Aus dem

Institut für Medizinische Informationsverarbeitung, Biometrie und Epidemiologie (IBE)

Institut der Ludwig-Maximilians-Universität München

Management of older adults with vertigo, dizziness, and balance problems across healthcare sectors: challenges and consequences for health-related quality of life and functioning

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Benedict Katzenberger

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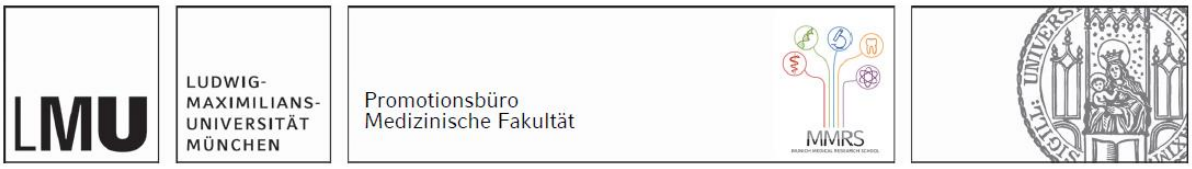

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I hereby declare, that the submitted thesis entitled:

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List of abbreviations

AS	Anticholinergic or Sedative
BE	Behavioral Economics
CI	Confidence Interval
DAG	Directed Acyclic Graph
DBI	Drug Burden Index
DEGAM	Deutsche Gesellschaft für Allgemeinmedizin und Familienmedizin (German Society of General Medicine and Family Medicine)
DHI	Dizziness Handicap Inventory
DSGZ	Deutsches Schwindel- und Gleichgewichtszentrum (German Center for Vertigo and Balance Disorders)
ENT	Ear, Nose, and Throat
HAQ-DI	Health Assessment Questionnaire Disability Index
HRQoL	Health-Related Quality of Life
ICD-10	International Classification of Diseases, 10th edition
LMU	Ludwig-Maximilians-Universität
MobilE-Net	Munich Network Health Care Research
MobilE-TRA	Patient trajectories and their impact on mobility, social participation and quality of life in patients with vertigo/dizziness/balance disorders and osteoarthritis
MobilE-TRA 2	Behavioural and patient-individual determinants of quality of life, functioning and physical activity in older adults
OR	Odds Ratio
PCP	Primary Care Physician
SSA	State Sequence Analysis
VAP	Vestibular Activities and Participation questionnaire
VAS	Visual Analogue Scale
VDB	Vertigo, Dizziness, and Balance problems

List of publications

Peer reviewed publications used for this doctoral thesis

- **Katzenberger B**, Fuchs S, Schwettmann L, Strobl R, Hauser A, Koller D, Grill E (2023). Association of self-efficacy, risk attitudes, and time preferences with functioning in older patients with vertigo, dizziness, and balance disorders in a tertiary care setting – Results from the MobilE-TRA2 cohort. Front Neurol 14: 1316081. DOI: 10.3389/fneur.2023.1316081

- **Katzenberger B**, Koller D, Strobl R, Kisch R, Sanftenberg L, Voigt K, Grill E (2023). Exposure to anticholinergic and sedative medication is associated with impaired functioning in older people with vertigo, dizziness and balance disorders – Results from the longitudinal multicenter study MobilE-TRA. Front Pharmacol 14: 1136757. DOI: 10.3389/fphar.1136757

- **Katzenberger B**, Koller D, Strobl R, Kisch R, Sanftenberg L, Voigt K, Grill E (2022). 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 269(12): 6211-21. DOI: 10.1007/s00415-022-11060-8

Additional peer reviewed publications

- Borchers P, Horstmannshoff C, **Katzenberger B**, Petermann J, Bauer P, Kiesel T, Müller M, Sanftenberger L, Voigt K (2023). Verordnung und Inanspruchnahme von Physiotherapie bei Schwindel und/oder Gleichgewichtsstörungen. Physioscience. DOI: 10.1055/a-2001-5026

- **Katzenberger B**, Brosch F, Besnard S, Grill E (2023). Chronic Vestibular Hypofunction Is Associated with Impaired Sleep: Results from the DizzyReg Patient Registry. J Clin Med 12(18): 5903. DOI: 10.3390/jcm12185903

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- Sanftenberg L, Dirscherl A, Schelling J, Gensichen J, Voigt K, Bergmann A, **Katzenberger B**, Grill E (2021). Quality of care in family practice and quality of life from the point of view of older patients with gon- and coxosteoarthritis – results from the MobilE-TRA cohort study. MMW Fortschr Med 163(Suppl 6): 19-26. DOI: 10.1007/s15006-021-0455-x

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Conference Contributions

- **Katzenberger B**, Fuchs S, Schwettmann L, Strobl R, Hauser A, Koller D, Grill E (2023). Risk attitude and self-efficacy are associated with vertigo-specific functioning in older patients with vertigo, dizziness and balance disorders – results from the longitudinal multicenter study MOBILE-TRA 2. 18. Jahrestagung DGEpi, oral presentation. Würzburg, Germany

- **Katzenberger B**, Stark R, Grill E, Peters A, and Schwettmann L. (2023). Risk attitudes moderate the association of vertigo, dizziness, and balance disorders with health-related quality of life – Results from the KORA-FF4 study. 15. dggö Jahrestagung, oral presentation. Hannover, Germany

- **Katzenberger B**, Koller D, Strobl R, Kisch R, Sanftenberg L, Voigt K, Grill E (2022). 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. 21. Deutscher Kongress für Versorgungsforschung (DKVF), oral presentation. Potsdam, Germany. DOI: 10.3205/22dkvf482

- Borchers P, Petermann J, **Katzenberger B**, Bauer P, Horstmannshoff C, Lechner T, Müller M, Voigt K (2022). Physiotherapie bei Schwindel und Gleichgewichtsstörungen: hausärztliche Verordnung und patientenseitige Inanspruchnahme (Ergebnisse aus der Kohortenstudie MobilE-TRA). 21. Deutscher Kongress für Versorgungsforschung (DKVF), poster. Potsdam, Germany. DOI: 10.3205/22dkvf452

- **Katzenberger B**, Koller D, Strobl R, Kisch R, Sanftenberg L, Voigt K, Grill E (2022). Exposure to anticholinergic and sedative medication impacts generic and disease-specific functioning in older patients with vertigo, dizziness and balance disorders – Results from the longitudinal multicenter study MobilE-TRA. 17. Jahrestagung der DGEpi, oral presentation. Greifswald, Germany

- Borchers P, Petermann J, **Katzenberger B**, Bauer P, Horstmannshoff C, Lechner T, Müller M, Voigt K (2022). Hausärztliche Verordnung und patientenseitige Inanspruchnahme von Physiotherapie bei Patient:innen mit Schwindel- und/oder Gleichgewichtsstörungen – Ergebnisse aus der Kohortenstudie MobilE-TRA. 56. Kongress für Allgemeinmedizin und Familienmedizin, poster. Greifswald, Germany. DOI: 10.3205/22degam167

- Dirscherl A, Sanftenberg L, Dreischulte T, Voigt K, Bergmann A, Schelling J, **Katzenberger B**, Grill E, Gensichen J (2021). Hausärztliche Versorgungsqualität und Lebensqualität aus Sicht älterer Patienten mit Gon- und Koxarthrose – Ergebnisse der Kohortenstudie MobilE-TRA. 55. Kongress für Allgemeinmedizin und Familienmedizin, oral presentation. Lübeck, Germany. DOI: 10.3205/21degam008

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- **Katzenberger B**, Koller D, Sanftenberg L, Voigt K, Grill E (2020). Referral trajectories in patients with vertigo, dizziness and balance disorders and their association with functioning and health-related quality of life – Results from the MobilE-TRA cohort study. SER 2020 Virtual Meeting, poster. Online

- **Katzenberger B**, Koller D, Sanftenberg L, Voigt K, Grill E (2020). Referral trajectories in patients with vertigo, dizziness and balance disorders and their association with functioning and health-related quality of life – Results from the MobilE-TRA cohort study. 15. Jahrestagung der DGEpi, oral presentation. Online

1 My contribution to the publications

1.1 Contribution to publication I

I, Benedict Katzenberger, performed the background research along with the conception of the methods and the analysis strategy for publication 1 and conducted the data analysis. I computed the drug burden index utilized within this publication, which then was validated by Daniela Koller (DK) for quality assurance. I was responsible for the interpretation and reporting of the results of the conducted analyses. In addition, I was in charge of the study's quality assessment and the processing of the collected data, with collaborative support from Eva Grill (EG), DK, and Rebecca Kisch (RK). In my capacity as the first author of publication 1, I drafted the manuscript and incorporated the co-authors' feedback into the final version.

EG supervised the publication, providing feedback concerning the conceptualization and the analysis of the project. She further revised and approved the manuscript during multiple stages. Ralf Strobl (RS) and DK verified the statistical methods and performed calculations. EG, DK, RS, RK, Karen Voigt (KV), and Linda Sanftenberg (LS) revised and approved the final manuscript.

The study design and execution of the first MobilE-TRA study, which served as the basis for publication 1, were planned by EG and DK. Material preparation and data collection were performed by RK, LS, and KV.

1.2 Contribution to publication II

I, Benedict Katzenberger, conducted the background research and planned the methods along with the analysis strategy for publication 2. I conducted the data analysis as well as the interpretation and the reporting of the findings. I further took charge of the study's quality assessment and the processing of collected data, supported by Eva Grill (EG), Daniela Koller (DK), and Rebecca Kisch (RK). As the first author of publication 2, I drafted the manuscript and integrated the co-authors' feedback into the final version.

EG was supervising the publication, granting feedback on the conceptualization and the analysis and revising the manuscript across multiple stages. Ralf Strobl (RS) validated the statistical methodologies and conducted calculations. EG, DK, RS, RK, Karen Voigt (KV), and Linda Sanftenberg (LS) reviewed and endorsed the final version of this publication.

Serving as the basis for publication 2, the study design and execution of the research project MobilE-TRA were planned by EG and DK. Material preparation and data collection were performed by RK, LS, and KV.

1.3 Contribution to publication III

I, Benedict Katzenberger, performed the background research and developed the conceptual framework and analysis strategy for publication 3. I conducted the data analysis and handled

the interpretation and reporting of the findings. Being the first author of publication 3, I drafted the manuscript, incorporating feedback from co-authors into the final version.

Sebastian Fuchs (SF) contributed his feedback on the conceptualization, the methods, the analysis, and the interpretation of results throughout all stages of the project. Supervising the publication, Eva Grill (EG) provided input on the conceptualization and the analysis across multiple manuscript stages. Lars Schwettmann (LS) verified the conceptualization of this research project. Ralf Strobl (RS) and Ari Hauser (AH) verified the statistical methods and performed calculations. AH also supported and verified the visualization of the results. The final manuscript was revised and approved by EG, SF, LS, DK, RS, and AH.

Serving as the basis for publication 3, the study design and execution of the research project MobilE-TRA 2 were planned by EG, LS, and DK. I coordinated the study at all stages. I drafted and published the study protocol and obtained the approval of the ethics committee at the medical faculty of the Ludwig-Maximilians-Universität (LMU) Munich and the data protection office at the LMU University Hospital. Additionally, I conducted the material preparation and coordinated the data collection for patients with vertigo, dizziness, and balance problems. Collaborating with SF, I conducted the processing of collected data and was in charge of the study's quality assessment, supported by EG, LS, RS, and DK.

2 Introductory summary

2.1 Background and relevance

The human ability to perceive self-motion, maintain orientation, and sustain balance is indispensable for numerous aspects of daily life. Under typical circumstances, the integration of vestibular, visual, and proprioceptive cues constructs a coherent perception of spatial orientation and self-motion [1]. Disruptions in any of the components involved in this process can lead to sensory discord, resulting in vertigo, dizziness, and balance problems (VDB) [2].

VDB are remarkably prevalent among older individuals, ranging from approximately 30% in those beyond 60 years of age [3–5], to as high as 50% in those over 85 [3]. A broad range of underlying conditions [6–8], often compounded and exacerbated by the aging process, impact the overall functional capability and resilience of the entire body [5, 8, 9].

The limitations imposed by VDB extend to many aspects of daily life [10, 11], affecting both occupational and social activities [12]. Routine tasks and even basic activities like walking or bending over become challenging [13, 14]. These restrictions are accompanied by a high incidence of symptom-related mental comorbidities, including anxiety or depression [15, 16]. While direct life-threatening complications are rare, functional impairment due to VDB leads to an increased risk of falls [17, 18] and significant disability [19]. When remaining untreated, VDB consequently leads to functional impairment and reduced health-related quality of life (HRQoL) [20, 21].

Effective diagnostics and treatment options are available for the majority of conditions related to VDB [22–24]. When the causes of VDB are adequately managed, HRQoL and functioning will improve [23, 25]. However, treating VDB remains challenging. Patients often strugge to articulate their complaints accurately [26]. Optimal treatment varies depending on the underlying pathology [7, 27, 28], requiring intensive interdisciplinary collaboration in many cases. To meet these challenges adequately with effective treatment, the surrounding healthcare system needs to provide specialized diagnostic and treatment procedures, along with well-trained providers. Transitions between care providers should be standardized and evidence-driven to make the best use of available resources and expertise.

Research evidence suggests a pronounced discrepancy between the available diagnostic and treatment options and the actual care provided [29–31], which often proves insufficient in addressing the complex challenges posed by VDB. As a result, patients with VDB under usual care conditions frequently find themselves unable to achieve improvements in patient-relevant outcomes [32]. These findings emphasize the pressing necessity for a critical evaluation of current healthcare practices.

Addressing knowledge gaps regarding underlying mechanisms and issues in these practices is a prerequisite for informing necessary adaptations and enhancements in current care strategies. Understanding how these practices influence HRQoL and functioning is essential to explain, why current health care often fails to improve patient-relevant outcomes and to ensure that adaptations align effectively with the needs of the patients. This PhD project intends to contribute to this endeavor by addressing three selected issues in the field of primary care, the transition

from primary to specialized care, and highly specialized tertiary care, exploring their influence on patients' HRQoL and functioning. A schematic representation of the topics covered within this thesis in relation to the tasks and challenges of different sectors in the care of patients with VDB is provided in Figure 1.

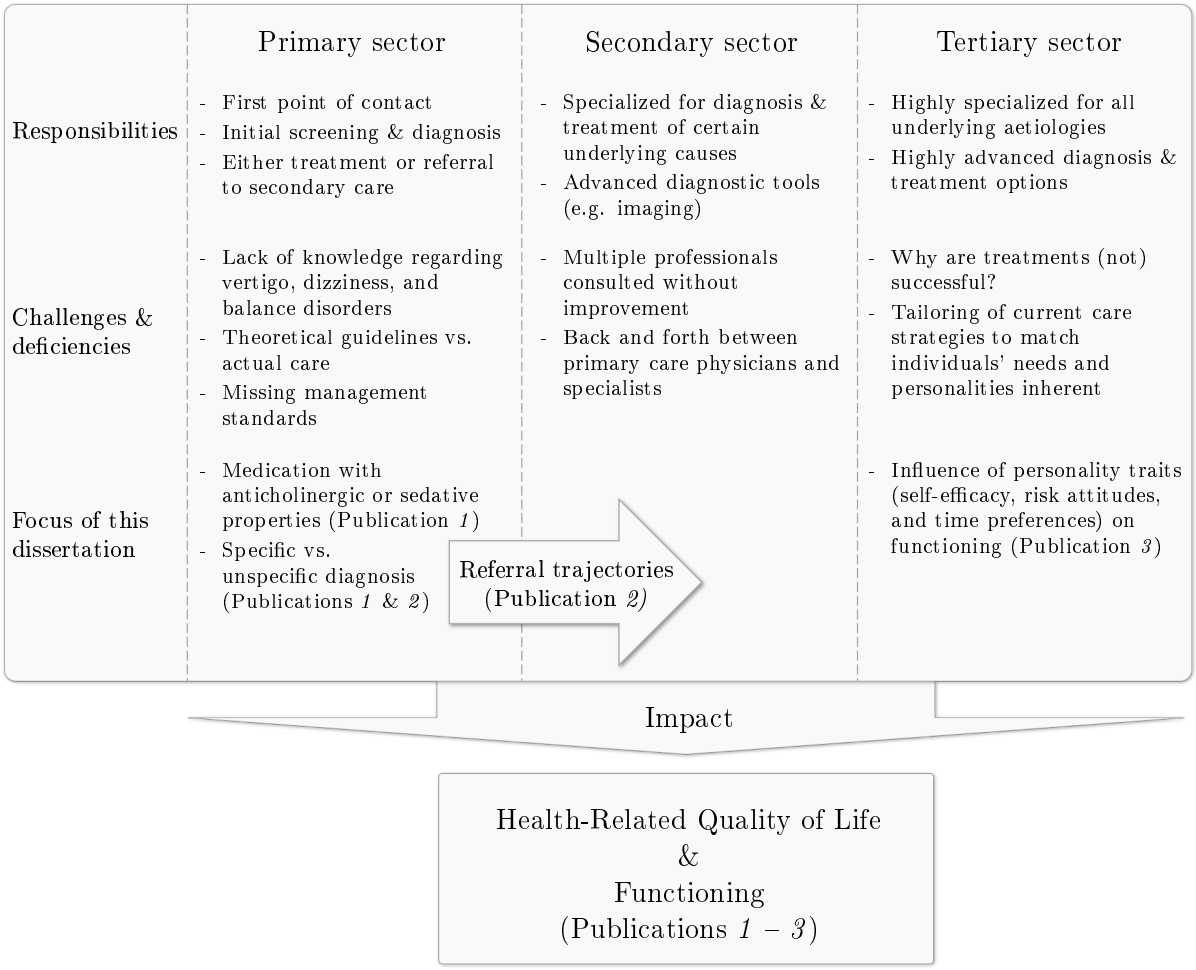

Figure 1: Integration of this doctoral thesis into the tasks and challenges of different care sectors in the care of older adults with vertigo, dizziness, and balance problems in Germany.

2.2 Exploring challenges and deficiencies in addressing vertigo, dizziness, and balance problems across different care sectors in the German healthcare system

2.2.1 Care responsibilities across diverse sectors in the German healthcare system with regard to vertigo, dizziness, and balance problems

The German healthcare system comprises primary, secondary, and tertiary care sectors, each taking distinct roles in addressing the specific needs of patients [33]. Being the first point of contact for the majority of patients with VDB [34, 35], primary care physicians (PCPs) conduct initial assessments, history-taking, and basic diagnostic procedures. They provide essential

treatments, offer lifestyle recommendations, and prescribe remedies such as physiotherapy or occupational therapy. If needed, they refer patients to secondary care specialists for more in-depth evaluation. Within secondary care, neurologists and ear, nose, and throat (ENT) specialists are the most often consulted specialists for VDB [36]. They conduct detailed examinations [37], utilize advanced diagnostic tools (such as imaging techniques), and offer specialized treatments. This may include medical management, vestibular rehabilitation, or further referrals to tertiary care if even more specialized diagnostics and care are warranted to address complex cases. Tertiary care involves acute care hospitals with specialized, often interdisciplinary, departments. Such hospitals provide highly specialized and comprehensive diagnostic services, advanced treatments, and surgical interventions if needed.

2.2.2 Medication challenges in primary care: Addressing inappropriate prescriptions of medication with anticholinergic or sedative properties

As stated above, most patients with VDB are initially seen by PCPs [34], making them central in the early identification and management of these conditions. PCPs face the task to form preliminary assessments of the affected systems, identifying a diagnosis or a spectrum of potential diagnoses. Subsequent to these initial evaluations, they need to distinguish between cases manageable within the realm of primary care and those that require referrals to specialized care. This can easily become challenging, since PCPs are often lacking neuro-otological expertise for the diagnosis and management of vestibular disorders. It therefore is of little surprise that there is a substantial shortfall in providing optimal diagnosis and therapy within the primary care system [30].

A striking example for this shortfall is the ongoing prescription of inappropriate medications, provoking or intensifying VDB, despite the presence of guidelines explicitly designed to avert such issues. Recognizing that VDB can result from unintended side effects of standard medication [38, 39], a comprehensive review of the patient's current medication plan to identify potentially inadequate medication becomes imperative. When feasible, medication inducing VDB should be substituted with better-tolerated alternatives. Although guidelines for the prescription and review of potentially inappropriate medication as well as potential alternatives are available [38, 40], studies indicate a persistent prevalence of inadequate medication among older VDB patients [41, 42].

