From the Institute for Medical Information Processing, Biometry and Epidemiology (IBE)
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THE IMPACT OF ANTICHOLINERGIC AND SEDATIVE MEDICATIONS ON VERTIGO, DIZZINESS AND BALANCE DISORDERS IN OLDER PEOPLE IN GERMANY

Dissertation
zum Erwerb des Doctor of Philosophy (Ph.D.) an der
Medizinischen Fakultät der
Ludwig-Maximilians-Universität zu München

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on:
March 26th, 2020

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Date of Oral Defense: July 28th, 2020

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List of Abbreviations

AS	Anticholinergic and Sedative
AOR	Adjusted Odds Ratio
ATC	Anatomical Therapeutic Chemical - Classification System
BPPV	Benign paroxysmal positioning vertigo
CI	Confidence Interval
CONTENT	CONTinuous morbidity registration Epidemiologic NeTwork
DBI	Drug Burden Index
DDD	Defined Daily Dose
DIMDI	Deutsches Institut für Medizinische Dokumentation und Information (German Institute of Medical Documentation and Information)
ICD-10	International Classification of Diseases 10th Revision
KORA	Kooperative Gesundheitsforschung in der Region Augsburg (Cooperative Health Research in the Region of Augsburg)
PCP	Primary Care Practitioners
VDB	Vertigo, Dizziness and Balance disorders

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Doctoral Thesis: THE IMPACT OF ANTICHOLINERGIC AND SEDATIVE MEDICATIONS ON VERTIGO, DIZZINESS AND BALANCE DISORDERS IN OLDER PEOPLE IN GERMANY

Introductory Summary:
Relevance/Problem Statement

Advancements in health care have provided people the opportunity to add life to years and not just years to life. Consequently, due to the progressive demographic shift, the population is gradually aging and are more susceptible to chronic diseases, adverse drug reactions, polypharmacy and comorbidity. According to the World Health Organization, by 2050 it is estimated that every 1 in 5 people will be 60 years or older and account for about half of the total growth of the world population (1, 2). Additionally, the oldest-old population (≥85 years old) accounts for a majority of health care spending in Europe (3-5). In Germany, 5% of health care users and over 30% of medication costs can be contributed to older people with comorbidities (4). As life expectancies increase with modern times, the challenge faced is the older population battling with chronic diseases all the while being very dependent on the health care system to conserve and prolong their quality of life (6).

Vertigo, dizziness or balance disorders (VDB) are among the most prevalent causes for falls (7) and among the most disabling symptoms in older people (8). Yearly, VDB was found to affect around 15 to over 20% of adults in large population-based studies and its prevalence rises with age (9) reaching up to 85% in those ≥80 years old (7). In Germany, lifetime prevalence of vertigo and dizziness in community-dwelling adults was found to be 29.3% (women: 35.9%, men: 22.6%) (9-11). Furthermore, a recent age and sex representative survey of the German population, found an overall 1-year prevalence of vertigo or dizziness to be 24.2% (12). In Bavaria, annually 10% of the adult population is diagnosed and treated for vertigo (13, 14). VDB are among the most common reasons for medical consultation (15) and have been found to be a major contributor to falls (7, 16-18) and disability (19) in older adults. Interestingly, VDB is multifaceted and can be a symptom from diagnosed vestibular diseases like benign paroxysmal positioning vertigo (BPPV), be a consequence of aging systems in the body, or result from other conditions such as cardiovascular diseases (20), hypotension (21), psychiatric conditions (22), or medication (23, 24). The physical impact of VDB on older people is often underrated. Medication is of utmost importance because it is a modifiable risk factor, which should be considered.

With comorbidity comes a necessity for medication and vulnerability to prolonged drug effects and increased risk to unwanted side effects in older people (25). Of specific interest, are medications with anticholinergic and sedative (AS) effects as they may negatively influence the health and well-being of older people. Of concern in older people, are the potential effects of AS medications like confusion, blurred vision, delirium, or unsolicited central and peripheral adverse events (26) since these medications are prescribed for a multitude of indications including urinary incontinence, sleep disturbances, mental illness, pain, and cardiovascular and gastrointestinal disorders (27). These medications can include antipsychotics, antidepressants, and antihistamines, of which some have been deemed potentially inappropriate for older people in Germany (28).

