. 2015;86(3):302-8.

[66] Huppert D, Straumann D, Magnusson M, Pyykko I, Brandt T. Dizziness in Europe: from licensed fitness to drive to licence without fitness to drive. J Neurol. 2018;265(Suppl 1):9-17.

[67] Hays RD, Fayers PM. Overlap of Depressive Symptoms with Health-Related Quality-of-Life Measures. Pharmacoeconomics. 2021;39(6):627-30.

[68] Kaplan RM, Hays RD. Health-Related Quality of Life Measurement in Public Health. Annu Rev Public Health. 2022;43:355-73.

[69] Hall CD, Herdman SJ, Whitney SL, Cass SP, Clendaniel RA, Fife TD, et al. Vestibular Rehabilitation for Peripheral Vestibular Hypofunction: An Evidence-Based Clinical Practice Guideline: FROM THE AMERICAN PHYSICAL THERAPY ASSOCIATION NEUROLOGY SECTION. J Neurol Phys Ther. 2016;40(2):124-55.

[70] McDonnell MN, Hillier SL. Vestibular rehabilitation for unilateral peripheral vestibular dysfunction. Cochrane Database Syst Rev. 2015;1:CD005397.

[71] van Vugt VA, van der Wouden JC, Essery R, Yardley L, Twisk JWR, van der Horst HE, 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:l5922.

[72] Alghadir AH, Anwer S. Effects of Vestibular Rehabilitation in the Management of a Vestibular Migraine: A Review. Front Neurol. 2018;9:440.

[73] van Esch BF, van der Scheer-Horst ES, van der Zaag-Loonen HJ, Bruintjes TD, van Benthem PP. The Effect of Vestibular Rehabilitation in Patients with Meniere's Disease. Otolaryngol Head Neck Surg. 2017;156(3):426-34.

[74] Zwergal A, Strupp M, Brandt T. Advances in pharmacotherapy of vestibular and ocular motor disorders. Expert Opin Pharmacother. 2019;20(10):1267-76.

[75] Stephan AJ, Kovacs E, Phillips A, Schelling J, Ulrich SM, Grill E. Barriers and facilitators for the management of vertigo: a qualitative study with primary care providers. Implement Sci. 2018;13(1):25.

[76] Katzenberger B, Koller D, Strobl R, Kisch R, Sanftenberg L, Voigt K, et al. Referral trajectories in patients with vertigo, dizziness and balance disorders and their impact on health-related quality of life and functioning: results from the longitudinal multicenter study MobilE-TRA. J Neurol. 2022;269(12):6211-21.

[77] Obermann M, Bock E, Sabev N, Lehmann N, Weber R, Gerwig 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):2083-91.

[78] Huber MB, Felix J, Vogelmann M, Leidl R. Health-Related Quality of Life of the General German Population in 2015: Results from the EQ-5D-5L. Int J Environ Res Public Health. 2017;14(4).

[79] Marten O, Greiner W. EQ-5D-5L reference values for the German general elderly population. Health Qual Life Outcomes. 2021;19(1):76.

[80] Janssen MF, Szende A, Cabases J, Ramos-Goni JM, Vilagut G, Konig HH. Population norms for the EQ-5D-3L: a cross-country analysis of population surveys for 20 countries. Eur J Health Econ. 2019;20(2):205-16.

[81] Hajian-Tilaki K, Heidari B, Hajian-Tilaki A. Are Gender Differences in Health-related Quality of Life Attributable to Sociodemographic Characteristics and Chronic Disease Conditions in Elderly People? Int J Prev Med. 2017;8:95.