Previous research on inappropriate medication highlights the importance of pharmaceuticals with anticholinergic or sedative (AS) features, given their potential to induce dizziness, delirium, blurred vision, and confusion [43, 44]. AS medication may exacerbate symptoms and hinder the performance of daily activities, contributing to the functional impairment caused by VDB. The general correlation between AS medication and functional impairment is well-documented [45, 46]. However, the specific role of these medications in persons already affected by VDB had not been sufficiently investigated until the initiation of this doctoral project.

2.2.3 Referral challenges from primary to specialized care: Trajectories, determinants, and impact on patient-relevant outcomes

In many cases, necessary diagnostic or therapy options exceed the scope and expertise of primary care, necessitating referral to more specialized secondary care. During this transition, PCPs must once again rely on their initial evaluations to identify the most suitable specialists. Ideally, referrals from PCP to specialists should be informed by the root cause, utilizing the tailored expertise of the specialists relevant to the particular disease [47, 48]. However, PCPs often face barriers in referring older patients with VDB [49]. These challenges originate from a lack of familiarity with specific diagnostic tests, leading to frequent under- and misdiagnosis [50] and uncertainty among PCPs. Time constraints and a healthcare landscape marked by fragmentation and the absence of standardized management guidelines in many areas further complicate referral decisions [49]. Consequently, it is not uncommon for patients to seek consultation from multiple healthcare professionals and still remain without a definitive diagnosis [30, 32, 50], ultimately resulting in non-targeted and potentially ineffective treatment [50].

Prior to the commencement of this doctoral project, there was a notable lack of knowledge about referral trajectories from the patients' perspective, i.e. the chronology and combination in which a patient is referred to specialists by the PCP. This aspect is crucial because relying solely on the information, whether a physician was seen or counting the number consultations may be overly simplistic. In reality, patients often consult physicians in specific combinations and follow a chronological order in their consultations. Both aspects could impact patient-relevant outcomes and should therefore be acknowledged in research.

As a result of the outlined challenges and barriers, the determinants influencing referral trajectories in VDB appear to extend beyond mere medical necessity and are likely influenced by additional factors. Investigations into other medical indications suggest that determinants for referral decisions can be broadly categorized into three dimensions: patient characteristics (gender, age, education) [51, 52], PCP experience [53], and variations in the local healthcare system, such as the availability of certain specialists within a specific area [54]. Nevertheless, the comprehension of these determinants in patients with VDB remained limited before the beginning of this doctoral project.

Lastly, referral trajectories may play an important role in achieving improvement in HRQoL and functioning. While improvement may indicate an effective referral process, the absence of such improvement may signal potential issues within the referral process.

This project assesses transitions from primary to specialized care by focusing on patient trajectories. It combines the identification of current referral patterns with an examination of predictors and an evaluation of their impact on patient-relevant outcomes. This approach aims to provide a more accurate representation of the complexities of healthcare reality.

2.2.4 Exploring the impact of personality traits on functional restrictions imposed by vertigo, dizziness, and balance problems in highly specialized tertiary care

In cases requiring highly specialized diagnostics and treatment, individuals with VDB are frequently referred to highly specialized tertiary care centers. Patients seeking assistance in these institutions often present with more complex manifestations of VDB, repeatedly coupled with an extensive medical backstory.

While evidence-based interdisciplinary assessments and treatments benefit many patients [23–25], the effectiveness of such interventions varies among individuals. The underlying reasons for this variability remain insufficiently examined. Moreover, it becomes evident that therapeutic interventions achieve optimal effectiveness when customized to the unique needs of each individual [55].

Gaining a more profound insight into how personality traits of patients with VDB impact both functional restrictions and therapeutic success has the potential to enhance and advance therapeutic strategies. Previous research indicates that specific personality structures may render individuals more susceptible to VDB and its consequences [56, 57]. In addition, there is evidence indicating variations in coping strategies among individuals dealing with the functional restrictions linked to VDB [58]. Personality traits could further influence, how patients approach challenges within their care process, similar to observations made in chronic disease management [59]. Consequently, it is plausible that personality traits could predict treatment outcomes to some extent. Nonetheless, evidence on these aspects had remained sparse prior to the start of this doctoral project.

Exploring the decision-making processes of individuals facing VDB-related challenges may be enhanced by integrating insights from the field of behavioral economics (BE). This interdisciplinary branch aims to comprehend why and how individuals make decisions by combining concepts from economics and psychology [60]. BE concepts acknowledge deviations from expected rationality in coping with diseases, attributing them to underlying personality traits. These traits include, but are not limited to, the patient's confidence in overcoming health challenges, individual risk attitudes, and time preferences.

Self-efficacy, as defined by Bandura (1997), refers to an individual's belief in their capability to execute courses of action required to accomplish specific goals [61]. Risk attitudes in the health context relate to the level of risk-taking of individuals when making decisions that have the potential to influence their health [62]. Time preferences correspond to an evaluation of the present in relation to the future, when confronted with decisions involving immediate health advantages or disadvantages and potential future consequences [63–65]. All three traits are widely acknowledged determinants of health behavior [59, 62, 66, 67]. Their specific role in people with VDB, however, had only been investigated in a limited number of individual studies [68, 69] before the initiation of this doctoral project. Gaining a more profound understanding on the impact of these personality traits may contribute to a better comprehension and prediction of functional restrictions in patients with VDB.

2.2.5 Research questions and objectives

This doctoral project aimed to answer the following research questions:

1. Primary care: Is exposure to AS medication associated with reduced generic and vertigo-specific functioning in older adults with VDB?
   In particular, our objectives were to investigate:
   1.1 Whether exposure to AS medication is associated with lower generic and verti-go-specific functioning during the first assessment.
   1.2 Whether exposure to AS medication impairs the development of generic and vertigo-specific functioning over the course of twelve months.
2. Transition to specialized care: What factors determine current referral trajectories of older patients with VDB from primary care to specialized care and how do these trajectories affect patients' functioning and HRQoL?
   Our specific aims were to:
   2.1 Identify and characterize current clusters of similar referral trajectories.
   2.2 Explore disease-related and other determinants influencing referral trajectories.
   2.3 Examine the impact of referral trajectories on HRQoL and vertigo-specific functioning.
3. Specialized tertiary care: Are self-efficacy, risk attitudes, and time preferences associated with the functional status of older patients with VDB before and after treatment in a specialized tertiary care center?
   Specifically, we wanted to investigate:
   3.1 Whether self-efficacy, risk attitudes, and time preferences are associated with the functional status of older adults with VDB during their initial visit, i.e. before the commencement of the assessment and treatment at the specialized tertiary care center.
   3.2 Whether self-efficacy, risk attitudes, and time preferences serve as predictors for functioning three months after the initial visit to the specialized tertiary care center.

2.2.6 Overview of the scientific publications comprised in this doctoral thesis

This doctoral thesis encompasses three scientific articles that were published in international peer-reviewed journals:

1. Katzenberger B, Koller D, Strobl R, Kisch R, Sanftenberg L, Voigt K, Grill E (2023). Exposure to anticholinergic and sedative medication is associated with impaired functioning in older people with vertigo, dizziness and balance disorders – Results from the longitudinal multicenter study MobilE-TRA. Front Pharmacol 14: 1136757. DOI: 10.3389/fphar.2023.1136757. (Referred to as 'Publication 1' or 'First publication' in the subsequent text)

2. Katzenberger B, Koller D, Strobl R, Kisch R, Sanftenberg L, Voigt K, Grill E (2022). 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 269(12): 6211-21. DOI: 10.1007/s00415-022-11060-8. (Referred to as 'Publication 2' or 'Second publication' in the subsequent text)

3. Katzenberger B, Fuchs S, Schwettmann L, Strobl R, Hauser A, Koller D, Grill E (2023). Association of self-efficacy, risk attitudes, and time preferences with functioning in older patients with vertigo, dizziness, and balance disorders in a tertiary care setting – Results from the MobilE-TRA2 cohort. Front Neurol 14: 1316081. DOI: 10.3389/fneur.2023.1316081 (Referred to as 'Publication 3' or 'Third publication' in the subsequent text)

2.3 Methods

2.3.1 Data sources

Data for this doctoral thesis were derived from the research projects MobilE-TRA ('Patient trajectories and their impact on mobility, social participation and quality of life in patients with vertigo/ dizziness/balance disorders and osteoarthritis') [70] and MobilE-TRA 2 ('Behavioural and patient-individual determinants of quality of life, functioning and physical activity in older adults') [71]. Both research projects are part of the project 'Munich Network Health Care Research – MobilE-Net' [72]. All participants in both studies provided written informed consent.

2.3.1.1 MobilE-TRA

MobilE-TRA is a longitudinal study conducted from September 2017 to October 2019 across 19 primary care practices in Bavaria and Saxony. Its primary objective was to assess the current state of care from the patient perspective in individuals with VDB and osteoarthritis aged 65 and older, with a specific emphasis on treatment trajectories and their impact on patient-relevant outcomes.

Given the focus of this PhD project on VDB, a sub-sample of 158 participants with VDB symptoms was utilized. Appropriate candidates were identified by examining the patient databases of participating PCPs, focusing on pre-selected ICD-10 codes linked to VDB. The relevant codes comprised: R42, A88.1, E53.8, F45.8, G11.8, G43.1, G45.0, G62, G63, H55, H83.0–2, I95.1, and N95.1. Data collection involved a baseline assessment and two subsequent assessments at six and twelve months after the individual baseline dates. There was no lost to follow-up for the patients with VDB. Participants completed self-administered health questionnaires, addressing questions regarding generic and disease-specific patient-relevant outcomes, including HRQoL and functioning, healthcare utilization (including visited physicians and medication intake), and sociodemographic information. Complementing this information, participating PCPs filled out a modified version of the Questionnaire of Chronic Illness Care in Primary Care [73]. They further provided information on underlying VDB diagnoses, comorbidities, and diagnostic and therapeutic procedures in an additional self-developed baseline questionnaire.

Further insights into the study design, study population, and data collection procedures are given elsewhere [70]. Ethics approval was granted by the Ethics Committee of the Ludwig-Maximilians-Universität München (#17-443) and the Ethics Committee of the Dresden University of Technology (#E365092017).

2.3.1.2 MobilE-TRA 2

MobilE-TRA 2 is a prospective cohort study conducted at the Munich University Hospital from December 2020 until June 2023. Following the initial MobilE-TRA study, MobilE-TRA 2 retained its focus on individuals with VDB and osteoarthritis. Based on insights from behavioral economics, specifically exploring self-efficacy, risk preferences, and time preferences, the study aimed to understand the determinants of functioning and HRQoL post-discharge from highly specialized care.

In the context of this PhD project, the analysis involved 337 patients aged 60 and older with VDB, who sought interdisciplinary assessment at the German Center for Vertigo and Balance Disorders (DSGZ). The PhD project focused on the baseline assessment and the initial follow-up, three months post-individual baseline assessment. Participants completed self-administered health questionnaires during their stay at the care center or dispatched them via mail. These questionnaires encompassed questions related to HRQoL and functioning, personality traits, and sociodemographic details. Complementing this information, information on the exact VDB diagnoses, sourced from medical discharge letters, were obtained via the prospective clinical patient registry DizzyReg of the DSGZ [74]. Patients were mailed two additional questionnaires to assess their functional restrictions three and twelve months after their individual baseline assessment.

A more comprehensive description of the study is given elsewhere [71]. The MobilE-TRA-2 study obtained ethics approval from the Ethics Committee at the medical faculty of LMU Munich (#20-727).

2.3.2 Measures

2.3.2.1 Exposure to medication with anticholinergic or sedative properties (Publication 1)

In the first publication, the drug burden index (DBI), which was developed to predict adverse outcomes related to medication use in older adults [75], was utilized to assess exposure to AS medication. A DBI index greater than zero implies an exposure to AS medication, with higher values indicating a greater AS burden. Medication intake as indicated by participants' self-report was compared to a list of AS medication, which was compiled based on previous work [41, 42].

$$DBI = \sum_{i=1}^{n} \frac{D_i}{\delta + D_i} \tag{1}$$

We computed the DBI (cf. equation 1) for each patient by dividing the prescribed daily dose (D) of an individual AS medication (i) by the sum of D and the defined daily dose (δ) in accordance with the guidelines of the Federal Institute for Drugs and Medical Devices [76] for

that specific AS medication. The cumulative DBI for each patient was obtained by summing the computed single burdens for all AS medications taken by that individual.

To address the identified zero-inflation in the DBI within the study sample of the first MobilE-TRA study, we categorized AS medication exposure into no exposure (DBI = 0), low exposure ($0 <$ DBI <1), and high exposure (DBI ≥ 1) based on established thresholds [75]. For statistical considerations, we additionally dichotomized AS exposure status into being present (at least one AS medication) or absent.

2.3.2.2 Referrals (Publication 2)

A referral trajectory in this project was defined as a chronological sequence of unique combinations of consulted practitioners. The required information on consulted physicians was obtained from participants, who were provided a standardized list of healthcare professionals as part of the Questionnaire for Health-Related Resource Use in an Elderly Population - FIMA [77]. Our analysis focused on consultations of the PCP, neurologists, or ENT specialists, given their prominence as the most frequently consulted physicians for individuals with VDB [36].

2.3.2.3 Personality traits (Publication 3)

The assessment of self-efficacy was accomplished by utilizing the General Self-Efficacy Short Scale, which consists of three items [78]. Participants stated their level of confidence on a five-point liker scale in (1) depending on their skills in challenging situations, (2) independently managing most issues effectively, and (3) successfully tackling demanding and intricate tasks. The self-efficacy score used for the analysis was calculated as the mean of these three ratings, ranging from 1 (very low self-efficacy) to 5 (very high self-efficacy). Risk attitudes in health-related topics were rated on an 11-point scale, varying between 0 (no risk taking at all) to 10 (very willed to take risks) [62]. Time preferences were assessed through two items: one measuring the willingness to delay a reward for a greater benefit in the future [65], and another capturing the patients' affirmation regarding their sole focus on the present and their belief that things will resolve themselves in the future [63].

2.3.2.4 Health-related quality of life and functioning (Publications 1 – 3)

To assess the influence of the selected topics in healthcare of older adults with VDB on patient-relevant outcomes, this project focused on HRQoL as well as generic and vertigo-specific functioning.

HRQoL, utilized in the second publication, was measured using the visual analog scale (VAS), a component of the EuroQol Five-Dimensional Five-Level Questionnaire [79]. The VAS allows participants to self-rate their overall health on a scale from 0 to 100 by marking a point between worst and best imaginable health states. The distance from 0 to the marked point is converted into a quantitative score, providing a numerical representation of the respondent's subjective health status with higher values indicating better health.

The first publication assessed generic patient-reported functioning by employing the German version of the Health Assessment Questionnaire Disability Index (HAQ-DI) [80, 81]. This questionnaire captures patients' challenges in carrying out activities of daily living across eight

domains (dressing and grooming, arising, eating, walking, hygiene, reach, grip, and common daily activities). Averaging the highest scores within each domain results in the functional disability index (range = 0 – 3), with higher values signifying more pronounced difficulties.

All three publications focused on vertigo-specific functioning, specifically addressing the impairment in everyday activities resulting from VDB. Publication one and two utilized the Vestibular Activities and Participation questionnaire (VAP) [82]. The VAP consists of two independent scales, with higher scores reflecting lower functioning. One scale (range = 0- 23) assesses difficulties in performing activities due to their predisposition to provoke symptoms, while the second scale (range = 0- 20) quantified the impact on activities related to mobility. In the third publication, functional restrictions due to VDB were assessed using the German translation of the Dizziness Handicap Inventory (DHI) [13, 83]. This commonly used instrument incorporates 25 items to assess functional impairment, categorized into three domains (functional, physical, and emotional), along with a total score (range 0 – 100). Higher scores indicate greater impairments in everyday activities.

2.3.2.5 Diagnosis of vertigo, dizziness, and balance problems (Publications 1 – 3)

In the initial MobilE-TRA study [70], serving as the data source for publications one and two, VDB diagnoses were reported by the PCP during baseline assessment. To align with current classifications [2], these diagnoses were categorized based on the reported cause of VDB. Diagnoses were labeled 'not specified' when the PCP did not provide additional details within the questionnaire. For subsequent analyses, the VDB diagnoses were grouped into a binary variable: 'specific' VDB included diagnoses with any specific cause (vestibular vertigo, central vertigo, cardiovascular problems, and psychogenic dizziness), while 'unspecific' VDB comprised cases with no specific diagnostic decision.

Diagnoses for the third publication were retrieved from medical discharge letters at the tertiary care center and were established through a thorough neurootological examination conducted at the DSGZ, aligning with current guidelines [84–89]. For statistical considerations, less frequent diagnoses were summarized under the category 'Other'. In instances where the experts at the DSGZ couldn't identify a single primary cause, patients were classified as having multifactorial VDB.

2.3.3 Statistical methods

In the first publication, unadjusted summary statistics were implied to compare differences regarding diagnoses, patient characteristics, and generic as well as vertigo-specific functioning depending on AS exposure. Group comparisons utilized the Kruskal-Wallis test for continuous variables and Fisher's exact test for categorical variables. A total of three linear mixed models were then computed to examine the association between baseline AS medication exposure (dichotomized DBI) and generic (HAQ-DI) as well as vertigo-specific (VAP Scales one and two) functioning over time. An interaction term consisting of the dichotomized DBI and time was added to each model to evaluate the effect of baseline AS exposure on the development of functional restrictions over time.

In the second publication, we employed a state sequence analysis (SSA) to identify clusters of similar referral trajectories from PCP to specialists [90–92], using a three-steps-approach. A workflow pertaining to the application of the SSA is illustrated in Figure 2. In a first step, we constructed individual referral trajectories using patients' self-reported information about visited physicians for all three assessments. Subsequently, we calculated the dissimilarity between these individual trajectories, representing the least amount of alterations required to convert one trajectory into another, through the application of optimal matching [90]. Utilizing the computed dissimilarities of step two, the final step encompassed the identification of clusters featuring similar referral trajectories, achieved through a partitioning around medoids algorithm [93]. Determination of the number of clusters followed the optimization of two quality criteria: Hubert's C index to assess the disparity between the obtained clustering and the theoretically optimal clustering and the weighted average silhouette width for overall cluster consistency. Additional details regarding this methodology can be found elsewhere [92, 93].

After identifying the clusters, the next step was to investigate possible determinants of cluster membership. For this purpose, multinomial regression models were calculated on the basis of the data from the baseline assessment. We incorporated the VDB diagnosis and present comorbidities to assess whether referral trajectories were predicted by the medical necessity. Based on our considerations that referral trajectories might be influenced by additional factors, we further incorporated patient characteristic (gender, age, education), the experience of the PCP, and the study location into the model. Ultimately, longitudinal linear mixed models were utilized to investigate the impact of the clusters on HRQoL and functional impairment. Separate regression models were formulated for the VAS and for each of the two scales of the VAP. Two interaction terms were integrated into each model: The first term involved time and clusters, aiming to evaluate whether changes in HRQoL and functional status over time varied among clusters. The second interaction between the VDB diagnosis and time was included to examine potential deviations over time in patients with specific and unspecific VDB diagnoses.