High uses of AS medications have been associated with reduced cognitive functioning and functional impairments (27, 29, 30). Use of medicines with anticholinergic properties was associated with complications in balance and mobility (26, 31). Sedatives have been connected to depressive symptoms, impaired cognition, impaired muscle strength, falls and fractures (32-36). With the goal of inevitably minimizing or eliminating burdening medications in older people, a review of AS medications from primary care practitioners (PCPs) could be beneficial (26), especially for VDB patients.

Research Question

This PhD project aimed to answer the following research question: Is exposure to AS medications associated with an increased risk of VDB in older people in Germany?

Objectives

Specifically, the following objectives were targeted:

1. Develop a list of AS medications based on the German health care setting, which allows for calculation and utilization of AS burden using the Drug Burden Index (DBI) where applicable.
2. Examine the prevalence of AS burden and VDB prevalence
    a. in a selected German patient population in the primary care setting and
    b. in an older German general population based setting.
3. To analyze the potential association of AS burden with VDB in these populations
    a. in a nested matched case-control study using primary care registry data and
    b. in a cross-sectional study using health survey data utilizing the DBI.

Overview of the Doctoral Thesis

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

1. Phillips, Amanda; Strobl, Ralf; Grill, Eva; Laux, Gunter (2018). Anticholinergic and sedative medications and the risk of vertigo or dizziness in the German primary care setting-A matched case-control study from the CONTENT registry. Pharmacoepidemiology and Drug Safety, Vol. 27, Nr. 8: P. 912-920, https://doi.org/10.1002/pds.4575

   (referred to as "Publication 1" in the succeeding text)

2. Phillips, Amanda; Heier, Margit; Strobl, Ralf; Linkohr, Birgit; Holle, Ralf; Peters, Annette; Grill, Eva (2019). Exposure to anticholinergic and sedative medications using the Drug Burden Index and its association with vertigo, dizziness and balance problems in older people – Results from the KORA-FF4 Study. Experimental Gerontology, Vol. 124C, 2019, 110644, https://doi.org/10.1016/j.exger.2019.110644

   (referred to as "Publication 2" in the succeeding text)

Table 1. Contribution of publications to research objectives

Publication	Research Objective 1	Research Objective 2a	Research Objective 2b	Research Objective 3a	Research Objective 3b
Publication 1	✓	✓		✓	
Publication 2	✓		✓		✓

These articles represent a 4.5-year research process targeted to address the aforementioned objectives and research question.

Methods

Data Source, Study Design and Participants

The research question and objectives were addressed using:

- **Publication 1:** primary care based registry data from the German CONTENT (CONTinuous morbidity registration Epidemiologic NeTwork) registry (2010-2014)
- **Publication 2:** cross-sectional data from the second follow-up of the KORA (Cooperative Health Research in the Region of Augsburg)-S4 cohort study in 2014 (KORA-FF4)

CONTENT

The German CONTENT is a prospective registry based on primary care encounters in 4 German federal states (Baden-Württemberg, Hessen, Lower Saxony and Rhineland-Palatinate) and has been described in detail elsewhere (37, 38). The registry is maintained by the Department of General Practice and Health Services Research of the University Hospital Heidelberg. Data used in this study were collected from just over 1.8 million physician/patient encounters comprising routine claims data (diagnoses and medications given on a specific consultation day) within the German primary healthcare system between 1.1.2010 and 31.12.2014. Vertigo or dizziness diagnoses were recorded according to the International Classification of Diseases 10th Revision (ICD-10). The participating PCPs are representative of practice size and location in Germany (39). Ethical approval for the CONTENT project was given by the University Hospital Heidelberg Ethics Committee (No. 442-2005).