Appendix A

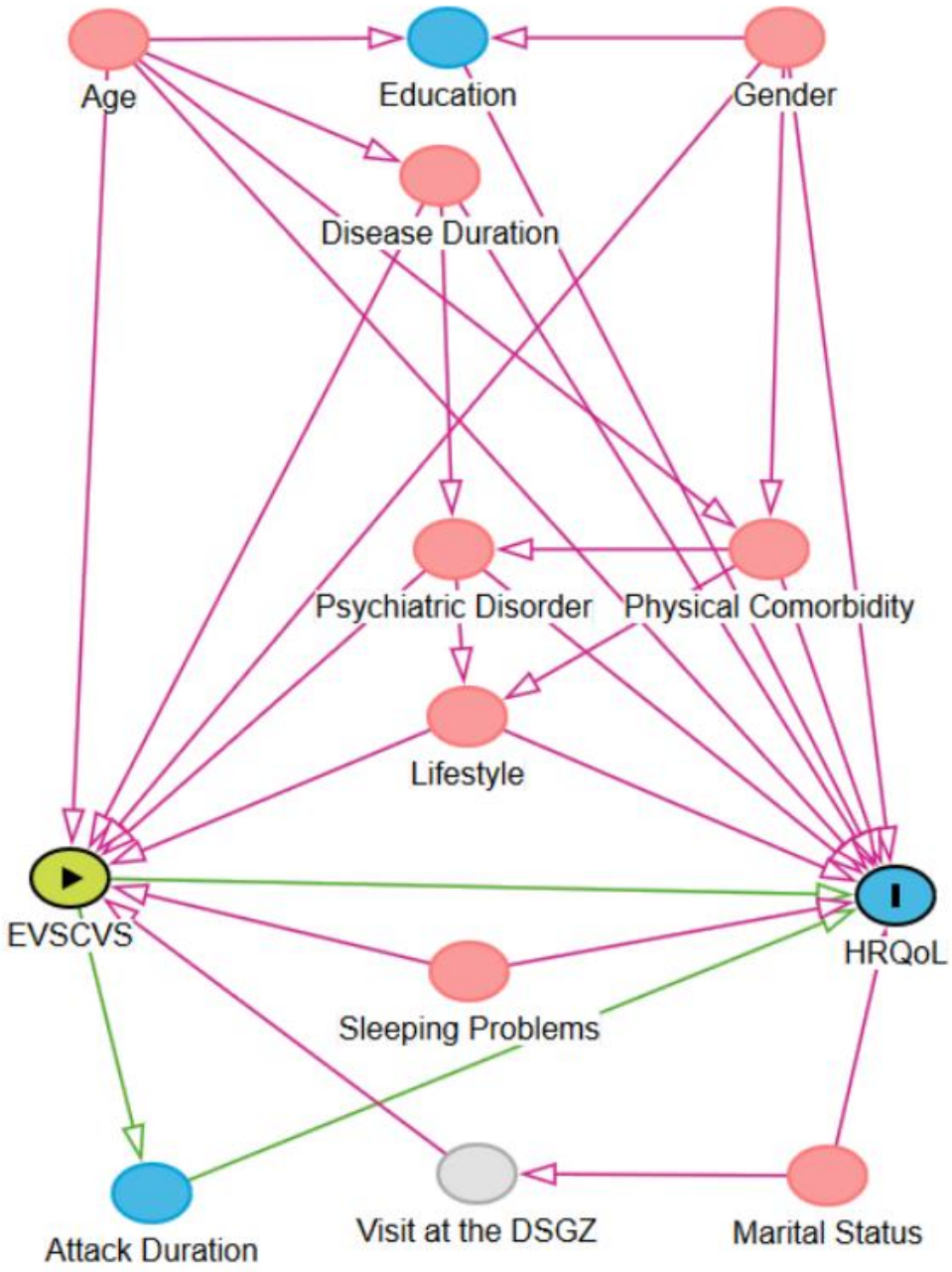


Figure 3 - Directed acyclic graph (DAGs) for the nature of vestibular syndromes and their effect on HRQoL: Parsimonious variable set

Strobl, R., S. Harajli, D. Huppert, A. Zwergal and E. Grill (2023). "Impact of episodic and chronic vestibular disorders on health-related quality of life and functioning-results from the DizzyReg patient registry." Qual Life Res.