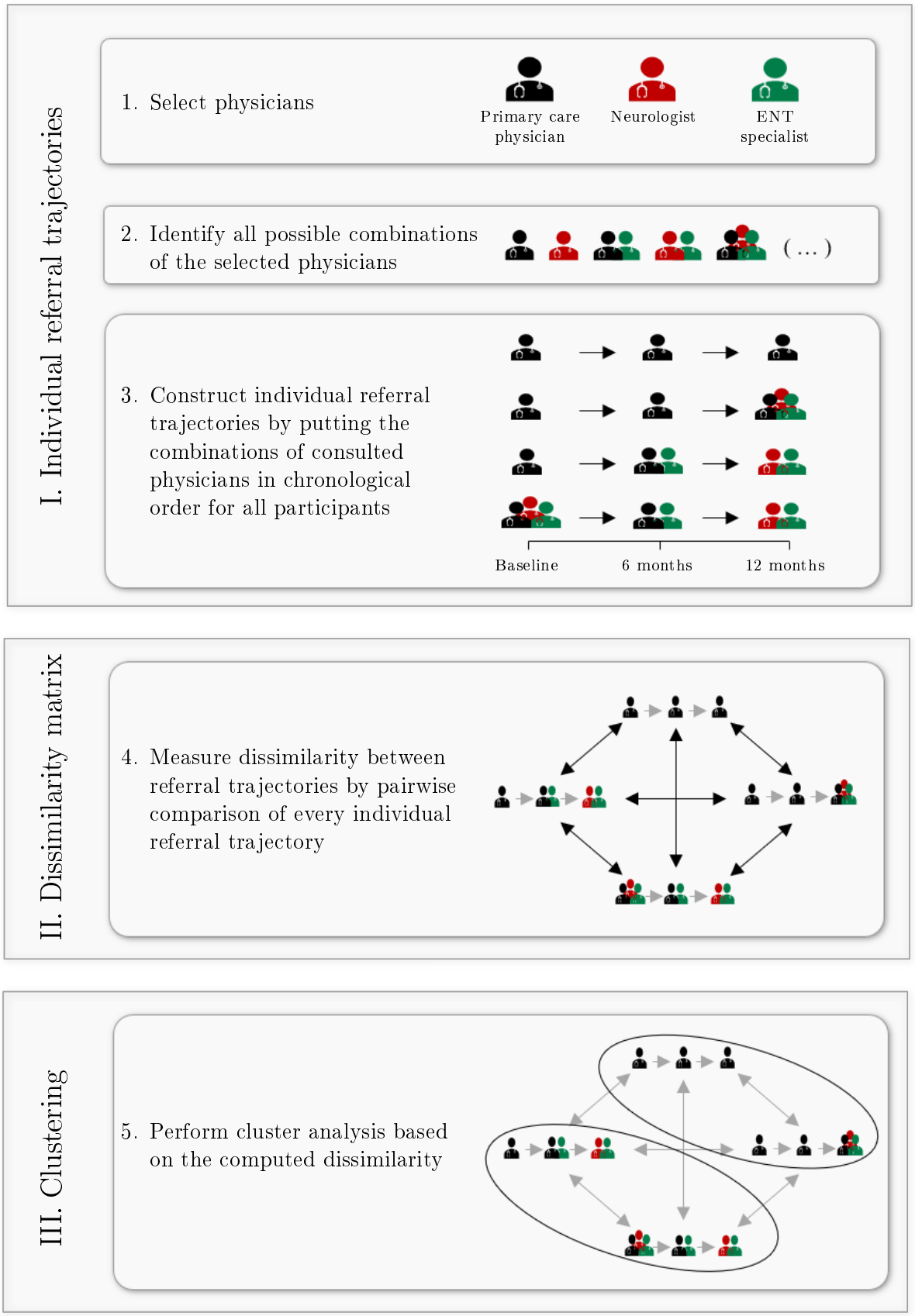

Figure 2: Workflow illustration of the state sequence analysis used in publication 2 featuring four exemplary trajectories.

For the third publication, we computed summary statistics for the entire sample and each VDB diagnosis to identify potential differences in observed variables among different VDB diagnoses. Linear mixed models were employed to explore the association between personality traits and functional impairment. Four models were established, with one dedicated to estimating overall functioning (overall DHI score) and individual models for each of the three sub-scales (functional, physical, and emotional) of the DHI. Within every model, simultaneous integration of all three personality traits was undertaken. This facilitated a precise estimation of the influence of each personality trait while accounting for the effects of the two remaining traits. In addition, three interaction terms, individually linking each of the three personality traits to time, were incorporated into all models. This was done to examine, whether the personality traits exhibited by the patients during their initial visit to the tertiary care center held predictive value for changes in functioning over the next three months.

Covariate selection for publications two and three was done using directed acyclic graphs (DAGs). Utilizing DAGs permitted the determination of the minimal adjustment set essential for controlling potential confounding, while simultaneously avoiding collider bias or over-adjustment [94]. Each DAG was constructed through a comprehensive literature review, supplemented by expert knowledge of the study team. DAGitty, a browser-based platform dedicated to constructing, editing, and analyzing causal models, was employed for the construction of the DAGs [95].

2.4 Main results

2.4.1 Exposure to medication with anticholinergic or sedative properties reduces functioning (Publication 1)

Adjusted for covariates, patients exposed to AS medication at baseline exhibited a significant increase of disability of 0.4 on the HAQ-DI scale (95%-CI [0.18; 0.61]) compared to those without exposure. AS exposure status explained nine percent of the overall variability in restrictions to generic functioning found in the sample.

Furthermore, AS medication at baseline was associated with more severe effects of VDB on activities provoking vertigo or dizziness, with an increase of 2.47 points (95%-CI [0.92; 4.02]) on the first VAP Scale and increased impairment on mobility-related activities by 3.74 points (95%-CI [2.23; 5.24]), assessed by the second VAP Scale. This baseline exposure contributed to twelve percent of the total variance in vertigo-related activity difficulties and seventeen percent in immediate mobility consequences. In contrast, the analyses provided no indication that AS exposure status had any significant influence on the development of functional limitations over time.

2.4.2 Referrals trajectories from primary to special care impact health-related quality of life (Publication 2)

We identified three distinct clusters each representing similar referral trajectories. The majority of patients in our study were managed by their PCP without referrals to either of the two specialists considered in the analysis (cluster one). The remaining two clusters were characterized

by a combination of PCP and neurologist, and PCP and ENT specialist, respectively.

Comorbidities and regional healthcare characteristics influenced these three referral patterns in our study. Patients with neurological comorbidities had approximately three times higher odds to consult both PCPs and neurologists (OR = 3.22, 95%-CI [1.003; 10.327]) rather than exclusively relying on PCPs. Conversely, individuals from Saxony showed a much lower chance of being in the PCP and neurologist cluster (OR = 0.08, 95%-CI [0.013; 0.419]), indicating less frequent referrals to neurologists. The present VDB diagnosis, on the other hand, had no influence on the referral pathway.

Our study provided evidence that patient-reported HRQoL was influenced by referral trajectories. At the beginning of the study, patients consulting both their primary care physician and a neurologist showed approximately 12 points lower HRQoL on the VAS scale of the EQ-5D (95%-CI [-21.27; -4.17]). Over the course of the follow-up, the HRQoL of these patients improved significantly better than that of the other patients, approaching the levels observed in the other patient clusters after 12 months. While patients in the PCP and neurologist referral cluster also displayed significantly worse functional restrictions during the baseline assessment, we found no evidence indicating a superior development in functioning over time compared to other referral trajectories identified in this study.

2.4.3 Unspecific diagnosis of vertigo, dizziness, and balance problems impairs functioning (Publications 1 and 2)

In a primary care setting, patients with an unspecific or unspecified diagnosis had more severe functional restrictions, both in generic and vertigo-specific aspects, compared to those with any specific diagnosis of VDB.

2.4.4 Personality traits influence functioning (Publication 3)

Patients' willingness to delay gratification significantly varied between VDB diagnoses, with those with functional vertigo showing the lowest willingness to postpone a reward. However, self-efficacy and willingness to take risks did not differ significantly among different VDB diagnoses. Patients overall showed a subtle yet statistically significant improvement in their functional restrictions over the course of the three-months follow-up period.

Patients with higher self-efficacy reported less functional restrictions at baseline with an estimate of -3.82 for the overall DHI score (95%-CI [-6.56; -1.08]). Higher self-efficacy also leads to greater reduction in overall functional restrictions after three months with an estimate of -4.21 points (95%-CI [-6.57; -1.84]). The extend of functional limitations, measured three months after the initial visit to the tertiary care center, thus was found to be predicted by the self-efficacy of the patients at the time of that visit. Although patients who stated a high disposition for risk-taking reported enhanced overall functioning during their initial visit, their rate of improvement over time did not differ from the rate of risk-averse patients. Time preferences did not exhibit a significant association with baseline functioning or change over time.

2.5 Strengths and limitations

This doctoral thesis has three major strengths: A consistently high methodological rigor and quality throughout the entire research process, the application of innovative analysis strategies, and the consideration of the expected frailty of the interviewees during the survey process.

Achieving methodological rigor involved using validated instruments wherever available and implementing rigorous quality controls during data collection and processing. To ensure unbiased effects estimation, DAGs were applied in the first and third publication, avoiding issues like over-adjustment or collider bias [94]. Utilizing DAGitty [95] in this context facilitated real-time retracing of modifications in the implied causality structure, enhancing both transparency and clarity in the analysis. The hierarchical and correlated nature of the data were addressed through the application of mixed-effect models [96] for all three publications. Two sensitivity analyses were incorporated in order to scrutinize decisions within the research process that could potentially influence the reported findings. The first sensitivity analysis was computed within the first publication and provided an indication of a dose-response relationship between AS exposure and functional impairment. Another sensitivity analysis was conducted in the third publication to examine whether the exact method of assessment of time preferences influenced the observed associations. The results from this sensitivity analysis indicated that this was not the case.

A second strength is the application of the SSA in the first publication to identify, examine, and cluster referral trajectories. The application of SSA in health care research is still relatively new and had been limited to the evaluation of health insurance data before this project. Applying SSA enabled us to uncover and analyze referral patterns that consider combination of specialists and sequences in which they had been consulted [90–92]. This innovative approach offers a more realistic representation of care scenarios compared to traditional examination methods. This doctoral thesis has demonstrated that the application of SSA is feasible and useful in primary data.

Our study samples involved a considerable portion of frail participants, who might have been easily overwhelmed by extensive questionnaires and demanding tasks. The assessment thus had to be grounded in a set of straightforward yet validated questions to ensure accessibility and meaningful participation. The adaptation of survey instruments to such frailty is evident in the third publication, where the assessment of personality traits in a tertiary care setting involved using a small number of self-assessment questions instead of extensive choice experiments. This intended departure from the conventional approach was supported by the well-established success of preference modules utilizing straightforward questions, as demonstrated in previous studies [97]. Another proactive measure to reduce bias was the provision of the study team's contact information to all participants to address any uncertainties that they might encounter while filling out the questionnaires.

Some noteworthy limitations linked to this project have to be considered. Most of the gathered data rely on self-reported measures, introducing potential bias. For instance, the self-reported assessment of medication intake details might have led to an underestimation of the true AS burden due to incomplete or inaccurate entries. While we took measures to mitigate bias through the use of validated instruments and the implementation of rigorous quality

controls, we acknowledge that the presence of bias in our data cannot be entirely ruled out. Limitations in the number of physicians considered in referral trajectories due to methodological and interpretational considerations [92, 98] and the exploratory nature of SSA call for careful interpretation and future validation through future research. VDB diagnoses in publications one and two were directly provided by the PCPs and categorized to align with current classification standards [2]. However, some limitations remain with this approach. Research highlights the tendency for PCPs to frequently diagnose unspecific VDB in cases, were specific causes became identifiable in in subsequent examinations conducted at more specialized facilities [50]. It remained unclear whether and at what point the initial diagnoses were adapted during the follow-up period. Diagnoses for publication three were not affected by this, since they stem from a thorough neurootological examination conducted at the DSGZ, aligning with current guidelines and ensuring a high level of accuracy.

2.6 Contribution of this doctoral thesis and outlook

This doctoral thesis contributes to the current state of scientific knowledge concerning the deficiencies and opportunities in the provision of health care in older adults with VDB. It accomplishes this by addressing the use of medication with AS properties, examining referral patterns from primary to specialized care, and emphasizing the impact of personality traits on treatment success.

Our study revealed the persistent use of medications with AS properties in older adults experiencing an acute episode of VDB in primary care, confirming previous findings [41, 42]. AS medication contributed to overall functional impairment, aligning with trends observed in various other cohorts [45, 46]. In addition, this project extends current knowledge by demonstrating that AS medication usage also aggravates the impact of VDB on daily activities, social participation, and mobility. Our results support the recommendation for thorough monitoring and substitution of medication with AS properties in older adults exhibiting VDB symptoms. The utilization of AS medication for symptomatic therapy in VDB should be confined to the first phase of the disease, with particular care exercised when administered to the older population [28].

Three referral patterns from primary to specialized care were identified within this project: PCP only, PCP and neurologist, and PCP and ENT specialist. PCPs were the primary care provider, aligning with previous findings [36, 99, 100]. While comorbidities predicted referrals, no evidence indicated that underlying VDB diagnoses were decisive for specialist referrals. The predominant perception seems to be that VDB in older adults can be effectively managed within primary care. This finding contradicts the rationale for essential specialist referrals in specific VDB cases, where specialist expertise is deemed necessary [47, 48]. Our findings further suggest that within a challenging diagnostic and treatment landscape, referral patterns for VDB patients are significantly shaped by the local healthcare environment, aligning with observations in other medical contexts [54]. Referral trajectories directly impacted patient-reported HRQoL. Patients consulting both PCP and neurologist initially had lower HRQoL during the first observation but enhanced over time, indicating effective management of the underlying neurological condition. Nevertheless, this effect did not extend to VDB-specific functioning, underscoring the ongoing

challenge of achieving adequate management for VDB [30, 49]. The work on referral from primary to specialized care conducted within this doctoral thesis underlines that overcoming reported barriers and establishing routines among PCPs for VDB diagnosis and treatment is crucial for improving current care strategies.

In this doctoral project, patients in primary care diagnosed with unspecific VDB faced a higher risk of unfavorable functional development. The complexity of VDB in older individuals, often characterized by multiple contributing factors [6, 8], leads to ambiguous symptoms, resulting in an excess of unspecific diagnoses [101]. This ambiguity may result in potentially ineffective treatments [50], causing and explaining the reduced functioning found in this project.

This doctoral thesis enhances the current understanding of how specific personality traits impact functioning in older VDB patients. Higher self-efficacy was associated with elevated functioning levels upon first clinic presentation and independently predicted better recovery three months post-initial assessment. These results are consistent with earlier studies that highlight the beneficial impact of self-efficacy on health results, evident in both VDB [68, 69] and broader contexts [59, 102, 103]. Our findings suggest that individuals with high self-efficacy likely have already established effective coping mechanisms before their visit to the tertiary care center, reducing the impact of VDB on functioning. Our results indicate a dual role of self-efficacy in VDB diagnostics, serving both as a necessary condition and a driving force for improvement. Patients with high self-efficacy displayed notable enhancements, whereas individuals with low self-efficacy showed a decline in functioning over time. Similar to studies on self-efficacy in chronic diseases [59], individuals with high self-efficacy in VDB may be more skillful at handling treatment-related challenges, such as assuming additional responsibilities and acquiring new skills. In light of these results, empowering patients to develop confidence in actively participating in their treatment should be a cornerstone of future strategies. Patients with a greater tendency to take risks demonstrated lower functional restrictions during their initial visit to the care center. Individuals with VDB routinely encounter risk assessments associated with daily activities, involving specific actions or environments that may worsen symptoms [13] and increase the risk of falls [18, 104]. Patients must carefully evaluate their engagement in health-related activities, balancing the potential risks with the benefits of maintaining overall functioning. Increased inclination for risk-taking may lead to more active engagement in activities fostering adaptation and improved functioning. These findings should not be misconstrued as an endorsement of promoting risk-taking behavior, considering the documented negative side effects in other studies [62, 66]. Future research should focus on identifying the underlying coping mechanisms of risk-prone individuals that help them to compensate for the impact of VDB symptoms and maintain their functioning.

In conclusion, this doctoral thesis underscores the substantial impact of AS medication on the functional status of older adults with VDB in primary care. These results call for a thorough review of current medication, identifying any contributors to VDB, and replacing them whenever feasible. PCPs remain the primary and often only source of treatment for the majority of older patients with VDB, irrespective of the underlying diagnosis. Referrals from primary to specialized care are influenced by comorbidities, but no evidence indicates that referrals are predicted by the underlying VDB diagnosis. The referral patterns identified within this project directly impacted the HRQoL of the patients. Unspecific VDB diagnoses lead to more

severe functional limitations, most likely caused by non-targeted and therefore ineffective care approaches. These findings are presumably a consequence of well-known barriers within primary care for patients with VDB. Addressing and reducing these barriers becomes imperative, as they lead to deviations from optimal care, harming the patients in the process. Establishing evidence-based, standardized care pathways stands out as a promising approach to address this challenge. Furthermore, this PhD project emphasizes the significance of patients' personal traits for therapy success, with self-efficacy playing a key role. Empowering individuals through clinical interventions and effective communication to actively engage in their treatment shows promise for improving overall well-being. The implementation of such measures should be accompanied by further research to ensure that the needs of patients with VDB are adequately addressed with the goal of ensuring and optimizing their beneficial effects.

3 Publication I

Exposure to anticholinergic and sedative medication is associated with impaired functioning in older people with vertigo, dizziness, and balance disorders — Results from the longitudinal multicenter study MobilE-TRA

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Exposure to anticholinergic and sedative medication is associated with impaired functioning in older people with vertigo, dizziness and balance disorders—Results from the longitudinal multicenter study MobilE-TRA

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Introduction: Anticholinergic and sedative medication is prescribed for various conditions in older patients. While the general association between anticholinergic and sedative medication and impaired functioning is well established, its specific role in older individuals with vertigo, dizziness, and balance disorders (VDB) is still incompletely understood. The objective of this study was to investigate, whether an exposure to anticholinergic and sedative medication is associated with lower generic and lower vertigo-specific functioning in older patients with VDB.

Methods: Data originates from the longitudinal multicenter study MobilE-TRA with two follow-ups, conducted from 2017 to 2019 in two German federal states. Exposure to anticholinergic and sedative medication was quantified using the drug burden index (DBI). Generic functioning was assessed by the Health Assessment Questionnaire Disability Index, appraising the amount of difficulties in performing activities of daily living (ADL). Vertigo-specific functioning was measured using the Vestibular Activities and Participation (VAP) questionnaire, assessing patient-reported functioning regarding activities of daily living that are difficult to perform because of their propensity to provoke VDB (Scale 1) as well as immediate consequences of VDB on activities and participation related to mobility (Scale 2). Longitudinal linear mixed models were applied to assess the association of exposure to anticholinergic and sedative medication at baseline and the level of generic and vertigo-specific functioning status over time.

Results: An overall of 19 (7 from Bavaria) primary care physicians (mean age = 54 years, 29% female) recruited 158 (59% from Bavaria) patients with VDB (median age = 78 years, 70% female). Anticholinergic and sedative medication at baseline was present in 56 (35%) patients. An exposure to anticholinergic and sedative medication at baseline was significantly associated with lower generic functioning

[Beta = 0.40, 95%-CI (0.18; 0.61)] and lower vertigo-specific functioning [VAP Scale 1: Beta = 2.47, 95%-CI (0.92; 4.02)], and VAP Scale 2: Beta = 3.74, 95%-CI [2.23; 5.24]).

Conclusion: Our results highlight the importance of a close monitoring of anticholinergic and sedative medication use in older patients with VDB. When feasible, anticholinergic and sedative medication should be replaced by equivalent alternative therapies in order to potentially reduce the burden of VDB.

KEYWORDS

vertigo, dizziness, balance disorders, anticholinergic and sedative medications, drug burden index, functioning

1 Introduction

Vertigo, dizziness, and balance disorders (VDB) affect approximately 30% of the population beyond 60 years of age (Jönsson et al., 2004; Barin and Dodson, 2011), and up to 50% of those over 85 (Jönsson et al., 2004). A considerable percentage of older adults beyond 65 years with VDB experience severe impairment in their everyday life (van Vugt et al., 2020).

The reasons for VDB are often multifactorial. Distinct treatable vestibular disease entities, cardiovascular diseases or metabolic disorders may align with symptoms of the ageing of vestibular, proprioceptive or somatosensory systems.

In addition, VDB may be an unintended side effect of standard medication (Holt et al., 2010; Hedna et al., 2015; Muncie Jr et al., 2017). This is one of the reasons why a continuous medication review is recommended for older adults (Beuscart et al., 2021; Leitliniengruppe Hessen Deutsche Gesellschaft für Allgemeinmedizin und Familienmedizin, 2021). Medication that is causing VDB should be replaced by equivalent but better tolerated alternatives, whenever this is possible.

Of particular interest in this context is medication with anticholinergic and sedative (AS) effects. AS medication is prescribed for a multitude of indications, including urinary incontinence, sleep disturbances, mental illness, pain, cardiovascular diseases, and gastrointestinal disorders (Kouladjian et al., 2014). Certain anticholinergic medication (e.g., Scopolamine or Dimenhydrinate) and selected sedatives (e.g., Diazepam or Lorazepam) might also be prescribed as vestibular suppressants, i.e., drugs that reduce the subjective symptoms and intensity of vertigo as well as the nystagmus evoked by vestibular imbalance, in symptomatic therapy of VDB (Casani et al., 2021).