Electronic patient data from a total of 151,446 patients were screened. A VDB diagnosis was identified in 6,971 (4.6%) patients (cases) and these cases were matched with 6,971 corresponding controls using propensity score matching (40) to obtain comparable cohorts. A nested matched case-control study of n=6,971 cases with a VDB diagnosis and n=6,971 controls without a VDB diagnosis were included in the analyses of Publication 1.

KORA-FF4

Data originates from the Cooperative Health Research in the Region of Augsburg (KORA) FF4 study, the second follow-up of the KORA S4 study, a population-based health survey conducted in the city of Augsburg and two surrounding counties between 1999 and 2001. A total sample of 6640 subjects was drawn from the target population consisting of all German residents of the region aged 25 to 74 years.

Of all 4261 participants of the S4 baseline study, 2279 also participated in the 14-year follow-up FF4 study. The study was conducted from June 2013 to September 2014. Persons were considered ineligible for FF4 if they had died in the meantime (n=455, 10.7%), lived too far outside the study region or were completely lost to follow-up (n=296, 6.9%), or had demanded deletion of their address data (n=191, 4.5%). Of the remaining 3319 eligible persons, 157 could not be contacted, 504 were unable to come because they were too ill or had no time, and 379 were not willing to participate in this follow-up, giving a response rate of 68.7%. A non-participant questionnaire was

received from n=622 people. Of the final 2279 participants, 883 were ≥65 years old and included in the analyses of Publication 2.

The KORA-FF4 study collected variables through a telephone or face-to-face interview, and direct measurements at the study center. The investigations and interviews were carried out in accordance with the Declaration of Helsinki, including written informed consent of all participants. The ethics committee of the Bavarian Chamber of Physicians, Munich (EC No. 06068), approved all study methods.

Conceptual Foundations

Individual-level – Measuring AS Burden

A universally accepted list of AS medications is not currently available. Over the last 15 years, there have been multiple efforts to define AS medications and their level of burden (41-44). The desire for one universally accepted list of AS medications is nearly impossible due to the variability of prescription methods in primary care, dosage recommendations, and medications on the market from country to country. This in turn makes comparisons from scale to scale and population to population difficult to interpret (45); nevertheless incorporating the prescribed dose was found to be the most reliable in predicting anticholinergic adverse events (46). Therefore, applying and interpreting research methods regarding AS burden needs to be directly related to the population at risk and consider the prescribed dose.

First, a list of AS medications was compiled using:

- relevant published AS medication lists (42, 47-51)
- potentially inappropriate medications with AS effects from the German PRISCUS List (6)
- licensed product information collected in this study including Anatomical Therapeutic Chemical Classification System (ATC-Codes) (52, 53)

AS medications not available on the German market were not included in this list. This list was then used as a basis to go a step further and employ the dose for each AS medication as a measure of AS burden.

In 2007, Professor Sarah Hilmer created a pharmacological index, the DBI, to measure exposure to anticholinergic and sedative medications (42) and their burden on functioning in older adults and can be used worldwide (27, 54). DBI scores have been associated with functional impairment and other adverse outcomes in USA, Australia, Finland, Ireland, the Netherlands, New Zealand, UK populations and recently in

Germany (42, 46-48, 50, 51, 54-65). If validated in other specific populations worldwide, this pharmacological tool has potential to provide an evidence-based guide for prescribing in older people (42, 51, 54).

First, the individual burden of each AS medication is weighted equally to determine a score from 0 to 1, with 0.5 indicating exposure at the prescribed daily dose. Then, all individual AS medication DBI scores for each participant were summed for the total DBI score using the following formula (42):

$$\boldsymbol{DBI} = \Sigma \frac{\boldsymbol{D}}{\boldsymbol{\delta} + \boldsymbol{D}}$$

where D denotes the prescribed daily dose of any AS medication, and δ is the defined daily dose (DDD) of the individual drug according to German Institute of Medical Documentation and Information (DIMDI) (53) to ensure all dosages pertain to the German market. The DBI includes all regularly taken AS medications. Any medications, which were topical, inhaled, or ophthalmological, as well as medications not taken regularly were excluded in order to include only those medications where an accurate DBI could be calculated. If a medication was classified as having both anticholinergic and sedative effects, it was only included once in the DBI calculation (42, 66). A DBI >0 demonstrates AS burden. The higher the DBI score, the more AS burden the participant has.