Table 7 - Poisson regression model: EVS and CVS incidence rate to answer “sometimes” and “yes” for the presence of impairment and its chronicity

Variables	**Number of “yes”**		**Number of “sometimes”**	
	coefficient [CI]	***p*-value**	**coefficient [CI]**	***p*-value**
(Intercept)	4.05 [2.66; 5.94]	< 0.0001	6.68 [4.92; 8.94]	< 0.0001
EVS (reference=CVS)	0.76 [0.70; 0.83]	< 0.0001	1.11 [1.01; 1.21]	0.0307
Problems falling asleep (reference=never)				
sometimes	1.14 [1.05; 1.23]	0.0026	1.06 [0.98; 1.14]	0.1803
often	1.44 [1.31; 1.58]	< 0.0001	0.93 [0.84; 1.03]	0.1859
Any psychiatric Disorder (reference = no)				
yes	1.14 [1.06; 1.24]	0.0009	1.02 [0.94; 1.10]	0.6498
Age	1.00 [1.00; 1.01]	0.2156	1.00 [1.00; 1.01]	0.9103
Gender (reference=female)				
male	0.86 [0.80; 0.93]	0.0002	0.85 [0.78; 0.91]	< 0.001

Strobl, R., S. Harajli, D. Huppert, A. Zwergal and E. Grill (2023). "Impact of episodic and chronic vestibular disorders on health-related quality of life and functioning-results from the DizzyReg patient registry." Qual Life Res.

Table 8 – Sensitivity analysis: Included and excluded patients with missing data in the DHI questionnaire for 548 participants

Variable	**Complete DHI (476)**	**Missing DHI (72)**	**Effectsize***	***p*-value**
Mean Age (±SD)	50.45 (SD=15.45)	57.29 (SD=15.23)	-0.4434	0.0005
Gender = F	273 (57%)	40 (56%)	0.0123	0.8733
Education			0.086	0.1872
Low	149 (38%)	25 (42%)		
Medium	134 (34%)	24 (41%)		
High	111 (28%)	10 (17%)		
Marital Status			0.0918	0.2141
Single	116 (25%)	11 (18%)		
Married	282 (60%)	41 (68%)		
Divorced	58 (12%)	4 (7%)		
Widowed	16 (3%)	4 (7%)		
Smoking			0.095	0.199
Never	8 (2%)	0 (0%)		
Former	187 (41%)	31 (54%)		
Current occasionally	193 (42%)	20 (35%)		
Current regular	71 (15%)	6 (11%)		
Alcohol consumption (Yes)	233 (49%)	32 (49%)	0.0005	1

Strobl, R., S. Harajli, D. Huppert, A. Zwergal and E. Grill (2023). "Impact of episodic and chronic vestibular disorders on health-related quality of life and functioning-results from the DizzyReg patient registry." Qual Life Res.

Table 9 - Sensitivity analysis: Included and excluded patients with missing data in the EQ5D3L questionnaire for 548 participants

Variable	Complete HRQoL (514)	Missing HRQoL (34)	Effectsize*	*p*-value
Mean Age (±SD)	50.53 (SD=15.45)	63.76 (SD=11.93)	-0.867	< 0.0001
Gender = F	289 (56%)	24 (71%)	0.07	0.1443
Education			0.0551	0.5028
Low	161 (38%)	13 (48%)		
Medium	151 (35%)	7 (26%)		
High	114 (27%)	7 (26%)		
Marital Status			0.1756	0.0090
Single	126 (25%)	1 (5%)		
Married	309 (61%)	14 (64%)		
Divorced	59 (12%)	3 (14%)		
Widowed	16 (3%)	4 (18%)		
Smoking			0.0432	0.8098
Never	8 (2%)	0 (0%)		
Former	211 (43%)	7 (35%)		
Current occasionally	203 (41%)	10 (50%)		
Current regular	74 (15%)	3 (15%)		
Alcohol consumption (Yes)	248 (49%)	17 (61%)	0.0541	0.2885

Strobl, R., S. Harajli, D. Huppert, A. Zwergal and E. Grill (2023). "Impact of episodic and chronic vestibular disorders on health-related quality of life and functioning-results from the DizzyReg patient registry." Qual Life Res.

Acknowledgements

First and foremost, I am extremely grateful to my dear husband for his endless support and patience during my PhD journey. Thank you Jamal for having encouraged me from day one and for always being there for me at my ups and downs. I definitely wouldn't have done it without you and your belief in me. Your love is what has gotten me through when I wanted to give up.

I would also like to thank my esteemed supervisors Prof. Dr. Eva Grill and Prof. Dr. Ulrich Mansmann for all the help, advice and tutelage during my PhD.