Previous research has shown that use of AS medication was higher in people with VDB than in the general population, especially in the old aged (Phillips et al., 2018; Phillips et al., 2019). This is of particular concern, since AS medication can lead to adverse effects such as confusion, blurred vision, delirium, and dizziness (Bell et al., 2012; Swain, 2020). Due to these adverse effects, a number of medication with AS properties such as selected antihistamines, urological spasmolytic agents, and benzodiazepines have been assessed as being potentially inappropriate for the general older population in Germany (Holt et al., 2010). The drug burden index (Hilmer et al., 2007) quantifies the combination of AS active substances with their respective dosage in a specific individual. Specifically in older adults, cognitive and physical impairment may be the consequence of a high AS drug burden (Landi et al., 2007; Cao et al., 2008; Hilmer et al., 2009; Koyama et al., 2014; Wouters et al., 2017; Byrne et al., 2019).

While the general association of AS medication and impaired functioning is well established, its specific role in individuals who are already affected by chronic or acute VDB is still incompletely understood.

It seems reasonable to hypothesize that use of AS medication considerably contributes to impaired functioning in two ways: First, it causes difficulties in performing activities of daily living (generic-functioning), such as hygiene, eating, grip, walking, and common daily activities. Furthermore, the use of AS medication could intensify the disease and therewith its direct impairment on the everyday life, especially on daily activities and social participation (vertigo-specific functioning).

The objective of this study thus was to investigate the impact of AS medication on both generic and vertigo-specific functioning in older adults with VDB.

2 Materials and methods

2.1 Study design, study population, and data collection procedures

Data for this research project was collected in the longitudinal multicenter study MobilE-TRA conducted in two German federal states (Bavaria and Saxony) from September 2017 until October 2019. A more detailed description of the study is given elsewhere (Kisch et al., 2018).

In short, patients aged 65 years and older were included if they had consulted their primary care physician (PCP) for an episode of VDB in the last quarter. The identification of suitable individuals was accomplished by approaching PCPs who were willing to participate and asking them to search their patient databases for the following ICD-10 codes associated with VDB: R42, A88.1, E53.8, F45.8, G11.8, G43.1, G45.0, G62, G63, H55, H83.0-2, I95.1, and N95.1. A detailed description of the diagnoses related to the ICD-10 codes is provided in the Supplementary Table S1. Additional inclusion criteria were a statutory health insurance, covering approximately 90% of the German population (The Federal Ministry of Health, 2020), as well as sufficient command of the German language.

Data collection consisted of three waves. The baseline assessment in between September 2017 and August 2018 comprised paper-based self-administered health questionnaires for both the patients and the

PCPs. For the two follow-ups 6 months and 12 months after individual baseline dates, a cover letter with instructions and the paper-based self-administered health questionnaire were sent *via* postal mail to the patients' home addresses. If no questionnaire was sent back within a month after the original follow-up invitation, a reminder was sent. In case of questions about the questionnaire, participants were able to contact the study team *via* e-mail or phone. There was no loss to follow-up between the study waves.

Ethics approval for MobiLE-TRA was obtained from the Ethics Committee of the Ludwig Maximilian University of Munich in Bavaria (#17-443) and the Ethics Committee of the Technical University Dresden in Saxony (#E365092017). Written informed consent was obtained from all participants. The study was performed in accordance with the Declaration of Helsinki principles.

2.2 Exposure to anticholinergic and sedative medication

Information on medication intake was obtained by the participants self-report during baseline assessment. Active pharmaceutical ingredients, the associated national identification number, and the prescribed daily dose for each medication taken within the last 7 days were recorded. The respective codes of the Anatomical Therapeutic Chemical Classification System (ATC-Codes) were matched to the national identification number.

AS medication was identified based on previous studies (Phillips et al., 2018; Phillips et al., 2019) using applicable published AS medication lists (Hilmer et al., 2007; Durán et al., 2013; Ailabouni et al., 2017; Wouters et al., 2017; Byrne et al., 2018; O'Connell et al., 2018) and potentially inappropriate AS medication from the German PRISCUS List (Holt et al., 2010), a collection of potentially inappropriate medication for older people. A detailed list of all AS medication and the related ATC-Codes present in this study sample is shown in Supplementary Table S2.

Since some AS medication might also be prescribed as vestibular suppressants in symptomatic therapy of VDB, we checked the information on prescribed drugs specifically for treatment of VDB, which was provided by the PCPs for each patient, in order to mitigate confounding by indication. No prescribed AS medication for treatment of VDB was detected.

To quantify the extent of the drug burden by AS medication at baseline, we calculated the drug burden index (DBI) (Hilmer et al., 2007). A DBI greater than zero represents a present AS drug burden with a higher index indicating higher AS burden.

The DBI of each participant was calculated using the following formula, where D denotes the prescribed daily dose of any AS medication for this participant, whereas δ is the defined daily dose (DDD) for this AS medication according to the Federal Institute for Drugs and Medical Devices (GKV-Arzneimittelindex im Wissenschaftlichen Institut der AOK, 2022):

$$DBI = \sum \frac{D}{\delta + D}$$

In order to ensure an adequate calculation of the DBI, we excluded all pro re nata medication as well as medication that was applied topically, ophthalmologically or by inhalation, since these dosing forms of medication have not been clearly defined (Kouladjian et al., 2014). Medication that was classified as having both anticholinergic and sedative effects was included only once in the calculation of the DBI (Hilmer et al., 2007; Best et al., 2013).

To handle the observed zero-inflation in the DBI of the study sample, exposure to AS medication at baseline was categorized following published cut-off points (Hilmer et al., 2007) into: No exposure (DBI = 0), low exposure (0 < DBI <1), and high exposure (DBI ≥1). Due to low observation numbers in the high exposure group, the DBI further was dichotomized into present (DBI greater than zero) and absent (DBI equals zero).

2.3 Generic and vertigo-specific functioning

Generic patient-reported functioning was assessed at baseline and both follow-ups by the German version of the Health Assessment Questionnaire Disability Index (HAQ-DI) (Fries et al., 1982; Brühlmann et al., 1994) in which patients reported the amount of difficulty they have in performing activities of daily living and instrumental activities of daily living (ADL and IADL). The overall HAQ-DI index was obtained by using the highest score within each of the eight domains (dressing and grooming, hygiene, arising, reach, eating, grip, walking, and common daily activities) and averaging these values into an overall HAQ-DI value (range = 0–3). Higher values in this overall index indicated stronger difficulties.

Vertigo-specific functioning was assessed at baseline and both follow-ups by the Vestibular Activities and Participation questionnaire (VAP) (Mueller et al., 2015). The VAP measures functioning in two dimensions by using two separate scales consisting of six items each. VAP Scale one measures patient-reported functioning regarding activities that are difficult to perform because of their propensity to provoke VDB (activity VAP). VAP Scale two indicates immediate consequences of VDB on activities and participation related to mobility (mobility VAP). Interval scaled overall scores (range scale 1 = 0–23; range scale 2 = 0–20) were used with higher scores indicating lower functioning.

2.4 Additional covariates

VDB diagnosis for each patient was reported by the respective PCP during baseline assessment as part of the self-administered health questionnaires given to the PCPs. Previous research has shown that unspecific diagnoses of VDB are remarkably over-diagnosed in primary care, resulting in a lack of adequate treatment for the actual underlying cause of VDB in the patients affected (Geser and Straumann, 2012). This lack of adequate treatment might manifest itself in reduced functioning. To account for this possibility and to facilitate analysis, we categorized the diagnoses with a specific cause (e.g., vestibular vertigo, central vertigo, cardiovascular problems, and psychogenic dizziness) as 'specific' VDB, whereas all other cases where no diagnostic decision was stated in the questionnaire were summarized as 'unspecific' VDB. The diagnosis was labeled as 'not specified' if the PCP did not specify any diagnosis in the questionnaire but enrolled the patient in the VDB survey.

Multimorbidity was included into the analysis since it increases the probability for medication and thereby the risk of unwanted effects in older people (Vrdoljak and Borovac, 2015) and is associated with reduced functioning (Loza et al., 2009). Multimorbidity was present, if a patient suffered from at least two chronic conditions additionally to VDB during baseline assessment. The assessment of chronic conditions in Mobile-TRA was accomplished by asking the PCP for existing comorbidities during baseline assessment and was based on the self-report-generated Charlson Comorbidity Index (Chaudhry et al., 2005), excluding HIV. Following (Kirchberger et al., 2012), further comorbidities that had shown to be of high relevance when examining multimorbidity with increasing age (Hunger et al., 2011) were added. Our approach results in an overall of 12 chronic conditions (Supplementary Material S1).

Information on gender (male/female) and age was based on patients' self-report. Federal states were included as a binary variable (Bavaria/Saxony).

2.5 Statistical analysis

Unadjusted summary statistics were calculated for the overall sample and separately for patients with and patients without exposure to AS medication to compare differences at baseline regarding diagnoses and characteristics of the patients as well as generic and vertigo-specific functioning. Median values and the interquartile range (IQR) between the 25% and 75% - quartiles were reported for continuous variables, relative and absolute frequencies were reported for categorical variables. Group comparison between patients with and patients without exposure to AS medication was based on Kruskal-Wallis-Test for continuous variables and Fisher's exact test for categorical variables.

We applied longitudinal linear mixed models with random intercepts and fixed slopes to assess the association of exposure to AS medication at baseline, represented by the dichotomized DBI, and the level of generic (HAQ-DI) and vertigo-specific (VAP) functioning status over time. To analyze the effect of baseline exposure on the change in functioning over time, we introduced an interaction term between AS exposure status at baseline and time. Multicollinearity among predictor variables was tested by calculating the variance inflation factor (VIF) for each model, with a highest tolerated VIF lower than five points.

In order to investigate the effect of the level of the AS drug burden, we additionally performed sensitivity analyses, computing the same longitudinal linear mixed models based on the categorized DBI values.

Random effects for the intercepts were reported. Intraclass correlation coefficients (ICC) were introduced for each model to examine the proportion of the overall variation in the respective functioning scale which is explained by the AS medication exposure status at baseline. To facilitate the interpretation of intercept estimates, we subtracted the minimum age of 65 as set by the inclusion criteria from the age in years for every patient in all mixed models.

All computational analyses were carried out with R version 4.1.0 (RStudio Team, 2020) using the nlme and misty libraries (Pinheiro et al., 2007; Yanagida and Yanagida, 2022). Significance level was set to 5% for all tests conducted.

3 Results

3.1 Study population

An overall of 19 PCPs (7 from Bavaria, 12 from Saxony; mean age = 54 years; 29% female) recruited 158 patients with VDB (59% from Bavaria; mean age = 77 years; 70% female). Exposure to AS medication at baseline was present in 56 (35%) patients. Of these, 49 (31%) patients had a low AS exposure status (0 < DBI<1), whereas 7 (4%) patients had a high AS exposure status (DBI ≥1). A total of 42% of the patients had a specific VDB diagnosis, 40% of the patients had an unspecific VDB diagnosis, and the VDB diagnosis was not specified in 18% of the patients. Median HAQ-DI at baseline was 0.38, median activities VAP was 7.36, and mean mobility VAP was 6.42. Patients exposed to AS medication reported significantly higher values for the HAQ-DI and both scales of the VAP scales during baseline assessment. Further details are presented in Table 1.

3.2 Impact of AS medication on generic and vertigo-specific functioning

Table 2 shows the adjusted estimates for the association of exposure to AS medication at baseline and generic and vertigo-specific functioning. Adjusted for covariates, generic functioning was significantly lower for patients that were exposed to AS medication at baseline [Beta = 0.40, 95%-CI (0.18; 0.61)]. Exposure to AS medication at baseline accounted for nine percent of the total variance observed in the generic functioning (ICC_HAQ-DI = 0.09). Exposure to AS medication at baseline also was significantly associated with higher values on the activity VAP Scale 1 [Beta = 2.47, 95%-CI (0.92; 4.02)] and mobility VAP Scale 2 [Beta = 3.74, 95%-CI (2.23; 5.24)], indicating lower vertigo-specific functioning. Exposure to AS medication at baseline accounted for twelve percent of the total variance observed in the activity VAP Scale 1 (ICC_VAP1 = 0.12) and 17 percent of the total variance observed in the mobility VAP Scale 2 (ICC_VAP2 = 0.17). Impairment in vertigo-specific activity-related functioning (activity VAP Scale 1) declined over time for the overall sample [Beta = −0.47, 95%-CI (-0.91; −0.03)]. No significant differences in the development of functioning over time between patients that were exposed to AS medication at baseline and patients that were not exposed were detected.

Patients with an unspecific diagnosis had lower generic functioning [Beta = 0.27, 95%-CI (0.04; 0.50)] and lower vertigo-specific mobility [Beta = 2.53, 95%-CI (1.04; 4.03)]. Patients in which the VDB diagnosis remained unspecified reported significantly worse vertigo-specific functioning on both VAP scales. Older participants and women were significantly more disabled.

The performed sensitivity analyses based on the categorized DBI showed, that patients with a low exposure to AS medication (0 < DBI<1) showed lower generic functioning and lower vertigo-specific functioning, when compared to patients without any AS exposure (DBI = 0). Patients with a high exposure to AS medication (DBI ≥1) had even lower vertigo-specific functioning on the VAP Scale 1 [Beta = 3.45, 95%-CI (0.15; 6.75)] and mobility VAP Scale 2 [Beta = 5.63, 95%-CI (1.93; 9.32)]. Further details are presented in Supplementary Table S3.

TABLE 1 Unadjusted summary statistics by exposure to AS medication at baseline assessment (n = 158). Median values and interquartile range for continuous variables and absolute and relative frequencies for categorical variables are reported.

	Overall	Exposure to AS medication			*p*-value
		No (DBI = 0)	Low (0 < DBI < 1)	High (DBI ≥ 1)	
N (%)	158 (100)	102 (65)	49 (31)	7 (4)	
Diagnosis of VDB					
Specific (n., %)	67 (100)	42 (63)	24 (36)	1 (1)	0.524
Unspecific (n., %)	29 (100)	19 (66)	8 (27)	2 (7)	
Not specified (n., %)	62 (100)	41 (66)	17 (27)	4 (7)	
Multimorbidity[a]					
No (n., %)	30 (100)	18 (60)	11 (37)	1 (3)	0.740
Yes[a] (n., %)	128 (100)	84 (66)	38 (30)	6 (4)	
Gender					
Male (n., %)	48 (100)	30 (62)	17 (36)	1 (2)	0.513
Female (n., %)	110 (100)	72 (65)	32 (29)	6 (6)	
Age (median, IQR)	78.00 (72.00; 82.00)	78.00 (73.00; 82.00)	79.00 (72.00; 82.00)	76.00 (73.00; 80.00)	0.922
Study location					
Bavaria (n., %)	94 (100)	62 (66)	27 (29)	5 (5)	0.645
Saxony (n., %)	64 (100)	40 (63)	22 (34)	2 (3)	
Generic functioning					
HAQ-DI (median, IQR)	0.38 (0.01; 1.00)	0.25 (0.00; 0.75)	0.62 (0.12; 1.38)	1.12 (0.75; 1.44)	0.002
Vertigo-specific Functioning					
Activity VAP Scale1 (median, IQR)	7.36 (4.38; 10.57)	6.55 (3.04; 9.82)	9.67 (5.83; 12.06)	11.76 (9.34; 13.79)	0.006
Mobility VAP Scale 2 (median, IQR)	6.42 (3.75; 9.61)	5.69 (2.21; 8.33)	7.71 (4.83; 12.60)	13.15 (10.51; 5.56)	0.001

AS, anticholinergic and sedative; DBI, drug burden index; VDB, vertigo, dizziness, and balance disorders; HAQ-DI, health assessment questionnaire disability index; VAP, vestibular activities and participation questionnaire; SD, standard deviation; IQR, interquartile range.

[a]'Yes', if patient suffered from at least two chronic conditions in addition to VDB, during baseline assessment.

p-values based on Kruskal-Wallis-Test for continuous variables and Fisher's exact test for categorical variables.

4 Discussion

Using data from a German primary care-based longitudinal multicenter study, we have shown that an exposure to AS medication was associated with lower values in both generic and vertigo-specific functioning in older patients with VDB. Patients in which the underlying mechanism of VDB remained unspecified were particularly at risk of impaired functioning.

In our study, patients that were exposed to AS medication at baseline had lower generic functioning than patients who were not exposed to AS medication. This is in line with previous findings stating that use of AS medication is associated with functional impairments (Landi et al., 2007; Cao et al., 2008; Hilmer et al., 2009; Koyama et al., 2014; Wouters et al., 2017; Byrne et al., 2019), due to its adverse effects (Holt et al., 2010; Bell et al., 2012) that are increasing the amount of difficulty that patients have in performing activities of their daily living.

The most striking observation of our study is that lower vertigo-specific functioning also was associated with exposure to AS medication. Apart from increasing difficulties in performing general tasks of daily living, the use of AS medication also intensifies the direct major impairment on the everyday life, especially on daily activities, social participation, and mobility. To our knowledge, no study has yet explicitly investigated this before. These results are highly alerting since it has been noted that use of AS medication was higher in people with VDB than in the general population, especially in the old aged (Phillips et al., 2018; Phillips et al., 2019).

Regardless of their exposure to AS medication, patients diagnosed with unspecific VDB, i.e., cases in which the cause of VDB remained unspecified by the respective PCP, and patients in which the entire diagnosis of VDB remained unspecified by their PCP, had lower functioning than patients with a specific diagnosis. It has been mentioned that VDB, especially in older patients, can have multiple causes (Maarsingh et al., 2010; Fernández et al., 2015) and that the symptoms often are ambiguous. It therefore is of little surprise that unspecific VDB is frequently over-diagnosed in primary care by as much as up to 60%, when compare to diagnostic procedures at specialized care centers, possibly resulting in inadequate treatment (Geser and Straumann, 2012). This inadequate treatment might ultimately manifest itself in worse functioning.

TABLE 2 Longitudinal linear mixed models to assess the influence of exposure to AS medication on generic functioning (HAQ-DI) and vertigo-specific functioning (Activity VAP Scale one and Mobility VAP Scale 2).

	Generic functioning	Vertigo- specific functioning	
	HAQ-DI (95% CI)	Activity VAP Scale 1 (95% CI)	Mobility VAP Scale 2 (95% CI)
Observations (n)	435 (158)	273 (127)	310 (139)
Fixed effects			
Intercept	−0.27 (-0.67; 0.12)	1.59 (−1.01; 4.19)	−1.14 (−3.74; 1.47)
Wave	0.03 (−0.01; 0.07)	**−0.47 (−0.91; −0.03)**	0.04 (−0.38; 0.45)
Exposure to AS medication[a] at baseline			
No	Reference	Reference	Reference
Yes	**0.40 (0.18; 0.61)**	**2.47 (0.92; 4.02)**	**3.74 (2.23; 5.24)**
Interaction terms exposure to AS medication at baseline * wave			
No * wave	Reference	Reference	Reference
Yes * wave	−0.01 (−0.07; 0.06)	0.27 (−0.49; 1.03)	−0.38 (−1.08; 0.31)
Diagnosis of VDB			
Specific	Reference	Reference	Reference
Unspecific	**0.27 (0.04; 0.50)**	1.28 (−0.27; 2.83)	**2.53 (1.04; 4.03)**
Not specified	0.26 (−0.03; 0.54)	**2.04 (0.16; 3.92)**	**2.38 (0.53; 4.24)**
Age[b]	**0.04 (0.02; 0.05)**	**0.16 (0.05; 0.27)**	**0.28 (0.17; 0.39)**
Study location			
Bavaria	Reference	Reference	Reference
Saxony	−0.05 (−0.27; 0.16)	0.24 (−1.22; 1.71)	0.73 (−0.69; 2.15)
Gender			
Male	Reference	Reference	Reference
Female	**0.30 (0.07; 0.53)**	**2.26 (0.69; 3.83)**	**2.55 (1.06; 4.05)**
Multimorbidity[c]			
No	Reference	Reference	Reference
Yes	−0.02 (−0.28; 0.25)	0.89 (−0.79; 2.57)	−0.24 (−1.90; 1.43)
Random effects			
Intercept (SD)	0.61	3.40	3.50
ICC	0.09	0.12	0.17

Significant results are highlighted in bold print.
AS, anticholinergic and sedative; VDB, vertigo, dizziness, and balance disorders; HAQ-DI, health assessment questionnaire disability index; VAP, vestibular activities and participation questionnaire; CI, confidence interval; ICC, Intraclass correlation coefficient.
[a]'Yes', if drug burden index greater than zero.
[b]The minimum age of 65 as set by the inclusion criteria was subtracted from age in years for each patient.
[c]'Yes', if patient suffered from at least two chronic conditions in addition to VDB, during baseline assessment.