To measure the prevalence of AS burden, various classifications were applied according to the data in each publication. In Publication 1 using CONTENT data, exposure to AS medications was defined as patients having an AS medication prescription any time within the study period (AS use). Patients who were not prescribed an AS medication during the study period were regarded as having no AS use. Information regarding the dosage, adherence, length of time medication was taken or if the medication was changed or stopped, was not available in this dataset. Therefore, AS exposure could not be quantified using the DBI, but instead AS use vs. no AS use was used to define AS burden. In Publication 2 using KORA-FF4 data, the DBI could be calculated and prevalence of AS burden (DBI >0) was estimated.

Population-level - Hypotheses on health outcomes

Primary Care Setting

As mentioned before, PCPs are frequently visited by VDB patients. While there are distinct vestibular and non vestibular etiologies of vertigo that can be addressed by specific therapy, many VDB complaints remain under- or misdiagnosed and as a result,

are inaccurately accommodated in primary care (67). According to the International Classification of Diseases 10th Revision (ICD-10) Codes, the following VDB related diseases or symptoms were examined, when appropriate, in this thesis:

H81.0 – "Meniere's Disease"

H81.1 – "Benign paroxysmal vertigo, unspecified ear"

H81.2 – "Vestibular neuronitis, unspecified ear"

H81.3 – "Other peripheral vertigo"

H81.4 – "Vertigo of central origin"

H81.8 – "Other disorders of vestibular function"

H81.9 – "Disorder of vestibular function, unspecified"

R42 – "Dizziness and giddiness"

First identifying an accurate diagnosis, and second assigning a suitable therapy is quite a challenge for PCPs (68-70). It was recently seen in two primary care studies that 87.2% (67) and 80.2% (69) of diagnoses were assigned with the ICD-10 Code R42, which is very unspecific in nature. It is recommended that patients with unspecific or vestibular VDB diagnoses should not be prescribed vestibular suppressants with AS effects as a treatment option; instead an in-depth medical patient history should be reviewed and alternatives should be considered when possible (71, 72). We know that vertigo or dizziness may also be a direct side-effect or adverse drug reaction to some AS medications. However, polypharmacy (73) and potentially inappropriate combinations of medications (24) have been shown to increase the risk of VDB. Therefore, to improve the management of VDB patients in primary care, examining the utilization of a potentially adjustable risk factor like AS medication for VDB disorders deserves attention. Since older people are more susceptible to VDB, comorbidities, and polypharmacy, caution should especially be taken in this age group.

Population-based setting

Clinical diagnosis of VDB is problematic due to its multifactorial nature and the perception of VDB is not easy for a patient to explain (74, 75). Therefore, VDB as a symptom often turns chronic or goes under- or misdiagnosed. However, from the individual's perspective the lasting effects of VDB on mobility (76), injuries and fractures (7), falls (7, 16-18), restrictions of social participation (77, 78), disability (19), and nursing care (79) still remain. Since the effects of VDB are still noticeable without

having a specific diagnosis, self-reported symptoms could be beneficial in epidemiological research. Not only can this be measured in representative and population-based populations, self-reported VDB still captures the true picture that participants have suffered from VDB symptoms, regardless of their severity and specificity (65). Self-reported VDB in this thesis was assessed, when appropriate, using standardized questions from the balance section of the National Health and Nutrition Examination Survey 2003-2004 (80).

Participants were asked about lifetime VDB, "Have you ever had vertigo, dizziness or difficulty with balance?" If the answer was "Yes", it was followed by a separate question on 12-month VDB, "In the last 12 months, have you had vertigo, dizziness or difficulty with balance?" Presence of VDB was defined as answering "Yes" to both lifetime and 12-month VDB questions.