I sincerely express my gratitude to Dr. Daniela Koller and Dr. Ralf Strobl for their treasured support at every stage of the research projects which was really influential in shaping my PhD experience. Their immense knowledge and plentiful experience have added a lot to mine. Thanks to everyone who have participated in the two projects and made them successful.

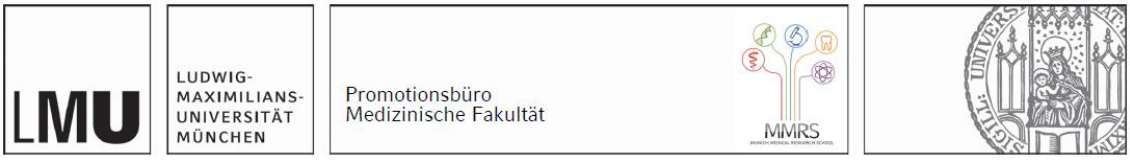
Next, I would like to thank Dr. Annette Hartmann and Monika Darchinger for their coordination and assistance at every stage of the PhD journey.

My appreciation also goes out to my family and friends for their encouragement and support all through my studies.

Finally, I am grateful to have had the privilege of attending the prestigious Ludwig Maximillian University of Munich. This opportunity has offered me the chance to learn from big names in the medical research field. Thank you for this opportunity.

This work is dedicated to my children Flora and Aram. You have made me stronger, better and more motivated than I could have ever imagined. I love you to the moon and back.

Affidavit



Affidavit

Harajli, Saly

I hereby declare, that the submitted thesis entitled:

The impact of episodic and chronic vestibular disorders and their specific vs. unspecific diagnosis on Health-related quality of life

is my own work. I have only used the sources indicated and have not made unauthorised use of services of a third party. Where the work of others has been quoted or reproduced, the source is always given.

I further declare that the dissertation presented here has not been submitted in the same or similar form to any other institution for the purpose of obtaining an academic degree.

München, 25.10.202 Saly Harajli

place, date Signature doctoral candidate

Confirmation of congruency

LMU LUDWIG-MAXIMILIANS-UNIVERSITÄT MÜNCHEN

Promotionsbüro
Medizinische Fakultät

MMRS

Confirmation of congruency between printed and electronic version of the doctoral thesis

Harajli, Saly

I hereby declare, that the submitted thesis entitled:

The impact of episodic and chronic vestibular disorders and their specific vs. unspecific diagnosis on Health-related quality of life

is congruent with the printed version both in content and format.

München, 25.10.202 _____

place, date

Saly Harajli _____

Signature doctoral candidate

List of publications

Published

Strobl, R., **S. Harajli**, D. Huppert, A. Zwergal and E. Grill (2023). "Impact of episodic and chronic vestibular disorders on health-related quality of life and functioning-results from the DizzyReg patient registry." Qual Life Res.

Ghazeeri, G., D. Zebian, A. H. Nassar, **S. Harajly**, A. Abdallah, S. Hakimian, B. Skaiff, H. A. Abbas and J. Awwad (2016). "Knowledge, attitudes and awareness regarding fertility preservation among oncologists and clinical practitioners in Lebanon." Hum Fertil (Camb) 19(2): 127-133.

Ghazeeri, G., H. A. Abbas, B. Skaff, **S. Harajly** and J. Awwad (2015). "Inadequacy of initiating rosuvastatin then metformin on biochemical profile of polycystic ovarian syndrome patients." J Endocrinol Invest 38(6): 643-651.

Ghazeeri, G., A. Fakih, H. A. Abbas, **S. Harajly** and J. Awwad (2013). "Anxiety, cognitive, and depressive assessment in adolescents with polycystic ovarian syndrome: a pilot study." J Pediatr Adolesc Gynecol 26(5): 269-273.

Manuscripts In preparation

Koller, D., **S. Harajli**, B. Katzenberger, R. Strobl, E. Grill, L. Sanftenberg, J. Schelling, J. Gensichen. " How a specific vs. unspecific diagnosis of vertigo and dizziness influences trajectories in health-related quality of life (HRQoL) - Results from the longitudinal study MobilE-TRA."