Our findings demonstrate that women are at risk of lower generic and vertigo-specific functioning. This is in line with recent findings that women at the age of 65 and above in Germany expect to spend less of their remaining life years in good health than men, due to their higher morbidity and despite their higher life expectancy (Stephan et al., 2021). It further has been shown that the overall potentially inappropriate medication use was higher in older women (Nothelle et al., 2017; Nothelle et al., 2019), possibly contributing to the lower functioning found in this study.

Several limitations of our study have to be considered. Information on medication intake was based on self-report. Chances are that patients did not indicate a comprehensive list or that the indicated doses taken was inaccurate. The true extent of the exposure to AS medication thus might have been underestimated. Likewise, the assessment of generic functioning *via* the HAQ-DI and vertigo-specific functioning *via* the VAP was based on the participants' self-report and thus might have potentially exposed to a variety of information bias. Though we cannot fully exclude the chance that such bias might be present in our data, self-reported measure is commonly seen as a valid outcome, assessing the patients' perspective. Both the HAQ-DI and the VAP are standardized and validated instruments which have frequently used in the past. Patients further were offered contact information of the study team in case of any uncertainty regarding their study participation or the questionnaire in order to reduce the risk of bias. The DBI within this study was calculated

using the DDD instead of the minimum effective dose as specified in the original calculation of the DBI (Hilmer et al., 2007) since the German ATC classification system was closely linked to the DDD. Using the DDD as a replacement of the minimum effective dose has been introduced in the past (Faure et al., 2013). This however might have resulted in an underestimation of the actual DBI, since the DBI is higher for some drugs, but not for others (Hilmer, 2018). Suitable subjects for this study were identified by searching for ICD-10 codes associated with VDB in the databases of the participating PCPs. The reliability of ICD-10 codes as a reliable classification system in primary care has been discussed in the past (Wockenfuss et al., 2009), especially since they became one of the corner stones of reimbursement in the German healthcare system and thus might be divergent from the actual diagnosis. While the diagnosis of VDB use in this analysis was given directly by the PCP as part of the questionnaire and therefore decoupled from the ICD codes, some potential participants might have been left out due to inaccurate ICD-10 codes that were not listed in our inclusion criteria. The VDB diagnoses used in this analysis were solely based on the assessments of the participating PCPs at baseline. This is of relevance, since previous research has shown that PCPs tend to frequently over-diagnose unspecific VDB in patients who later were diagnosed with a specific cause of VDB (Geser and Straumann, 2012) due to reported difficulties in establishing an accurate VDB diagnosis in the past (Stephan et al., 2018). Also, we do not know if (and when) the PCP or specialist made a specific diagnosis during the follow-up time. While the list of assessed comorbidities within this study was comprehensive, it did not include all comorbidities that are associated with the use of AS medication, such as sleep and pain disorders, urinary incontinence, mental disorders, and dementia (Kouladjian et al., 2014). Single comorbidities might also differ with regard to their relation with VDB, the prescription frequency of AS medication, and their direct impact on generic and vertigo-specific functioning. Using multimorbidity as a substitute, the estimation of the impact of AS medication on functioning might be distorted due to unaccounted confounders. We therefore strongly suggest to further review our findings, including a more detailed assessment of the present medication intake and existing comorbidities.

In conclusion, we found that an exposure to AS medication was associated with lower values in both generic and vertigo-specific functioning in older patients with VDB. When feasible, AS medication thus should be replaced by equivalent alternative therapies that are adapted to the situation and needs of each patient individually. Valid approaches have already been examined and include change of medication as well as non-pharmacological treatment, such as physical exercises or behavioral therapy (Holt et al., 2010). The use of AS medication in symptomatic therapy of VDB remains debated (Hunter et al., 2022). Our results support recent recommendations that their use as vestibular suppressants should be limited only to the acute phase of the disease and must be used with special caution in the older population (Casani et al., 2021).

A close monitoring of AS medication use in older patients with VDB symptoms is crucial and should be considered as an integral component in medication monitoring guidelines in a primary care setting, as, for example, happened in the German DEGAM-Guideline (S3) for polypharmacy (Leitliniengruppe Hessen Deutsche Gesellschaft für Allgemeinmedizin und Familienmedizin (DEGAM), 2021). Using the drug burden index could be a valid approach to do so and should be accompanied by implementation studies in order to ensure feasibility. In doing so, exposure to AS medication could be reduced and thus help to potentially reduce the burden of VDB.

Previous research aimed at evaluating the utility of the DBI in practice showed that, while using the DBI as an assessment tool in older adults can have the potential to reduce AS burden in some studies (Nishtala et al., 2009; Castelino et al., 2010), the effect could not always be shown (van der Meer et al., 2018) or was lower than anticipated (Gnjidic et al., 2010). Agreement is that future research needs to be implemented targeting multidisciplinary and multifactorial approaches, including the DBI, to evaluate drug prescription and to evaluate functional outcomes in older adults (Kouladjian et al., 2014).

Data availability statement

The datasets presented in this article are not readily available because of data privacy regulations that apply in the country of data collection. Requests to access the datasets should be directed to the corresponding author BK (benedict.katzenberger@med.uni-muenchen.de).

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of the Ludwig Maximilian University of Munich in Bavaria (#17-443) and the Ethics Committee of the Technical University Dresden in Saxony (#E365092017). The patients/participants provided their written informed consent to participate in this study.

Author contributions

All authors contributed to the study conception and execution. Material preparation and data collection were performed by RK, LS, and KV, DK, BK, RK, and EG are responsible for the study's quality assessment. The data analysis was performed by BK, DK, and RS. The first draft of the manuscript was written by BK and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Conflict of interest

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

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2023.1136757/full#supplementary-material

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4 Publication II

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

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ORIGINAL COMMUNICATION

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

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Abstract

Background Due to reported barriers in the management of patients with vertigo, dizziness and balance problems (VDB), referral trajectories starting from primary care might be determined by other factors than medical necessity. The objective of this paper was to examine the impact of disease-related and other determinants on referral trajectories of older patients with VDB and to investigate, how these trajectories affect the patients' functioning and health-related quality of life (HRQoL).

Methods Data originate from the longitudinal multicenter study MobilE-TRA, conducted in two German federal states. Referrals to neurologists or ear-nose-throat (ENT) specialists were considered. Referral patterns were visualized using a state sequence analysis. Predictors of referral trajectories were examined using a multinomial logistic regression model. Linear mixed models were calculated to assess the impact of referral patterns on the patients' HRQoL and functioning.

Results We identified three patterns of referral trajectories: primary care physician (PCP) only, PCP and neurologist, and PCP and ENT. Chances of referral to a neurologist were higher for patients with a neurological comorbidity (OR = 3.22, 95%-CI [1.003; 10.327]) and lower for patients from Saxony (OR = 0.08, 95%-CI [0.013; 0.419]). Patients with a PCP and neurologist referral pattern had a lower HRQoL and lower functioning at baseline assessment. Patients with unspecific diagnoses also had lower functioning.

Conclusion Referral trajectories were determined by present comorbidities and the regional healthcare characteristics. Referral trajectories affected patients' HRQoL. Unspecific VDB diagnoses seem to increase the risk of ineffective management and consequently impaired functioning.

Keywords Referral trajectories · Vertigo, dizziness and balance disorders · State sequence analysis · Health-related quality of life · Functioning · MobilE-TRA

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Introduction

With an annual prevalence of 9% in medical claims databases [1] and a total of up to 4.2% of all visits, vertigo, dizziness and balance problems (VDB) are among the most frequent reasons for older adults to consult primary care [2].

There is evidence for inappropriate management of VDB in primary care, both in Germany and internationally [3, 4]. The reasons for this are still poorly understood.

Usually, patients with VDB are initially seen by primary care physicians (PCP), who then have to decide whether additional tests, a strategy of watchful waiting, referral to secondary care, or straightforward therapy are needed. This decision is additionally challenging since it has been shown that dizziness in the aged can have multiple causes [5, 6]. Distinct treatable vestibular disease entities, dizziness caused by medication, cardiovascular disease or diabetes may align with symptoms of the ageing of vestibular, proprioceptive or somatosensory systems. Therefore, a considerable percentage of older adults with confirmed vestibular vertigo experience limited functioning and impairment in their health-related quality of life (HRQoL) due to their untreated VDB [7, 8].

Ideally, referral trajectories from the PCP to a specialist should be guided by the underlying cause, making use of the specialist's expertise for the respective disease [9, 10]. However, PCPs report barriers in the referral routines of older patients with VDB. This may be due to a lack of experience with specific diagnostic tests, fragmentation of the health care system, not having enough time for interaction with patients, or missing guidance, such as missing management standards for VDB [11]. Thus, it seems hardly surprising that many patients consult multiple health care professionals, often without getting a definite diagnosis [3]. To give an example, in the US over 36% of older patients with VDB were seen by more than three health professionals, yet 40% of the patients with VDB remained without definite diagnosis [4].

As a result, referral trajectories in VDB might be determined not only by medical necessity but also by other factors. To date, very little is known about the role of such determinants of referral in patients with VDB. Taking a more generalized look at other indications reveals, that such other determinants for referral decisions from primary care to a specialist can in general be categorized into three dimensions: the characteristics of the patients, the characteristics of the PCP, and the surrounding health care characteristics [12–15].

Regarding patient characteristics, male gender and advanced age [12] as well as a higher educational level [13] increase the likelihood for referral. Chances of referral further differed based on the experience of the PCP [15]. Regarding system characteristics, studies conducted in the US and England have shown that differences in the local health care characteristics did influence referral frequency [12, 14].

It has been shown that patients with VDB under usual care conditions often were not able to improve in patient-relevant outcomes [16], yet that improvement is possible when the causes of VDB are adequately cared for [17]. Referral trajectories may play an important role in whether or not such an improvement can be obtained.

The objective of this paper thus was to investigate the impact of both disease-related and not disease-related determinants on referral trajectories in patients with VDB. Also, we wanted to investigate, how current referral trajectories affect patient-relevant outcomes such as functioning and HRQoL.

Methods

Study design, study population, and data collection procedures

Data for this research project emanated from the longitudinal multicenter study MobilE-TRA conducted in two German federal states (Bavaria and Saxony) from September 2017 until October 2019. A more detailed description of the study can be found elsewhere [18]. In brief, patients aged 65 years and older were included if they had consulted their PCP for an acute episode of VDB in the last quarter. The identification of suitable individuals was accomplished by approaching PCPs who were willing to participate and asking them to search their patient databases for the following ICD-10 codes associated with VDB: R42, A88.1, E53.8, F45.8, G11.8, G43.1, G45.0, G62, G63, H55, H83.0–2, I95.1, and N95.1. A detailed list of the ICD-10 codes and the related diagnoses are listed in Online resource 1. Patients additionally had to have statutory health insurance (covering approx. 90% of the German population [19]) as well as sufficient command of the German language.

Baseline assessment was conducted in between September 2017 and August 2018 and consisted of a self-administered health questionnaire, which was sent to each patient. Participating PCPs were asked to complete an adapted version of the standardized Questionnaire of Chronic Illness Care in Primary Care (QCPC) [20]. PCP in addition were asked to give information on each included patient comprising an additional self-developed baseline questionnaire covering the diagnosis, information on referrals to other specialists, and the treatment strategy. The study consisted of two additional waves: Follow-up invitations were sent to the patients 6 months and 12 months after individual baseline

dates. Assessments for follow-up one and follow-up two consisted of the self-administered health questionnaire, only.

Ethics approval for MobiLE-TRA was obtained from the Ethics Committee of the Ludwig-Maximilians-Universität München (#17-443) and the Ethics Committee of the Technische Universität Dresden (#E365092017). Written informed consent was obtained from all participants. The study was performed in accordance with the Declaration of Helsinki principles.

The population of this analysis is composed of all patients with VDB with valid information on consulted physicians for baseline and at least one follow-up, based on their questionnaire. A more detailed flowchart can be found in Online Resource 2.

Referrals

Referrals to specialists were indirectly assessed by asking the patients about the physicians they had been consulting within the last three months prior to each assessment. For this purpose, patients were presented a standardized list of physicians (Questionnaire for Health-Related Resource Use in an Elderly Population—FIMA) [21]. As the most obvious choice of consultation in case of VDB is the PCP, or a referral to a neurology or otorhinolaryngology specialist, we concentrated for our analyses on PCPs, neurologists and ear-nose-throat (ENT) specialists [22].

Disease-related and other determinants of referral trajectories

VDB diagnosis was reported by the PCP during baseline assessment. To facilitate analysis and in line with current classifications [23], we categorized these diagnoses based on the reported cause of VDB into vestibular vertigo (e.g., BPPV, Meniere's disease, and Vestibular neuritis), central vertigo (e.g., stroke and vestibular migraine), other specific diagnoses (i.e., cardiovascular problems, psychogenic dizziness), and unspecific vertigo. We hypothesized that referrals to a neurologist should be more likely in the case of central vertigo. Vestibular vertigo should increase the chance of referral to an ENT-specialist. All other specific diagnoses should generally not lead to referral to neither a neurologist nor an ENT-specialist. The diagnosis was labeled as 'not specified' if the PCP did not specify a diagnosis but enrolled the patient in the VDB survey. For further analyses, VDB diagnosis was also categorized into a binary variable, listing all diagnoses with a specific cause (vestibular vertigo, central vertigo, cardiovascular problems, and psychogenic dizziness) as 'specific' VDB, whereas all other cases where no diagnostic decision was made were summarized as 'unspecific' VDB. Diagnoses that were labeled as 'not specified' were not included into this binary variable and thus were treated as missing values.

Comorbidities were reported by the PCP using the Charlson Comorbidity Index [24]. Following recommendations [25], we added further comorbidities to the index list that had shown to be of high relevance in older adult populations and potentially might influence HRQoL [26]. A detailed list of the comorbidities is shown in the Online Resource 3. These comorbidities were then categorized into 'neurological' comorbidities (including stroke), 'ENT – related' comorbidities, and 'none / other' comorbidities.

Information on gender (male/female) and age was based on patients' self-report. Education levels were categorized on the basis of the German educational system as follows: no graduation or lower secondary education (equals 9 years of school or less), lower secondary education (equals 10 years of school), upper secondary education (equals 12 or 13 years of school) and tertiary education (university, university of applied sciences). The PCP's experience was approximated by the number of years that a PCP was working after licensure. Differences in referrals due to differences in the surrounding health care characteristics were addressed by including the federal state as binary variable (Bavaria/Saxony).

Health-related quality of life and functioning

HRQoL was measured using the visual analog scale (VAS) which is part of the EuroQol Five-Dimensional Five-Level Questionnaire (EQ-5D-5L), developed by the EuroQol Group [27]. Patients were asked to rate their present health on a scale from 0 to 100, where 100 indicates perfect health and 0 indicates the worst health imaginable.

Functioning was assessed by the two-scale version of the Vestibular Activities and Participation questionnaire (VAP) [28], which is consisting of two separate scales. VAP Scale 1 measures patient-reported functioning regarding activities that are difficult to perform because of their propensity to provoke vertigo or dizziness (activity VAP). VAP Scale 2 indicates immediate consequences of vertigo and dizziness on activities and participation related to mobility (mobility VAP). Interval scaled overall scores (range scale 1 = 0–23; range scale 2 = 0–20) were used with higher scores indicating lower functioning.

Statistical analysis

Constructing referral trajectories and clustering them using state sequence analysis

To identify clusters of similar referrals trajectories, we used state sequence analysis (SSA) which has already been successfully applied in care pathways research settings [29–31].

For the purpose of this study, a referral trajectory is defined as a sequence of distinct combinations of consulted practitioners, technically termed as states, which are ordered in their chronological sequence.

Each individual trajectory consisted of three states—one for each wave. Each trajectory started with the completion of the baseline questionnaire, including the last 6 months prior to that time point, and stopped, when the follow-up two questionnaire was completed. To provide an example: An individual trajectory may consist of PCP consultation at baseline, the simultaneous consultation of the PCP and a neurologist at follow-up one and the sole consultation of the PCP at follow-up 2.

Patients may consult multiple physicians simultaneously. The resulting list of states included in this study therefore is as follows: PCP only, ENT specialist only, neurologist only, PCP and neurologist, PCP and ENT specialist, ENT specialist and neurologist, and PCP, ENT specialist and neurologist. In case of a missing state for baseline assessment, we assumed that every patient did exclusively consult the PCP (as defaulted in our inclusion criteria).

In a second step, dissimilarity between referral trajectories, i.e., the minimal cost to transform one trajectory into another, was measured using optimal matching (OM), based on the transition rates present in the dataset [32].

The clusters of similar referral trajectories finally were obtained using a Partitioning Around Medoids (PAM) – algorithm [33], which was based on the acquired dissimilarity. The optimal number of clusters was determined by two quality criteria: The weighted average silhouette width (ASWw), measuring the overall consistency of the clusters, and the Hubert's C index (HC), reflecting the gap between the clustering obtained and the best theoretically possible clustering based on the numbers of groups and distances present. Further details about this approach are described elsewhere [29, 33].

State distribution over time is shown with the help of a state distribution plot, which displays the general pattern of states over time on a group level on the x-axis while the cumulative proportion of patients in the different states is presented on the y-axis. The actual trajectories of each cluster are represented using an index plot, with the trajectories shown on the x-axis while the bar height of each trajectory is proportional to the number of observations assigned to each trajectory.

Descriptive analysis, cluster comparison and examination of potential determinants of cluster membership

Summary statistics were calculated for the overall sample and separately for each cluster to compare differences in diagnoses, comorbidities, characteristics of the patients and the PCPs, the federal states, as well as baseline HRQoL and functioning. Mean and standard deviation were reported for continuous variables, relative and absolute frequencies were reported for categorical variables.

A multinomial logistic regression model was calculated based on data from the baseline assessment to test for potential determinants of the identified clusters, with the PCP cluster as a reference.

Examining the impact of cluster membership on the patient's health-related quality of life and functioning

We calculated longitudinal linear mixed models with random intercepts and random slopes to assess whether HRQoL and functioning was determined by the clusters of similar referral trajectories. Regression models were separately calculated for the VAS, the activity VAP Scale 1, and the mobility VAP Scale 2. To address differences between the clusters in the development of HRQoL and functioning over time, we introduced interaction terms between the waves and the clusters. We introduced a second interaction term between the waves and the diagnosis of VDB (specific or unspecific) to address potential differences in the development over time between patients with a specific and an unspecific diagnosis of VDB. Random effects for intercept and slope were reported along with the Bayesian information criterion (BIC).

Variable selections was done using directed acyclic graphs (DAGs) (see Online Resource 4) to avoid bias by over-adjustment or collider bias and to arrive at a parsimonious set of variables, the minimal sufficient adjustment set, for estimating the effect of referral clusters on HRQoL and functioning [34]. The resulting minimal adjustment set consisted of VDB diagnosis, present comorbidities, federal state, gender, age, and education.

To facilitate interpretation of intercept estimates, the minimum age of 65 as set by the inclusion criteria was subtracted from age in years for each patient.

All computational analyses were carried out with R Studio Version 4.0.3 [35] using the TraMineR, Weighted Cluster and nlme libraries [32, 33, 36]. Significance level was set to 5% for all tests conducted. To construct the DAGs for this study, we used DAGitty, a browser-based environment for creating, editing, and analyzing causal models [37].

Results

Study population

A total of 19 PCPs (7 from Bavaria, 12 from Saxony; mean age = 54 years; 29% female) recruited 158 patients with VDB. Of these, a total of 141 patients (mean

age = 76.8 years, 70% female, 60% from Bavaria) had information on consultations for baseline and at least 1 follow-up and thus were included into the analysis.

A total of 39% had a specific VDB diagnosis (9.2% vestibular vertigo, 12.1% neurological central vertigo, 17.7% other specific diagnoses), 44% of the patients had an unspecific VDB diagnosis.