Statistical Analyses

In Publication 1, descriptive statistics were used to describe differences between cases and controls using t-tests for continuous variables and chi-squared tests for categorical variables. Adjusted matched odds ratios (AOR) and 95% confidence intervals (CI) were calculated using a multivariable conditional logistic regression model to approximate the risk of vertigo or dizziness in AS use versus no AS use, adjusted for potential confounding factors. Sensitivity analyses were conducted looking at associations between 1) AS use within 1 year before and 2) within 60 days after a VDB diagnosis to mimic a cause-effect relationship and have a look into prescription patterns after a VDB diagnosis.

In Publication 2 using KORA-FF4 data, the prevalence of AS burden (DBI >0) was estimated, as well as, stratified by sex and age groups in those with and without VDB. Adjusted odds ratios (AOR) and 95% confidence intervals (95% CI) were computed using multivariable logistic regression analysis to estimate the risk of VDB in those with a DBI >0 (AS burden) versus no DBI (no AS burden). Furthermore, sensitivity analyses yielded similar results using 1) a higher DBI cut-off value, 2) a subgroup analysis of those with a DBI >0 on a continuous scale including a chi-square test for trend, and 3) a model adjusting for all co-morbidities which would minimize the likelihood that positive associations between AS burden and VDB are due to the treatment of multiple diseases with multiple medications.

Main Results and Scientific Contribution

Publication 1

AS and VDB prevalence in the German primary care setting (Publication 1):

Out of 151,446 patients, 6971 cases (4.6%) were diagnosed with at least one vertigo or dizziness diagnosis between the study period 2010-2014. Cases had 10,552 consultation days with at least 1 vertigo or dizziness diagnosis. AS medication was prescribed on 1,072 of 10,552 (10.2%) days of vertigo or dizziness diagnoses. Dizziness and giddiness (ICD-10 Code R42) was diagnosed most often (87.2%) by PCPs, followed by BPPV (6.7%) (ICD-10 Code H81.1). a higher prevalence of AS prescriptions was seen in cases with vertigo or dizziness (63.4%) compared with controls (42.2%) without vertigo or dizziness, especially in cases aged ≥ 65 years old (71.2%) compared with controls aged ≥ 65 years old 50.9% (67).

Association of AS use and VDB in the German primary care setting (Publication 1):

Using a matched case-control design on a complete survey of primary care prescriptions in Germany, we found that after adjusting for covariates, a significant association was seen between AS medication use and a higher risk of vertigo or dizziness (AOR: 1.37, 95% CI: 1.18-1.58, $P < 0.001$). Additionally, sensitivity analyses were conducted looking at associations between 1) AS use within 1 year before (AOR: 1.61, 95% CI: 1.36-1.92, $P < 0.001$), or 2) within 60 days after a VDB diagnosis (AOR: 1.18, 95% CI: 1.09-1.28, $P < 0.001$), of which both analyses yielded similar results.

The scientific contribution of Publication 1 is summarized in Box 1.

Box 1: Scientific Contribution of Publication 1

- AS medication use was higher in cases with vertigo or dizziness than in controls without vertigo or dizziness, highlighting the persistent prescribing of AS medication to vertigo or dizziness patients although these medications could be aggravating symptoms.
- AS use was more prevalent in older cases compared to older controls. Caution should be taken when prescribing AS medications to older adults (≥65 years old). Systematical calculations of AS medication burden could help acknowledge this issue and raise awareness for prescription habits in primary care.
- AS medication use was associated with a higher risk of vertigo or dizziness suggesting AS medication has the potential to contribute to the burden of disease. PCPs should consider AS medication as a risk factor for vertigo or dizziness.
- Vertigo and dizziness diagnoses in our study were rather unspecific which underlies the lack of accurate diagnoses and a need for PCP vertigo/dizziness expertise in the German primary care setting.