Mean baseline HRQoL was 64.2 (SD = 19.9), mean activities VAP was 7.2 (SD = 4.1), and mean mobility VAP was 6.4 (SD = 4.8).

Clusters of similar referral trajectories

We identified three distinct clusters of similar referral trajectories (see Fig. 1). Cluster 1 ('PCP' cluster) consisted of 77 persons that consulted only the PCP and were not or hardly ever referred. Patients in cluster 2 ('PCP & Neurol', $n = 36$) most frequently consulted both PCP and neurologists or PCP, Neurologists and ENT simultaneously. Patients in cluster 3 ('PCP & ENT', $n = 28$) most commonly consulted both PCP and ENT simultaneously.

Determinants of cluster membership

Table 1 shows the summary statistics by cluster of similar referral trajectories at baseline assessment.

Table 2 shows the results of the multinomial logistic regression model, which was computed to test for potential determinants of the identified clusters. Odds ratios (OR) are reported to represent the odds to be in the respective cluster as compared to the odds to be in the reference PCP cluster.

Patients with a neurological comorbidity were significantly more likely to see PCPs and neurologists (OR = 3.22, 95%CI [1.003; 10.327]), as compared to being seen by PCPs exclusively. Patients from Saxony were less frequently referred to neurologists, as expressed by a lower likelihood to be in the PCP & Neurol cluster (OR = 0.08, 95%CI [0.013; 0.419]).

Examining the impact of referral on the patient's health-related quality of life and functioning

Adjusted estimates for the association of referral cluster and HRQoL and functioning are shown in Table 3.

Patient-reported HRQoL at baseline was significantly lower for patients in the PCP & Neurol referral cluster

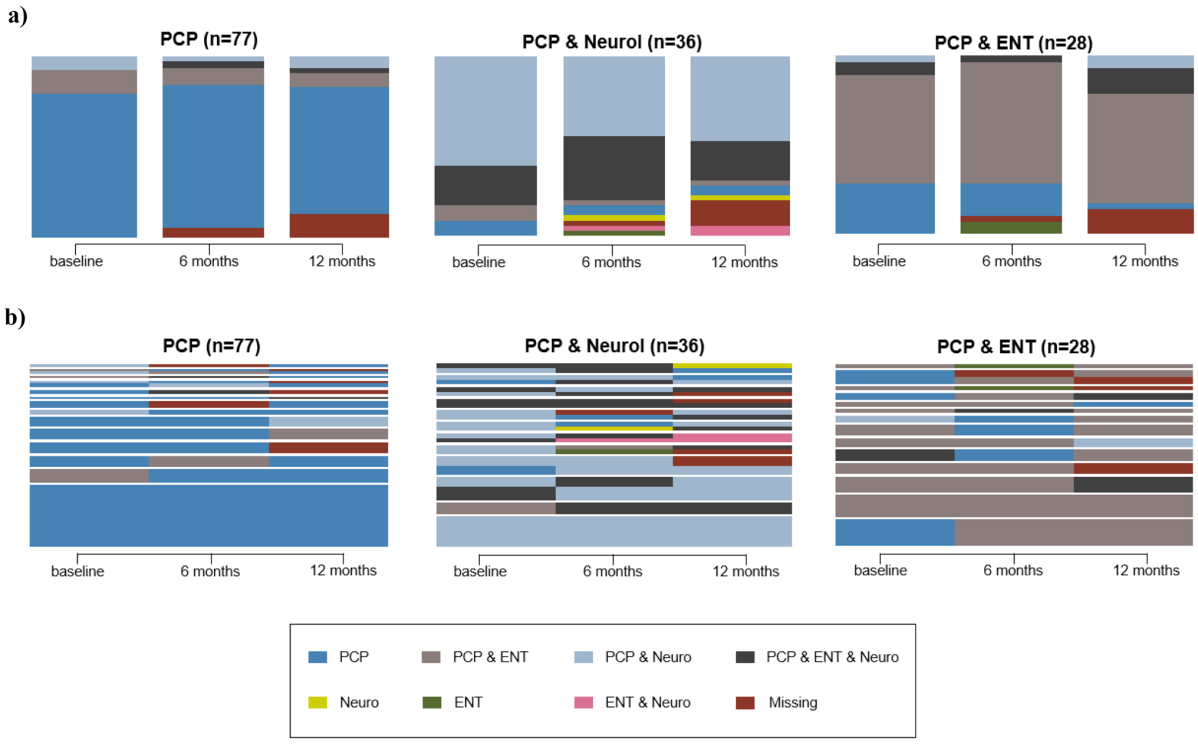

Fig. 1 State distribution plot (**a**), displaying the general pattern of states over time on the *x*-axis while presenting the cumulative proportion of patients in the different states on the *y*-axis. Index plot (**b**) representing the actual referral trajectories in each cluster on the *x*-axis. The bar height of each trajectory is proportional to the assigned number of observations

Table 1 Unadjusted summary statistics by trajectory cluster at baseline assessment ($n = 141$)

	Overall	Clusters of similar referral trajectories		
		Cluster 'PCP'	Cluster 'PCP & Neurol'	Cluster 'PCP & ENT'
N (%)	141 (100)	77 (55)	36 (25)	28 (20)
Diagnosis of VDB				
Vestibular (*n*, %)	13 (100)	7 (54)	5 (38)	1 (8)
Central (*n*, %)	17 (100)	6 (35)	8 (47)	3 (18)
Unspecific (*n*, %)	62 (100)	34 (55)	16 (26)	12 (19)
Other specific diagnoses (*n*, %)	25 (100)	15 (60)	3 (12)	7 (28)
Not specified (*n*, %)	24 (100)	15 (62)	4 (17)	5 (21)
Comorbidities				
None / Other (*n*, %)	102 (100)	58 (56)	22 (22)	22 (22)
Neurological (*n*, %)	26 (100)	12 (46)	12 (46)	2 (8)
ENT-related (*n*, %)	13 (100)	7 (54)	2 (15)	4 (31)
Location				
Bavaria (*n*, %)	85 (100)	41 (48)	33 (39)	11 (13)
Saxony (*n*, %)	56 (100)	36 (64)	3 (5)	17 (30)
Gender				
Male (*n*, %)	43 (100)	25 (58)	8 (19)	10 (23)
Female (*n*, %)	98 (100)	52 (53)	28 (29)	18 (18)
Age (mean, SD)	76.8 (6.1)	77.2 (5.8)	76.8 (6.5)	76.0 (6.4)
Education[a]				
No graduation (*n*, %)	2 (100)	1 (50)	1 (50)	0 (0)
Lower secondary education 1 (*n*, %)	62 (100)	37 (60)	15 (24)	10 (16)
Lower secondary education 2 (*n*, %)	30 (100)	13 (43)	12 (40)	5 (17)
Upper secondary education (*n*, %)	10 (100)	5 (50)	2 (20)	3 (30)
Tertiary education (*n*, %)	29 (100)	18 (62)	5 (17)	6 (21)
Missing values (*n*, %)	8 (100)	3 (37)	1 (13)	4 (50)
Experience of the PCP (mean, SD)	18.5 (7.4)	18.3 (7.7)	19.1 (5.2)	18.0 (9.3)
Missing values (*n*, %)	6 (100)	4 (66)	1 (17)	1 (17)
HRQoL				
VAS (*mean, SD*)	64.2 (19.9)	68.6 (19.7)	54.3 (20.1)	64.5 (16.4)
Missing values (*n*, %)	4 (100)	2 (50)	2 (50)	
Functioning				
Activity VAP Scale1 (mean, SD)	7.2 (4.1)	6.7 (4.0)	8.3 (4.4)	7.3 (3.9)
Missing values (*n*, %)	51 (100)	29 (57)	15 (29)	7 (14)
Mobility VAP Scale 2 (mean, SD)	6.4 (4.8)	5.9 (4.8)	7.4 (5.2)	6.3 (4.6)
Missing values (*n*, %)	39 (100)	23 (59)	13 (33)	3 (8)

We report mean and SD for continuous variables and absolute and relative frequencies for categorical variables.

VDB Vertigo, dizziness and balance problems, *PCP* primary care physician, *Neurol* Neurologist, *ENT* ear, nose and throat, *HRQoL* health-related quality of life, *VAS* Visual analog scale, *VAP* Vestibular Activities and Participation questionnaire, *SD* standard deviation

[a] Lower secondary education 1 equals 9 years of school, Lower secondary education 1 equals 10 years of school, upper secondary education equals 12 or 13 years of school

(Beta = − 12.72, 95%-CI [− 21.27; − 4.17]). Yet the development of the HRQoL over time, represented by the interaction term of the clusters of similar referral trajectories and the study waves, was significantly better for these patients (4.04, [0.15; 7.92]), resulting in an overall increase over time. Patients in the PCP & Neurol referral cluster had significantly worse functioning at baseline (2.22, [0.01; 4.43]).

Functioning increased over time for patients with a specific VDB diagnosis (− 1.05, [− 1.78; − 0.32]). The development of functioning in patients with an unspecific diagnosis was significantly worse for both the activity VAP Scale 1

Table 2 Multinomial regression models to assess predictors for cluster membership during baseline assessment. The reference cluster is 'PCP'

	Clusters of similar referral trajectories (Reference cluster is 'PCP')	
	Cluster 'PCP & Neurol' (OR)	Cluster 'PCP & ENT' (OR)
Intercept	6.67 (0.01; 3643.71)	0.55 (0.00; 862.69)
Diagnosis of VDB		
Other specific diagnoses	Reference	Reference
Vestibular	2.49 (0.32; 19.14)	0.36 (0.03; 3.74)
Central	2.81 (0.42; 18.91)	1.34 (0.20; 9.09)
Unspecific	1.35 (0.28; 6.64)	0.64 (0.17; 2.43)
Not specified	1.01 (0.14; 7.34)	0.78 (0.15; 3.97)
Present comorbidities		
None / Other	Reference	Reference
Neurological	**3.22 (1.00; 10.33)**	0.42 (0.08; 2.38)
ENT-related	0.29 (0.03; 2.99)	1.70 (0.37; 7.73)
Location		
Bavaria	Reference	Reference
Saxony	**0.08 (0.01; 0.42)**	2.66 (0.83; 8.57)
Gender		
Male	Reference	Reference
Female	0.96 (0.26; 3.53)	1.23 (0.32; 4.70)
Age	0.96 (0.89; 1.04)	0.99 (0.90; 1.08)
Education[a]		
No graduation or lower secondary education 1	Reference	Reference
Lower secondary education 2	2.17 (0.66; 7.13)	1.34 (0.32; 5.57)
Upper secondary education	1.49 (0.19; 11.63)	1.56 (0.25; 9.64)
Tertiary education	1.47 (0.25; 8.73)	0.78 (0.17; 3.69)
Experience of the PCP	1.01 (0.94; 1.10)	1.00 (0.94; 1.07)
McFadden R^2	0.175	

Odds ratios rounded to two decimals. Significant results are highlighted in bold print

VDB Vertigo, dizziness and balance problems, *PCP* primary care physician, *Neurol* Neurologist, *ENT* ear, nose and throat, *OR* Odds ratio

[a]Lower secondary education 1 equals 9 years of school, Lower secondary education 1 equals 10 years of school, upper secondary education equals 12 or 13 years of school

(1.16, [0.36; 1.95]) and mobility VAP Scale 2 (0.86, [0.04; 1.67]), resulting in a decrease over time. Further details are shown in Table 3.

Figure 2 displays the differences in the predicted values between the distinct combinations of clusters and diagnosis of VDB for HRQoL and functioning over time for a fictional person based on the longitudinal linear mixed models. The predicted values apply for a 78-year-old exemplary female patient, living in Bavaria with no comorbidities related to a neurologist or ENT-specialist and no graduation or lower secondary education 1.

Discussion

This is one of the first studies to systematically analyze referral trajectories of older patients with vertigo, dizziness and balance problems (VDB) in primary care. In our study, we identified three referral patterns using state sequence analysis (SSA).

Primary care physician (PCP) only without further referral, PCP and neurologist, and PCP and ENT specialist. Comorbidities and regional health care characteristics determined these typical referral patterns. Referral patterns and specificity of diagnosis were predictors of patient's health-related quality of life (HRQoL). Patients with an unspecific diagnosis of VDB were at risk of reduced HRQoL and limited functioning.

It is not surprising that patients in our study were most frequently managed solely by the PCP without further referral to a neurologist or an ENT specialist, which confirms earlier findings from the literature [22, 38, 39].

Specific VDB diagnoses were not an indicator for referral to a specialist in our study. Arguably, VDB in older adults is seen as a health problem that can be managed in primary care. While most VDB diagnoses can be managed by the PCP, as proposed by the German DEGAM-Guideline (S3) for the treatment of VDB in the primary care setting [40], our earlier work indicated that PCPs report considerable uncertainty and lack of routine in VDB diagnosis and treatment [11]. Thus, absence of referral to the specialist partially undermines the logic that referral is needed in certain cases of VDB to make use of the specialist's expertise for the respective disease [9, 10]. In contrast, VDB patients in our study with a neurological comorbidity (such as multiple sclerosis, Parkinson's disease, and epilepsy) indeed were more often referred to neurologists, suggesting that these health conditions were seen as severe enough to elicit a referral.

Interestingly, the referral patterns greatly differed between the two federal states with patients from Saxony being less likely to be referred to specialist care. It has to be noted that Saxony is one of the eastern federal states of the former German Democratic Republic (GDR). Health system in the GDR was largely based on public ambulatory PCP clinics. Our results thus imply that in a situation, where getting the correct diagnosis and efficient treatment is a great challenge [3, 4], referral patterns in patients with VDB are influenced

Table 3 Longitudinal linear mixed models to assess the influence of clusters of similar referral trajectories on health-related quality of life (VAS) and functioning (activity VAP Scale 1 and mobility VAP Scale 2)

	HRQoL	Functioning	
	VAS (95% CI)	Activity VAP Scale 1 (95% CI)	Mobility VAP Scale 2 (95% CI)
Observations (*n*)	318 (109)	195 (89)	231 (99)
Fixed effects			
Intercept	79.83 (66.40; 93.26)	2.96 (-0.34; 6.26)	-1.39 (-5.03; 2.26)
Wave	− 1.49 (− 4.37; 1.39)	**− 1.05 (− 1.78; − 0.32)**	− 0.21 (− 0.92; 0.50)
Cluster of similar referral trajectories			
PCP	Reference	Reference	Reference
PCP & Neurol	**− 12.72 (− 21.27; − 4.17)**	**2.22 (0.01; 4.43)**	1.80 (− 0.70; 4.29)
PCP & ENT	− 7.88 (− 16.95; 1.19)	2.12 (− 0.10; 4.34)	1.70 (− 0.79; 4.19)
Interaction terms cluster of similar referral trajectories * wave			
PCP * wave	Reference	Reference	Reference
PCP & Neurol * wave	**4.04 (0.15; 7.92)**	0.45 (− 0.49; 1.39)	− 0.04 (− 1.02; 0.95)
PCP & ENT * wave	1.76 (− 2.71; 6.24)	0.12 (− 0.87; 1.11)	− 0.43 (− 1.43; 0.56)
Diagnosis of VDB			
Specific	Reference	Reference	Reference
Unspecific	− 6.33 (− 13.02; 0.36)	0.40 (− 1.34; 2.15)	1.65 (− 0.31; 3.60)
Interaction term diagnosis of VDB * wave			
Specific * wave	Reference	Reference	Reference
Unspecific * wave	− 2.11 (− 5.44; 1.22)	**1.16 (0.36; 1.95)**	**0.86 (0.04, 1.67)**
Random effects			
Intercept (SD)	13.80	3.27	4.03
Wave (SD)	3.94	0.56	0.93
BIC	2765.0	1096.1	1331.3

All models are controlled for present comorbidities, the study location, gender, age, and education. Significant results are highlighted in bold print

PCP Primary care physician, *VDB* vertigo, dizziness and balance problems, *Neurol* Neurologist, *ENT* ear, nose and throat, *HRQoL* health-related quality of life, *VAS* visual analog scale, *VAP* Vestibular Activities and Participation questionnaire, *CI* confidence interval

by the surrounding health care characteristics, as has also been reported for other indications [12, 14, 15].

Our study found evidence that patient reported HRQoL was affected by referral trajectories. Patients that consulted both the PCP and a neurologist had a significantly lower HRQoL at the beginning of the study, but did improve over time, approaching the HRQoL of the other patients. This might reflect the specific referral process where a neurologist was able to contribute to the effective management of the underlying neurological condition. However, our results also indicate that this potentially effective management of VDB did not affect VDB-specific functioning. This is in line with earlier studies showing that adequate management of VDB is a challenge [3].

In our study, patients with an unspecific diagnosis of VDB, i.e., cases in which the specific cause of VDB remained unspecified, were significantly at risk of unfavorable development of functioning. It has been mentioned repeatedly that VDB in older patients can have multiple causes [5, 6] and often expresses itself in ambiguous symptoms, resulting in unspecific diagnoses [41] and therefore unspecific and potentially ineffective treatment [42]. It has been shown that PCPs tend to abstain from referral of patients with symptoms that are either ambiguous or unfamiliar [38].

We are aware that our study has some limitations. Information on referrals in our study was based on self-report. Whether a reported consultation was related to VDB and whether the patients were actually referred to the specialists by the PCP was not assessed. Chances are given that patients did consult a specialist without having been referred by the PCP, which is possible in the German health care system. However, we are confident that this is only the minority of cases as the patients do have an acute episode of VDB and referrals to neurologists and ENT-specialists are rather common in this group of patients [22]. The VDB diagnoses used in this analysis were solely based on the assessments

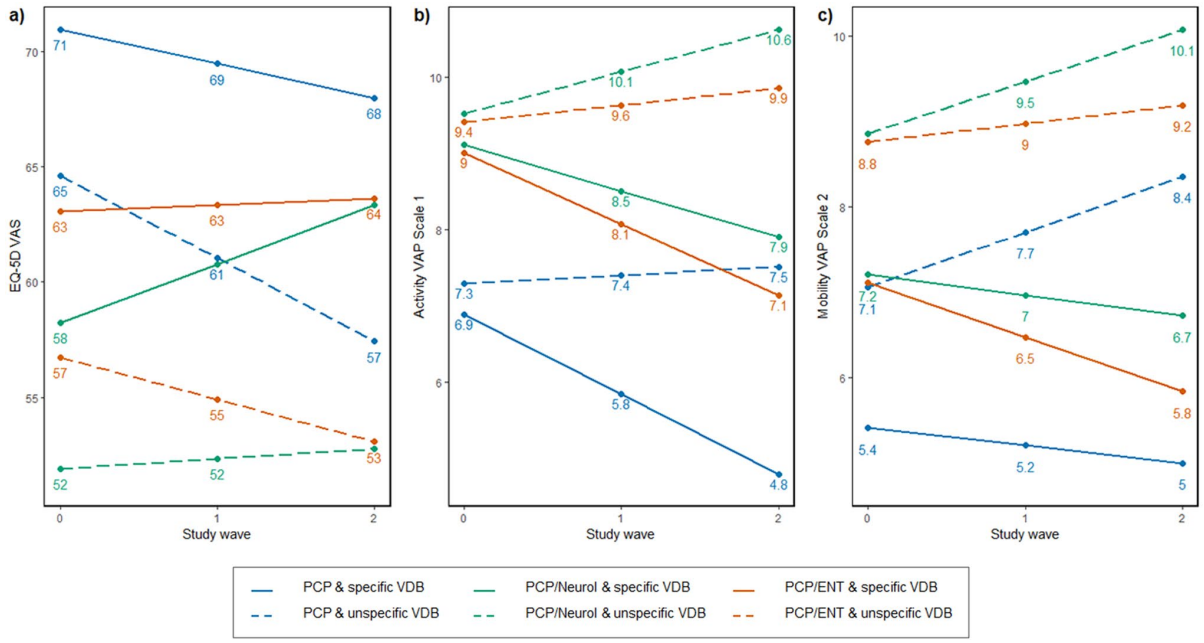

Fig. 2 Difference in the predicted values of an exemplary patient between the distinct combination of referral cluster and diagnosis of VDB for **a** health-related quality of life measured by the visual analogue scale of the EQ-5D and functioning measured by the **b** activity scale and **c** mobility scale of the vestibular activities and participation questionnaire. The *numbers* show the predicted value at each time point

of the participating PCPs and thus might be partially inaccurate, since PCPs reported difficulties in establishing an accurate VDB diagnosis in the past [11] therefore frequently over-diagnosing unspecific VDB in patients who later were diagnosed with a specific cause of VDB [42]. The SSA used in this study is of an exploratory nature. An average silhouette width of 0.44 and a Hubert's C index of 0.08, which were used as quality indicators for the clustering, indicate that the clustering structure identified has to be considered weak, yet existent. Referral trajectories in this study consist of three waves and do not allow any statements for longer than 1 year. This is especially important as we are not able to predict whether the trend for the different development of HRQoL between the referral patterns and for the different development of functioning between the patients with a specific and patients with an unspecific diagnosis, which we found in our analysis, continues. We therefore strongly suggest to further review our findings, including higher case numbers and a longer follow-up period.