Publication 2

AS and VDB prevalence in an older German general population (Publication 2):

Out of 883 older participants, 257 (29.1%) reported having VDB during the last 12 months. AS burden (DBI >0) was higher in those with VDB: 27.6% compared to those without VDB (15.3%) ($p < 0.001$). Higher AS burden (DBI > 0.5) was also seen in those with VDB (10.9%) compared to those without (4.0%). In particular, those with VDB and ≥80 years old had a higher prevalence of AS burden compared to those without VDB in the same age group (44.8% vs. 16.8%). Independent of VDB, overall AS burden was present in 18.9% of participants, with highest prevalence of AS burden seen in those ≥80 years old (26.3%).

Association of AS use, using the DBI, with VDB and falls in an older German general population (Publication 2):

After adjustment of clinically relevant confounders, this multivariable logistic regression analysis from a large population-based sample in Germany identified a significant association between AS burden (AOR: 1.73 [95% CI, 1.16–2.56]), age (AOR: 1.03, [95% CI, 1.00–1.05]), sex (AOR: 1.95, [95% CI, 1.43–2.66]), insomnia (AOR: 2.53, [95% CI, 1.44–4.45]), and Parkinson's disease (AOR: 4.06, [95% CI, 1.37–13.67]) and VDB. Most notably, sensitivity analyses revealed a DBI >0.5 (AOR: 2.27, [95% CI, 1.18-4.36]) compared to no DBI was significantly associated with VDB. Moreover, a chi-squared test for trend ($p< 0.001$) indicated a linear increase in proportions of VDB cases as the DBI category increased by 0.5.

The scientific contribution of Publication 2 is summarized in Box 2.

Box 2: Scientific Contribution of Publication 2

- Prevalence of AS burden (DBI >0) was high in the general aging population, especially in those with VDB and ≥80 years old. These results highlight the importance of monitoring AS medication use in older age groups, specifically those with VDB symptoms, since they are a possible contributing factor that should be avoided.
- We found AS burden to be significantly and independently associated with VDB. These finding suggest that AS medications used in the calculation of the DBI could contribute to the burden of VDB and despite several evidence based regulations and guidelines for avoiding AS use in older adults, this issue still warrants attention in health care.
- The calculation of AS burden, for example using the DBI, could be helpful as a routine risk assessment in ambulatory medical care.

Strengths and Limitations

Many strengths and some limitations were faced in the compilation of this doctoral thesis work. Although VDB is a common complaint in community dwelling and in many patient specific populations, as mentioned before its diagnosis and prognosis are very complex. With many cases going under- or misdiagnosed, evaluating both self-reported and confirmed diagnoses of VDB in nature was a key strength of this doctoral thesis work. Self-reported VDB could lead to a misrepresentation of self-observation, however it actually captures the true picture in reality that many suffer from VDB symptoms although not officially diagnosed. When investigating specific VDB diagnoses in the primary care setting there are two major advantages. One, we could evaluate how PCPs diagnose such a difficult to handle and complex disease and second, we could examine how AS medications play a role in prescription patterns and occurrence of diagnosed VDB.

Furthermore, no universally accepted list of AS medications currently exists. This was a challenge to compile a German-specific list of AS medications and their corresponding dosages. However, consensus lists were used from existing DBI literature (47-51, 59) and German dosages according to DIMDI (53) were utilized in gathering an appropriate AS medication list to use in this doctoral thesis on German populations. Additionally, we used the DDD when calculating DBI scores in place of the recommended minimum licensed daily dose (MDD) (81) based on the availability of licensed medicinal product information in Germany. The DDD is much higher than the MDD for some drugs, but not all (81) and has been considered as an alternative approach to be used in different populations (58, 81). With this being said, a more conservative approach in calculating AS burden using the DBI was applied and estimates could have been underestimated. Nevertheless, associations were found between AS burden and VDB in this doctoral thesis work.