In conclusion, current referral trajectories in a primary care setting in older patients with VDB were determined by present comorbidities of the patients and the regional healthcare characteristics. Referral patterns affected patients' HRQoL. Although our analysis was of exploratory nature it indicates that unspecific VDB diagnoses increase the risk of ineffective management and consequently impaired functioning. Implementation of evidence-based standardized care pathways for management and referral of patients with VDB might be one potential solution to this problem.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00415-022-11060-8.

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Authors´ contributions All authors contributed to the study conception and execution. Material preparation and data collection were performed by RK, LS, and KV. DK, BK, RK and EG are responsible for the study's quality assessment. The data analysis was performed by BK with the assistance of RS. The first draft of the manuscript was written by BK and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Declarations

Conflicts of interest The authors declare that they have no conflict of interest.

Ethics approval and consent to participate Ethics approval for MobiLE-TRA was obtained from the Ethics Committee of the Ludwig-Maximilians-Universität München (#17–443) and the Ethics Committee of the Technische Universität Dresden (#E365092017). Written informed consent was obtained from all participants. The study was performed in accordance with the Declaration of Helsinki principles.

Consent for publication Not applicable.

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5 Publication III

Association of self-efficacy, risk attitudes, and time preferences with functioning in older patients with vertigo, dizziness, and balance disorders in a tertiary care setting — Results from the mobile-TRA2 cohort

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Association of self-efficacy, risk attitudes, and time preferences with functioning in older patients with vertigo, dizziness, and balance disorders in a tertiary care setting—Results from the MobilE-TRA2 cohort

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Introduction: The functional burden of vertigo, dizziness, and balance problems (VDB) might depend on the personality traits of the patients affected. The aim of this study thus was to investigate the impact of self-efficacy, risk attitudes, and time preferences on functioning in older patients with VDB before and after treatment in a specialized tertiary care center.

Methods: Data for this study was obtained from the MobilE-TRA2 cohort study, conducted at a specialized tertiary care center in Germany. Patients aged 60 and older were assessed during their initial stay at the care center and 3 months later, using self-administered questionnaires. Self-efficacy was measured on a scale from 1 (very low) to 5 (very high). Health-related risk attitudes were inquired using an 11-point scale. Time preferences were measured by evaluating patients' willingness to postpone a reward in favor of a greater benefit on an 11-point Likert scale. Functioning was evaluated using the Dizziness Handicap Inventory, representing functional, emotional, and physical aspects of functional disability caused by VDB. Mixed-effects regression models were used to analyze the association between the selected personality traits and functioning over time. Interaction terms with time were incorporated for each personality trait, enabling the assessment of their influence on functioning 3 months following the initial observation period.

Results: An overall of 337 patients (53% women, median age at baseline = 70 years) were included. Patients with higher self-efficacy (Beta = −3.82, 95%-CI [−6.56; −1.08]) and higher willingness to take risks (Beta = −1.31, 95%-CI [−2.31; −0.31]) reported better functioning during their initial visit at the care center. Self-efficacy significantly predicted functioning after 3 months for overall functioning (Beta = −4.21, 95%-CI [−6.57; −1.84]) and all three domains.

Conclusion: Our findings suggest that patients with high self-efficacy and high willingness to take risks may exhibit better coping mechanisms when faced with the challenges of VDB. Promoting self-efficacy may help patients to better manage the duties accompanying their treatment, leading to improved functioning. These insights may inform the development of personalized treatment aimed at reducing the functional burden of VDB in older patients.

KEYWORDS

vertigo, dizziness, balance disorders, functioning, self-efficacy, risk attitudes, time preferences

1 Introduction

Vertigo, dizziness, and balance problems (VDB) are common and challenging syndromes, especially in older adults. They affect over 30% of the population over the age of 60 (1–3) and result in relevant and often persistent functional decline (4). While VDB commonly are a result of disorders of the vestibular system, they also can be provoked by other diseases, such as orthostatic hypotension or polyneuropathy. People with VDB are often faced with a wide range of problems in carrying out tasks of their daily lives (5, 6), including work-related and social activities (7). Household chores and grocery shopping, traveling, reading, and even walking, bending over or dressing can become challenging (8, 9). Depression and anxiety are common comorbidities (10, 11), arguably provoked by feelings of reduced self-esteem, fear, vulnerability, frustration, and isolation (12).

Earlier research suggests that people with certain personality structures are particularly susceptible to VDB and its effects (13, 14) and that individuals differ in their ways of coping with functional restrictions caused by VDB (15). In the context of highly specialized tertiary care, personality traits might influence the patients' ability to navigate the challenges inherent in their care process, as observed in the management of chronic diseases (16). As such, it is conceivable that personality traits may hold predictive value in determining treatment outcomes to some extent. Nevertheless, the current state of research on the impact of personality traits on functional restrictions in patients with VDB remains sparse.

Further insights may come from the field of behavioral economics, which is a branch of economics that combines approaches and methods from economics and psychology to understand how and why individuals make decisions and choices (17). Concepts from behavioral economics recognize that patients may not consistently conform to the expected rationality when coping with their disease and the associated restrictions. This deviation can be attributed to variations in underlying personality traits, including but not limited to the patient's confidence in their ability to overcome a health problem, their risk-taking propensity, and the way they assess the benefits or harms that lie in the distant future (18). Such insights could be helpful to better understand and predict functional restrictions in patients with VDB. The present work focuses on three prominent personality traits, namely self-efficacy, individual risk attitudes, and time preferences, as three selected BE concepts in the realm of health-related decision-making, which are known to be major determinants of health behavior (16, 19–21).

Self-efficacy denotes the belief in one's ability to organize and execute the courses of action required to successfully achieve set goals (22). The positive influence of self-efficacy on various health outcomes is well-known in the literature (16, 23–25). With regard to VDB, it may indicate patients' willingness to actively confront their problems. This has been shown, e.g., for visual height intolerance (26), a condition characterized by discomfort or anxiety when individuals are exposed to heights or elevated places, even if they are safe and enclosed. Likewise, patients with high levels of self-efficacy and resilience were less likely to develop secondary somatoform dizziness and vertigo (27). Also, internal health locus of control, i.e., the belief that individuals themselves are in control of managing their health condition (28), was found to support coping in VDB (29). Although internal locus of control encompasses a broader belief in the control over one's health condition, while self-efficacy is more focused on task-specific confidence, these findings underline the importance of patients' perceptions of control.

Health-related risk attitudes refer to an individual's general propensity to take or avoid risks in health-related decision situations (21). They hold significance in understanding coping styles within VDB, where individuals regularly face risk-related decisions linked to daily activities, involving certain actions or environments that may exacerbate symptoms. Moreover, individuals with VDB have to consider their elevated propensity for falls (30, 31). Patients with VDB thus must carefully assess the level of engagement in health-related activities, such as performing physical exercise, that pose some risk of triggering symptoms or falls but may contribute to maintaining overall functioning. Some individuals may be very risk-averse, resulting in excessive caution (11, 32), exaggerated self-restriction, or even complete avoidance of environments they perceive as safe (33). Such self-imposed restriction could then result in adverse consequences, including diminished core stability and restricted participation in various activities. Conversely, those more willing to take risks may not be as susceptible to fear and exaggerated self-restriction possibly mitigating the negative impact of VDB on functioning.

Finally, time preferences, reflecting the patient's valuation of the present over the future when deciding between immediate health

benefits or harms and potential benefits or harms in the future (34–36), can influence health behavior. It has been demonstrated that more present-oriented individuals tend to be less likely to adopt healthy lifestyles than future-oriented individuals (20, 37) and engage in fewer self-management activities (38, 39). On the other hand, individuals with a stronger present orientation reported lower levels of concern about future illness (40). Consequently, they might be more optimistic about the future and therefore experience lower levels of self-imposed restrictions (33) than their future-oriented counterparts.

It is widely recognized that patients with VDB derive substantial benefit from evidence-based and interdisciplinary rehabilitation programs in many different underlying pathologies (41–45). The effects of such rehabilitation programs seem to be even larger when the interventions are tailored to the patients' specific needs (46). In this context, gaining a better understanding of how the selected personality traits influence functioning and recovery in patients with VDB before and after their visit to a highly specialized tertiary care center may help to adapt and further improve existing therapeutic approaches.

The objective of this article thus was to investigate the impact of self-efficacy, risk attitudes, and time preferences on the development of functioning in older patients with VDB before and after treatment in a specialized tertiary care setting.

2 Materials and methods

2.1 Study design and study population

Data for this research project was collected in the prospective cohort study MobilE-TRA2 ("Behavioral and patient-individual determinants of quality of life, functioning and physical activity in older adults") at the interdisciplinary outpatient clinic of the German Center for Vertigo and Balance Disorders (DSGZ) at the Munich University Hospital. The DSGZ is one of the world's leading centers for diagnosis, treatment, and research of vertigo. Patients usually present at the clinic after referral from primary care. The study included patients aged 60 and older with VDB who presented for their initial interdisciplinary evaluation at the DSGZ. Patients with terminal diseases, cognitive impairment, or insufficient command of the German language were excluded. A more detailed description of the study is given elsewhere (47).

The sample size calculation for MobilE-TRA 2 was guided by a clinically significant difference of 10.0 points on the DHI, assuming a standard deviation of 25. Targeting a power of 0.8 (alpha = 0.05) necessitated a sample size of 52 patients. Given the longitudinal nature of MobilE-TRA 2, spanning three waves, and anticipating a 20% loss to follow-up between each wave, we established a minimum sample size of 81 patients. As different underlying pathologies had to be considered in order to control for their impact on our estimates, we quadrupled this figure, arriving at a target sample size of 324 patients.

The MobilE-TRA-2 study received ethics approval from the Ethics Committee at the medical faculty of Ludwig Maximilian University of Munich (#20-727). Written informed consent was obtained from all participants and the study was performed in accordance with the Declaration of Helsinki principles.

2.2 Data collection procedures

Baseline assessment was conducted between December 2020 and June 2022 and consisted of a self-administered questionnaire which patients either completed during their stay at the DSGZ or sent back via postal mail. Information from the patient registry DizzyReg of the DSGZ (48) was used to complement the baseline assessment. In brief, DizzyReg is an ongoing prospective clinical patient registry that collects and combines information stored in electronic health records and medical discharge letters with patient-reported information gathered by self-administered questionnaires. For the follow-up of the MobilE-TRA2 cohort, patients were mailed a questionnaire 3 months after the individual baseline assessment. Patients who did not respond to the initial follow-up questionnaire within 1 month received a reminder and were supplied with an identical duplicate of the initial follow-up questionnaire.

2.3 Personality traits

Self-efficacy was rated based on the three items of the General Self-Efficacy Short Scale (49). Patients report their confidence that they (1) can rely on their abilities in difficult situations, (2) can handle most problems well on their own, and (3) can usually solve even demanding and complex tasks effectively. The level of confidence is rated on a scale from 1 ("doesn't apply at all") to 5 ("applies completely"). The level of self-efficacy was calculated as the arithmetic mean of all three answers, resulting in a scale from 1 (very low self-efficacy) to 5 (very high self-efficacy). To measure health-related risk attitudes, a single item with an 11-point scale was used, ranging from 0 ("not at all willing to take risks") to 10 ("very willing to take risks") (21). The concept of time preferences used in this analysis was assessed by two items. One item measures the willingness to postpone a reward (0 = not willing at all, 10 = very willing) for the sake of a greater benefit in the future (36) and one item assesses the patient's orientation toward the present rather than in the future ("I am only concerned about the present, because I trust that things will work themselves out in the future," 1 = totally disagree, 5 = "totally agree") (34).

2.4 Functioning

Functioning was assessed using the German version of the Dizziness Handicap Inventory (DHI) (8, 50). The DHI is the most commonly used instrument to assess functioning loss caused by dizziness in everyday activities, including activity limitation, participation restrictions, and experienced difficulties. It incorporates 25 single items that can be summarized into three domains, representing functional (range 0–36), physical (range 0–28), and emotional (range 0 – 36) aspects of functioning, as well as a total score (range 0–100). Higher scores indicate more severe limitation or restriction.

2.5 Covariables

The selection of covariables for this study was based on the directed acyclic graph (DAG) presented in Supplementary Figure S1. This approach allowed us to identify the minimal sufficient adjustment set necessary to control for potential confounding while simultaneously avoiding bias from over-adjustment or collider bias (51). The construction of the DAG was informed by a review of the literature and experts' knowledge at the DSGZ. The resulting minimal adjustment set contained the specific VDB diagnosis, multimorbidity, a history of falls prior to the visit at the DSGZ, as well as information on the age, gender, education, and marital status of the participants.

The specific diagnosis of VDB was based on an extensive neurootological workup performed at the DSGZ, conforming to current guidelines (52–57). This workup includes a comprehensive battery of bedside tests, audiologic and vestibular function tests, as well as imaging if necessary. We focused on the most frequent diagnoses at the DSGZ, namely benign paroxysmal positional vertigo (BPPV), unilateral vestibulopathy, bilateral vestibulopathy, Menière's disease, vestibular migraine, central vestibular disorders, functional vertigo, orthostatic vertigo, and vertigo caused by polyneuropathy. Less frequent diagnoses were assigned to "Other" to facilitate statistical analysis. If no single leading cause was identifiable by the experts at the DSGZ, patients were classified as having multifactorial VDB.

Additional information was provided by patients regarding existing comorbidities related to the heart, lungs, liver, kidneys, neurological conditions, high blood pressure, inflammatory joint diseases, and further diseases specifically indicated by the participants. This approach yielded a compilation of 13 potential comorbidities, which can be found in Supplementary Table S1. We used this information to identify multimorbid patients, i.e., patients that suffered from at least two chronic conditions in addition to VDB. Multi-morbidity was added as binary information (yes/no) in the analysis.

During baseline assessment, patients reported whether they had fallen within the last 12 months prior to their visit at the DSGZ using a single yes-or-no question. Information on age and gender (male/female) was based on patients' self-report. Education levels were categorized based on the German educational system into: no graduation, lower secondary education 1 (equals 9 years of school), lower secondary education 2 (equals 10 years of school), upper secondary education (equals 12 or 13 years of school), and tertiary education (university, university of applied sciences). Marital status was self-reported (single, married, divorced, or widowed).

2.6 Statistical analysis

Summary statistics were calculated for the overall sample and separately for each diagnosis of VDB. Mean and standard deviation were reported for normally distributed continuous variables, median and the interquartile range for non-normally distributed variables, and relative and absolute frequencies for categorical variables. Potential differences in the observed variables between different diagnoses of VDB were examined using one-way ANOVA for normally distributed continuous variables, Kruskal-Wallis test for non-normally distributed continuous variables, and Chi-squared test for categorical variables.

Longitudinal linear mixed models with random intercept and fixed slopes were applied to assess the association between the selected personality traits and the level of functioning over time. We computed four distinct models: one for the overall DHI to estimate overall functioning and separate models for each of the three DHI sub-scales. Each beta coefficient obtained from the models represents the estimated change in the respective DHI score associated with a one-unit change in the corresponding predictor variable while controlling for the influence of all other variables in the model. Within each model, we simultaneously integrated the variables indicating self-efficacy, risk attitudes, and time preferences. This approach allowed us to accurately estimate the impact of each personality trait while simultaneously controlling for the influence of the other two traits. To assess potential multicollinearity issues among the personality traits and other covariates, we computed variance inflation factors (VIF) (58) using a predetermined threshold of 5 points. Furthermore, we introduced interaction terms involving time for each personality trait within each model, enabling us to investigate whether changes in functioning over time were predicted by the patients' respective personality traits.

In the regression analyses, we adopted a strategy of centering the measures of self-efficacy, risk attitudes, and time preferences around their respective means. This decision was informed by the observed concentration of values around the mid-range, with comparatively few instances of extremely low or high values. By employing centered models, we derived estimators for the intercept and overall change over time that are representative for individuals with moderate levels of these personality traits. These estimators directly capture a significantly larger portion of our study cohort compared to non-centered models. Given the minimum age criterion established in the inclusion criteria, we also subtracted the minimum age of 60 from the patients' age in years. Consequently, the reported estimates for the intercepts and the overall change over time in the centered models apply to patients at the age of 60 with mean personality traits.

Time preferences were represented by patients' willingness to postpone a reward within the primary analysis. To assess the robustness of our findings, we performed sensitivity analyses in which we re-evaluated the identical longitudinal linear mixed models. However, in these analyses, we measured time preferences based on patients' present-time orientation ("I am only concerned about the present, because I trust that things will work themselves out in the future"). This was done to examine whether the specific assessment of time preferences has an impact on the results.

The significance level was set to 5%. All computational analyses were carried out with R Version 4.1.2, including the usage of the *nlme* library (59). Regression assumptions were tested visually. We employed DAGitty, a browser-based, open-source tool to construct, edit, and analyze the DAG central to our study (60). In essence, users utilize a graphical interface to create the DAG, and the tool automatically identifies and highlights causal and biasing paths using distinct colors. This dynamic feature allows researchers to promptly and interactively assess the impact of

DAG modifications, such as adding new arrows or variables or inverting arrows with unclear causal direction. Additionally, DAGitty identifies the minimal adjustment set by and underlying algorithm, providing real-time feedback to the user along with the underlying assumptions.

3 Results

A total of 337 patients (53 % women, median age at baseline = 70 years, IQR = [64, 78]) were included in the baseline assessment. Of these, 299 (89%) returned the follow-up questionnaires, which were sent out 3 months after their respective baseline assessment. The most frequent diagnoses at baseline were BPPV [$n = 48$, (21%)] and functional vertigo ($n = 48$), followed by balance problems caused by polyneuropathy ($n = 43$). Thirty patients were classified as having multifactorial VDB. A third ($n = 112$, 33%) of the patients reported to have experienced at least one fall within the last 12 months prior to their visit. Additional details can be found in Table 1.

The mean overall DHI score across all patients at baseline was 41 points, indicating a moderate level of handicap due to VDB, with 62 (18%) patients reaching an overall DHI of more than 60 points (severe handicap) (61). The overall DHI score as well as all three sub-scores differed significantly across the diagnoses of VDB. Patients with bilateral vestibulopathy and patients with functional vertigo reported the highest level of impairment with DHI scores of 48.57 and 47.70, respectively. Conversely, patients with orthostatic vertigo and patients with other forms of VDB presented with better functioning (DHI = 29.21, resp. DHI = 28.10). The patients' willingness to postpone a reward (mean = 6.19, SD = 2.16) differed significantly across VDB diagnoses. Patients with functional vertigo exhibited the lowest willingness to delay gratification (mean = 5.42, SD = 2.19). The measures related to self-efficacy (mean = 3.96, SD = 0.85) and willingness to take risks (mean = 4.63, SD = 2.33) did not significantly differ across the various VDB diagnoses.

The mean overall DHI score at the follow-up assessment was 39 points across all patients. The overall DHI score again varied across the diagnoses of VDB, with corresponding differences in the functional and physical sub-scales of the DHI. A comprehensive list of the overall DHI scores and the three distinct DHI sub-scales for each diagnosis at follow-up is provided in Supplementary Table S2.

Adjusted for all covariates, the overall functional status increased on average by 2.56 points (95%-CI [−4.47; −0.65]) over the course of 3 months. Patients with higher self-efficacy reported better overall functioning at baseline (Beta = −3.82, 95%-CI [−6.56; −1.08]) and experienced greater improvement after 3 months (Beta = −4.21, 95%-CI [−6.57; −1.84]). While patients displaying a greater willingness to take risks reported slightly better overall functioning at baseline (Beta = −1.31, 95%-CI [−2.31; −0.31]), there were no statistically significant differences in their rate of improvement over time compared to risk-averse patients. Time preferences were neither significantly associated with baseline functioning nor with improvement over time. More detailed results of the mixed models for the DHI overall scales and the DHI subscales are presented in Table 2.

The performed sensitivity analysis revealed that using the patient's orientation toward the present as an alternative operationalization of time preferences did not change the association found in the main model (Supplementary Table S3). This consistency underscores the robustness of our findings.

Figure 1 displays a graphical representation of the predicted values from our models. It illustrates the overall functioning at the baseline assessment and the three-month follow-up for various values of the selected personality traits. Based on these predictions, a threshold of 3.29 points on the self-efficacy scale was identified as necessary for patients to experience an improvement in functioning over the course of 3 months. Patients below this threshold had lower functioning compared to their baseline assessment.

4 Discussion

We analyzed the impact of self-efficacy, risk attitudes, and time preferences on functioning in older patients with vertigo, dizziness, and balance disorders (VDB) using cohort data from a specialized tertiary academic care clinic. Patients with higher self-efficacy and more willingness to take risks reported higher levels of functioning when presenting at the clinic. Higher self-efficacy was also found to be an independent predictor of a better recovery at 3 months after initial assessment.

Overall, patients showed a small but significant improvement in functioning over time which might in part be due to the standardized diagnostic workup at the DSGZ and the long-standing experience of the clinic with management of VDB. These findings are in good agreement with previous research, highlighting the potential benefits of evidence-based and interdisciplinary assessment and vestibular rehabilitation therapy (42, 44) for patients with VDB.

Our analysis showed that patients with higher levels of self-efficacy were less restricted by their symptoms. These findings align with previous studies that have emphasized the positive influence of self-efficacy on various health outcomes, both within VDB (26, 27) and in general (16, 23, 25). Our results suggest that individuals who have a greater belief in their abilities to handle difficult situations, solve problems, and rely on their skills might have already developed effective coping mechanisms and adopted them in their daily life, thereby mitigating the impact of VDB on their functioning.

Our most striking observation was that self-efficacy predicted functional status of the patients 3 months after their initial visit. This indicates that patients may require a certain level of self-efficacy to experience functional improvement over time. Patients with very high self-efficacy demonstrated remarkable improvements, while those with low self-efficacy displayed an even lower functioning status after 3 months than during their first visit at the DSGZ. This suggests that self-efficacy may have a dual role in VDB diagnostics, serving as both a prerequisite and a catalyst for functional improvement after visiting a specialized care center. One possible explanation for this observation lies in the challenges

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TABLE 1 Unadjusted summary statistics stratified by diagnosis at baseline assessment ($n = 337$).

	Diagnosis												
	Overall	BPPV	Unilateral vestibulopathy	Bilateral vestibulopathy	Ménière's disease	Vestibular migraine	Central vestibular	Functional vertigo	Orthostatic vertigo	Polyneuropathy	Multifactorial	Other	*p*-value[a]
N (%)	337	48	18	14	33	29	22	48	29	43	30	23	
Socio-economic information and medical background													
Age (median, IQR)	70.00 [64.00, 78.00]	69.00 [65.00, 77.25]	67.00 [60.50, 70.50]	69.00 [64.75, 77.75]	72.00 [67.00, 77.00]	64.00 [61.00, 71.00]	68.50 [63.00, 75.75]	64.50 [61.75, 70.25]	75.00 [62.00, 78.00]	78.00 [73.00, 81.50]	77.50 [73.25, 82.00]	65.00 [62.50, 71.50]	<0.001
Gender (*n*, %)													
Female	179 (53.1)	29 (60.4)	8 (44.4)	6 (42.9)	21 (63.6)	20 (69.0)	9 (40.9)	39 (81.2)	13 (44.8)	15 (34.9)	11 (36.7)	8 (34.8)	<0.001
Male	158 (46.9)	19 (39.6)	10 (55.6)	8 (57.1)	12 (36.4)	9 (31.0)	13 (59.1)	9 (18.8)	16 (55.2)	28 (65.1)	19 (63.3)	15 (65.2)	
Fall within last 12 months (*n*, %)													
No	220 (66.3)	30 (63.8)	12 (66.7)	8 (57.1)	26 (78.8)	25 (86.2)	14 (66.7)	34 (72.3)	16 (55.2)	26 (61.9)	16 (53.3)	13 (59.1)	0.192
Yes	112 (33.7)	17 (36.2)	6 (33.3)	6 (42.9)	7 (21.2)	4 (13.8)	7 (33.3)	13 (27.7)	13 (44.8)	16 (38.1)	14 (46.7)	9 (40.9)	
Multimorbidity (≥2 Comorbidities) (*n*, %)													
No	142 (42.1)	16 (33.3)	8 (44.4)	6 (42.9)	19 (57.6)	13 (44.8)	10 (45.5)	23 (47.9)	12 (41.4)	12 (27.9)	9 (30.0)	14 (60.9)	0.158
Yes	195 (57.9)	32 (66.7)	10 (55.6)	8 (57.1)	14 (42.4)	16 (55.2)	12 (54.5)	25 (52.1)	17 (58.6)	31 (72.1)	21 (70.0)	9 (39.1)	
Education[b] (*n*, %)													
Lower secondary education 1	119 (36.3)	18 (37.5)	6 (35.3)	5 (35.7)	12 (37.5)	9 (32.1)	6 (27.3)	13 (28.3)	14 (51.9)	17 (39.5)	12 (41.4)	7 (31.8)	0.981
Lower secondary education 2	81 (24.7)	14 (29.2)	5 (29.4)	4 (28.6)	5 (15.6)	5 (17.9)	10 (45.5)	14 (30.4)	4 (14.8)	10 (23.3)	6 (20.7)	4 (18.2)	
Upper secondary education	40 (12.2)	4 (8.3)	2 (11.8)	2 (14.3)	5 (15.6)	5 (17.9)	2 (9.1)	6 (13.0)	3 (11.1)	6 (14.0)	2 (6.9)	3 (13.6)	
Tertiary education	87 (26.5)	11 (22.9)	4 (23.5)	3 (21.4)	10 (31.2)	9 (32.1)	4 (18.2)	13 (28.3)	6 (22.2)	10 (23.3)	9 (31.0)	8 (36.4)	
No graduation	1 (0.3)	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Marital status (*n*, %)													
Single	22 (6.5)	6 (12.5)	3 (16.7)	1 (7.1)	1 (3.0)	1 (3.4)	2 (9.1)	2 (4.2)	3 (10.3)	0 (0.0)	2 (6.7)	1 (4.3)	0.727

(Continued)

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TABLE 1 (Continued)

	Diagnosis												
	Overall	BPPV	Unilateral vestibulopathy	Bilateral vestibulopathy	Ménière's disease	Vestibular migraine	Central vestibular	Functional vertigo	Orthostatic vertigo	Polyneuropathy	Multifactorial	Other	*p*-value[a]
Married	227 (67.4)	31 (64.6)	13 (72.2)	9 (64.3)	22 (66.7)	18 (62.1)	17 (77.3)	33 (68.8)	20 (69.0)	28 (65.1)	20 (66.7)	16 (69.6)	
Divorced	49 (14.5)	7 (14.6)	2 (11.1)	2 (14.3)	4 (12.1)	6 (20.7)	3 (13.6)	9 (18.8)	2 (6.9)	6 (14.0)	4 (13.3)	4 (17.4)	
Widowed	39 (11.6)	4 (8.3)	0 (0.0)	2 (14.3)	6 (18.2)	4 (13.8)	0 (0.0)	4 (8.3)	4 (13.8)	9 (20.9)	4 (13.3)	2 (8.7)	
Personality traits													
Self-efficacy (mean, SD)	3.96 (0.85)	3.85 (0.74)	4.02 (0.77)	4.03 (0.75)	4.00 (0.69)	4.25 (0.89)	3.83 (0.91)	4.02 (0.93)	4.00 (1.10)	3.75 (0.85)	3.94 (0.74)	4.03 (1.01)	0.562
Health-related risk attitudes (mean, SD)	4.63 (2.33)	4.34 (2.42)	4.59 (2.58)	5.21 (2.58)	5.36 (2.25)	3.68 (2.13)	4.59 (2.61)	4.19 (2.21)	5.14 (2.22)	4.76 (2.01)	4.80 (2.12)	4.83 (2.82)	0.217
Time preferences—willingness to postpone a reward (mean, SD)	6.19 (2.16)	6.15 (2.04)	7.50 (1.95)	6.79 (2.26)	7.03 (2.01)	6.44 (2.34)	5.86 (2.05)	5.42 (2.19)	5.86 (2.21)	5.62 (1.93)	6.50 (1.85)	6.39 (2.48)	0.007
Time preferences—present-orientation (mean, SD)	2.53 (1.03)	2.37 (0.97)	2.41 (1.06)	2.57 (1.09)	2.68 (1.08)	2.42 (1.06)	2.62 (0.86)	2.71 (0.92)	2.82 (1.09)	2.54 (1.10)	2.34 (1.11)	2.18 (1.10)	0.490
Functioning													
DHI overall score (mean, SD)	40.93 (21.40)	43.83 (22.39)	45.00 (23.09)	48.57 (20.58)	43.67 (19.92)	32.83 (24.41)	44.00 (22.35)	47.70 (17.87)	29.21 (14.89)	38.70 (21.05)	44.64 (20.87)	28.10 (21.59)	0.001
DHI functional score (mean, SD)	16.53 (9.80)	17.17 (10.50)	17.75 (9.49)	19.29 (8.69)	17.74 (8.34)	13.23 (10.73)	18.00 (10.32)	19.62 (8.99)	13.21 (7.88)	15.35 (9.08)	18.50 (10.99)	10.19 (9.59)	0.007
DHI physical score (mean, SD)	11.41 (6.95)	13.87 (6.03)	14.25 (7.41)	15.00 (7.72)	10.13 (7.78)	7.67 (6.66)	12.57 (6.85)	11.67 (6.34)	7.50 (4.95)	11.68 (7.98)	12.69 (5.81)	9.00 (6.26)	<0.001
DHI emotional score (mean, SD)	13.04 (8.14)	12.78 (8.78)	13.00 (8.36)	14.29 (7.68)	16.00 (8.27)	11.62 (8.73)	13.43 (8.51)	16.38 (6.66)	8.50 (6.41)	11.68 (7.17)	13.50 (8.28)	10.27 (8.93)	0.003

BPPV, Benign paroxysmal positional vertigo; DHI, Dizziness Handicap Inventory; IQR, Interquartile range; SD, Standard deviation. [a]ANOVA, Kruskal-Wallis test, Chi-squared test. [b]Lower secondary education 1 equals 9 years of school, Lower secondary education 2 equals 10 years of school, upper secondary education equals 12 or 13 years of school.

TABLE 2 Longitudinal linear mixed models to assess the association between personality traits and functioning.

	Dizziness handicap inventory (95%−CI)			
	M1: overall score	M2: functional score	M3: physical score	M4: emotional score
Observations (n)	557 (305)	559 (305)	560 (306)	562 (306)
(Intercept)[a]	44.53 (33.07; 56.00)	18.38 (13.13; 23.62)	11.75 (7.95; 15.55)	14.49 (10.20; 18.79)
Wave[a]				
Baseline	Reference	Reference	Reference	Reference
Follow-up (3 months later)	**−2.56 (−4.47; −0.65)**	**−1.17 (−2.03; −0.32)**	−0.04 (−0.75; 0.67)	**−1.44 (−2.17; −0.71)**
Personality traits (centered to the respective mean)				
Self-efficacy[b]				
Self-efficacy	**−3.82 (−6.56; −1.08)**	**−1.76 (−3.01; −0.52)**	−0.60 (−1.51; 0.31)	**−1.49 (−2.51; −0.48)**
Self-efficacy* time	**−4.21 (−6.57; −1.84)**	**−1.65 (−2.71; −0.59)**	**−1.03 (−1.89; −0.17)**	**−1.43 (−2.32; −0.55)**
Health-related risk attitudes[c]				
Risk attitudes	**−1.31 (−2.31; −0.31)**	**−0.54 (−0.99; −0.09)**	−0.07 (−0.40; 0.27)	**−0.71 (−1.09; −0.34)**
Risk attitudes* time	0.29 (−0.56; 1.14)	0.16 (−0.22; 0.54)	−0.01 (−0.32; 0.31)	0.13 (−0.20; 0.45)
Time preferences—willingness to postpone a reward (WPR)[d]				
WPR	−0.38 (−1.48; 0.73)	−0.21 (−0.72; 0.29)	0.11 (−0.25; 0.48)	−0.28 (−0.69; 0.13)
WPR* time	−0.12 (−1.05; 0.81)	0.03 (−0.39; 0.44)	−0.21 (−0.55; 0.13)	0.01 (−0.34; 0.36)
Random effects				
Intercept (SD)	15.49	7.13	4.89	5.75

Higher scores indicate worse functioning. Significant findings are printed in bold. All models are controlled for the diagnosis, present falls within the last 12 months, multimorbidity, age, gender, education, and marital status. CI, Confidence interval; M1–M4, Models 1 to 4, one model per score; SD, Standard deviation. [a]Applies for patients aged 60 with mean self-efficacy of 3.96, mean risk attitudes of 4.63, and mean willingness to postpone a reward of 6.19. [b]Centered to mean self-efficacy of 3.96. [c]Centered to mean risk attitudes of 4.63. [d]Centered to mean willingness to postpone a reward of 6.19.

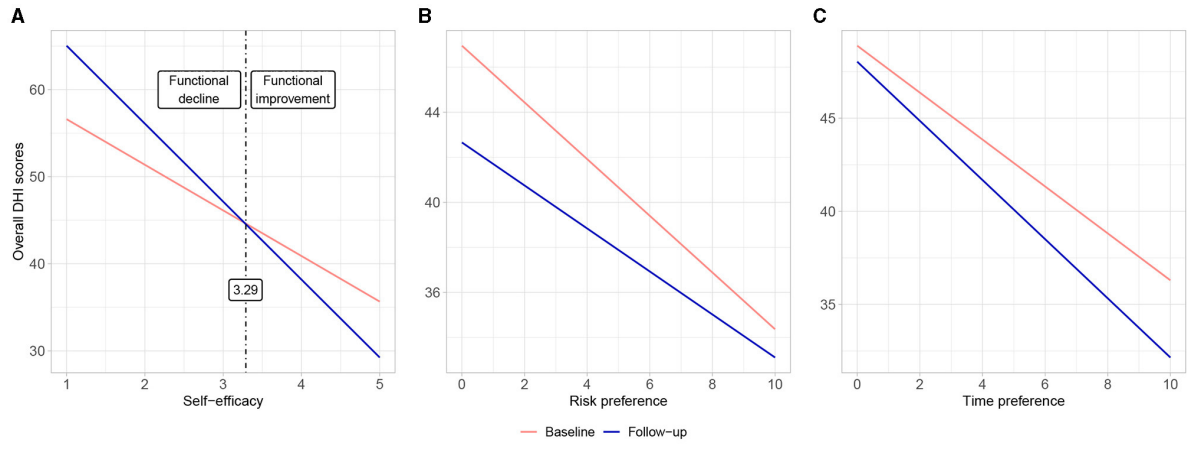

FIGURE 1
Comparison of predicted values for the overall functioning during baseline and follow-up assessment (3 months later) for different values of **(A)** self-efficacy, **(B)** risk attitudes, and **(C)** time preferences (willingness to postpone a reward). Higher values in the DHI scores indicate worse functioning.

that patients may find themselves confronted with when leaving the care center after their initial visit. Recommendations for future treatment options which, depending on the underlying pathology, may involve exercises, consultations with specialists, or additional diagnostic procedures, often require patients to take on new responsibilities and learn new skills. Consistent with this, previous research on self-efficacy in the management of chronic diseases suggests that patients with high self-efficacy are better able to cope with these challenges (16). This likely applies to patients with VDB leaving the care center as well. Therefore, empowering patients

to develop confidence in their abilities to actively participate in their treatment should be an important pillar of future treatment strategies. Self-efficacy enhancing interventions, which have proven to be of use in many other diseases (62–64), should be adapted and tested to meet the personal needs of patients with VDB (65).

Interestingly, our study revealed that patients with higher willingness to take risks demonstrated better functioning during their initial visit to the care center. This finding might appear surprising at first sight, considering that higher willingness to take risks is generally associated with a less healthy lifestyle (19, 21). However, in the case of VDB, patients with higher risk-taking tendencies may have developed strategies that contribute to maintaining their functioning. Individuals who are more inclined to take risks might more vigorously engage in activities that challenge their balance and mobility, leading to better adaptation and improved functioning. Additionally, they may be less affected by fears and uncertainties associated with the disease (5, 32). It is important to note that the results of this study should not be interpreted as a recommendation to promote risk-taking behavior in general, given the negative side effects of higher risk-taking found in other studies (19, 21). Instead, future research should focus on unraveling the specific strategies employed by patients with higher risk-taking tendencies to promote functioning.

Several limitations of this study have to be considered. First, most of the data gathered within this study relied on self-reported measures, which may be susceptible to potential information bias. Although we cannot exclude the possibility of such bias being present in our data, we want to emphasize that validated instruments were used, wherever available, and data collection and processing was accompanied by constant quality controls. The assessment of the personality traits relied on a set of self-assessment questions, rather than more extensive choice experiments. Usually, in the economic literature risk attitudes are elicited by a series of hypothetical or even monetarily incentivized lotteries, whereas setting to measure time preferences describe intertemporal trade-offs. However, our sample comprised a considerable portion of frail study participants, many of whom were older and in poor health. These participants might have been overwhelmed by the often-demanding choice experiments, resulting in biased, inaccurate, or incomplete data. Preference modules involving such comparably simple questions used within this study are well established and yielded good and comparable results in the past (66). Second, while personality traits had long been considered to be mostly stable over time (67), recent studies have questioned this traditional assumption, especially in the cases of health shocks (68, 69). This might also be of relevance in our field of application. Though it may be possible that self-efficacy, risk attitudes, or time preferences have changed between the baseline assessment and the follow-up, especially in the case of (very) successful or (very) unsuccessful treatments, a follow-up time of 3 months likely was too short for profound changes in the personality structure. Third, the data collection of this study took place during the COVID-19 pandemic, which might have influenced participants' experiences, perceptions, and behaviors, thus potentially entailing systematic differences in their personality traits. These pandemic-related factors could have affected the generalizability of our findings to non-pandemic periods. One indication for such an effect could be a systematic difference in the personality traits between time points of high incidence rates and rigorous restrictions and time points of low incidence rates and more loosened restrictions through the course of the baseline assessment. Though this was not the focus of this article, a performed descriptive sensitivity analysis showed that the personality traits remained somewhat stable over the course of the baseline assessment and did not reveal any indication of temporal trends.

Patients with vertigo, dizziness, or balance disorders often face considerable limitations and restrictions in functioning. In conclusion, our study contributes to the understanding of the influence of selected personality traits on functioning in older patients with VDB. Further research is warranted to elucidate the underlying mechanisms driving the observed associations found in this study. Adaptations to current treatment strategies are necessary to improve functioning as some patient groups, especially those with low self-efficacy, don't seem to benefit from current care pathways. Our findings provide an initial foundation for the development of tailored interventions that address personality traits, thereby contributing to the optimization of VDB management strategies. Promoting self-efficacy through clinical interventions and thoughtful communication can empower patients to play an active part in their treatment and thus holds promise for improving functioning and overall wellbeing in individuals with VDB.

Data availability statement

The datasets presented in this article are not readily available because of data privacy regulations that apply in the country of data collection. Requests to access the datasets should be directed to BK, benedict.katzenberger@med.uni-muenchen.de.

Ethics statement

The studies involving humans were approved by the Ethics Committee at the Medical Faculty of Ludwig Maximilian University of Munich (#20-727). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

BK: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Visualization, Writing—original draft, Writing—review & editing. SF: Methodology, Validation, Writing—review & editing, Data curation. LS: Conceptualization, Funding acquisition, Supervision, Writing—review & editing. RS: Methodology, Validation, Writing—review & editing. AH: Validation, Visualization, Writing—review & editing. DK: Project administration, Writing—review & editing. EG: Conceptualization, Funding

acquisition, Resources, Supervision, Writing—review & editing.

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Conflict of interest

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

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1316081/full#supplementary-material

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