Moreover, both analyses confronted the task of covariate selection by implying different methods. The main goal was to minimize confounding and ensure clear interpretability and comparability of the results. In Publication1, cases and controls were matched using propensity scores based on significant determinants of VDB in order to obtain comparable cohorts. Then a directed acyclic graph (DAG) was employed to identify potential confounders as a minimal adjustment set of covariates needed to estimate the effect of AS use on VDB (82). In Publication2, potential confounders that could potentially influence the association of AS burden and VDB were chosen based on

existing DBI literature to increase comparability to other studies. Both publications investigated possible effect modification by testing possible appropriate interaction effects, which were included in the models when significant.

Due to the case-control and cross-sectional study designs of Publication1 and Publication2 in this doctoral thesis, we cannot claim any causal relationship between AS burden and VDB; rather we can only assume associations. However, the data sources in this doctoral thesis work allowed for analyses in two important settings when considering AS burden and VDB; namely the primary care and real-world perspectives. The CONTENT dataset provided registry data over a 5-year time span from over 150,000 VDB patients to investigate AS burden in a specific context, while quality data from the large national population-based KORA-FF4 dataset allowed for a more generalizable interpretation of results.

Finally, a main strength of this doctoral thesis work was the sensitivity analyses, which attempted to analyze the objectives from all different angles. In Publication1, time played an important role in how to interpret the results. Therefore, we also tested AS use strictly before a VDB diagnosis and conversely examined if a VDB diagnosis lead to AS prescriptions within 60 days after the diagnosis. Both of which yielded higher risks. In Publication2, a higher threshold of AS burden using other DBI score cut-offs, a sub-group analyses of only those with AS burden (DBI>0) to examine a possible dose-response relationship, and a model controlling for all comorbidities were assessed in order to test the robustness of our results. These further analyses give additional perspectives on our underlying results and allowed for a well-rounded testing of the objectives at hand.

Outlook of Doctoral Thesis

This research set out to identify AS burden and VDB prevalence and associations in both the German primary care and population based setting. Based on two quantitative scientific analyses (Publication1 and Publication2), it can be concluded that AS burden is an important factor to consider when evaluating and diagnosing VDB. The results indicate that potential strategies designed to target this patient-population should unequivocally include AS burden measurement and evaluation.

This doctoral thesis clearly indicates a strong association between AS burden and VDB, but it also opens the question of long-term effects and trajectories. To better realize the

implications of these results, future research could address the cause and effect relationship between changes of AS burden and VDB or explore prevention efforts to minimize AS burden and report the effects on patient populations. To date, very few randomized-controlled trials (RCT) have been conducted investigating AS burden, using the DBI, and the effects its reduction has in susceptible older populations (83, 84). In fact, no RCT or longitudinal study has been performed in such a vulnerable patient population like those with VDB. While our cross-sectional analyses limits the temporal causation aspect of the results, this approach offers insight into the future research strategies regarding AS burden in older patient populations.

In conclusion, implications from the analyses in this doctoral thesis are that health care professionals should consider AS medications as an important, yet modifiable risk factor for VDB. Caution should be taken when prescribing these medications to older adults due to their sensitivity to their side-effects and for the potential that these medications could increase the risk of VDB or further aggravate existing symptoms. Translation into practice could be realized through the calculation of AS burden in ambulatory care as a routine risk assessment and applied within existing multidisciplinary medication review services (65, 81). As the world age and average life expectancies increase, attention needs to be brought to a conceivable solution to maximize the quality of those years and maintain health in older people.

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Publications

Publication 1: Anticholinergic and sedative medications and the risk of vertigo or dizziness in the German primary care setting-A matched case-control study from the CONTENT registry

Phillips, Amanda; Strobl, Ralf; Grill, Eva; Laux, Gunter (2018). Anticholinergic and sedative medications and the risk of vertigo or dizziness in the German primary care setting-A matched case-control study from the CONTENT registry. Pharmacoepidemiology and Drug Safety, Vol. 27, Nr. 8: P. 912-920, https://doi.org/10.1002/pds.4575

Publication 2: Exposure to anticholinergic and sedative medications using the Drug Burden Index and its association with vertigo, dizziness and balance problems in older people – Results from the KORA-FF4 Study

Phillips, Amanda; Heier, Margit; Strobl, Ralf; Linkohr, Birgit; Holle, Rolf; Peters, Annette; Grill, Eva (2019). Exposure to anticholinergic and sedative medications using the Drug Burden Index and its association with vertigo, dizziness and balance problems in older people – Results from the KORA-FF4 Study. Experimental Gerontology, Vol. 124C, 2019, 110644, https://doi.org/10.1016/j.exger.2019.110644

Scientific Publications

- Phillips, Amanda; Heier, Margit; Strobl, Ralf; Linkohr, Birgit; Holle, Rolf; Peters, Annette; Grill, Eva (2019) Exposure to anticholinergic and sedative medications using the Drug Burden Index and its association with vertigo, dizziness and balance problems in older people - Results from the KORA-FF4 Study
  In: Experimental Gerontology : Vol. 124C, 110644

- Phillips, Amanda; Strobl, Ralf; Grill, Eva; Laux, Gunter (2018) Anticholinergic and sedative medications and the risk of vertigo or dizziness in the German primary care setting-A matched case-control study from the CONTENT registry
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- Stephan, Anna-Janina; Kovacs, Eva; Phillips, Amanda; Schelling, Jörg; Ulrich, Susanne; Grill, Eva (2018) Barriers and facilitators for the management of vertigo: a qualitative study with primary care providers
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- Kovacs, Eva; Stephan, Anna-Janina; Phillips, Amanda; Schelling, J.; Strobl, Ralf; Grill, Eva (2018) Pilot cluster randomized controlled trial of a complex intervention to improve management of vertigo in primary care (PRIMA-Vertigo): study protocol
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- Kovacs, Eva; Strobl, Ralf; Phillips, Amanda; Stephan, Anna-Janina; Muller, Martin; Gensichen, Jochen; Grill, Eva (2018) Systematic Review and Meta-analysis of the Effectiveness of Implementation Strategies for Non-communicable Disease Guidelines in Primary Health Care
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  In: Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA, Vol. 28, Nr. 7: S. 2069-2079

Acknowledgments

First and foremost I would like to give much gratitude to my supervisor Prof. Dr. Eva Grill who supplied her expertise and guidance along this rocky, but incredible journey down PhD lane. Thank you not only for believing in me, but providing me with the tools and knowledge I can now take with me into my scientific career. I am deeply grateful to Prof. Dr. med. Klaus Jahn and Prof. Dr. Markus Ege for their valid feedback and support as a part of my Thesis Advisory Committee.

I would like to recognize all institutions and helping parties such as, Prof. Dr. Thomas Brandt at the German Center for Dizziness and Balance Disorders and Prof. Dr. Ulrich Mansmann, Dr. Magda Beer-Radermacher, Monika Darchinger and Catherine Mason the IBE for their continuing support.

This would not have been possible without Anna-Janina Stephan, my trusting colleague and fellow PhD-ler who always lent a helping hand, shoulder, head, or whatever was needed along the way ☺ Ralf Strobl cannot go without mentioning for his continuous statistical advice, contribution and many coffee breaks with all my questions that always lasted much longer than I said they would!

I would like to take the opportunity to thank all the mentors and scholars that have helped me get to where I am today. Diving into Epidemiology at FAU Erlangen with PD. Dr. Karim Abu-Omar and Prof. John Knorr for teaching and mentoring me throughout my studies at St. Edward's University and Ingo Leven for taking a gamble on me as an athlete and all the help and support getting my life started here in Munich.

I would not be where I am today or the person I have become without the valuable and undying support of my family and closest friends. I give my deepest gratitude to my parents Larry and Marcia Phillips, for allowing me to live out my dream and play softball half way across the world in Germany. They never would have thought 10 years ago I would still be here in Munich and have been my backbone throughout it all. All my softball girls were always there for me ready to listen and always found a way to put a smile on my face. Thank you so much for your continued support.

Last but not least, I owe so much to my loving boyfriend Dominik Hartinger who was always there for me through all the ups and downs and who pushes me to be a better person every day. Thank you for always believing in me and providing all the emotional support I always needed.