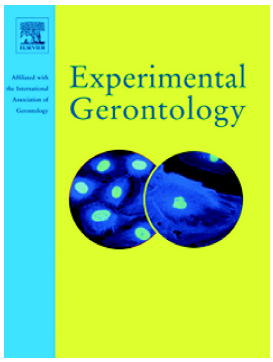

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Exposure to anticholinergic and sedative medications using the Drug Burden Index and its association with vertigo, dizziness and balance problems in older people – Results from the KORA-FF4 Study

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Abstract

Aims: This study examines exposure to anticholinergic and sedative (AS) medications in the general aging population using the Drug Burden Index (DBI) and to analyze the association of AS burden with vertigo, dizziness and balance problems (VDB, primary outcome) and falls (secondary outcome).

Methods: We performed a cross-sectional analysis of data from the second follow-up (FF4) in 2013/14 of the Cooperative Health Research in the Region of Augsburg (KORA)-S4 study. AS burden was classified as DBI > 0. Self-reported data of VDB and falls during the previous 12 months were collected. Multivariable logistic regression was used to estimate the association of AS burden with VDB and falls.

Results: 883 participants were included in this study (mean age 73.8 years, 48.4% female). AS burden was present in 167 (18.9%) participants, with the highest prevalence in those aged ≥80 years old (26.3%). In the adjusted analysis, AS burden was independently and significantly associated with VDB (Adjusted Odds Ratio (AOR): 1.73 [95% CI: 1.16, 2.56].

Conclusion: This study provides reliable prevalence estimates of AS burden in older people using the DBI in Germany, also indicating a positive and significant association with VDB. As VDB are among the main reasons for falls, we do recommend including the AS burden calculation as routine risk assessment in ambulatory medical care.

Keywords: Drug Burden Index, Anticholinergic, Sedative, Dizziness, Vertigo

1. Introduction

Medications with anticholinergic and sedative effects (AS) may negatively influence the health and well-being of older people. AS medications were consistently shown to be associated with impairment of balance (Bell et al., 2012), mobility (Bell et al., 2012), an increased risk for falls (Berdot et al., 2009; Holt et al., 2010), and have unwanted central and peripheral effects on the body (Bell et al., 2012). Specifically in older adults, AS medications (Lin and Aligene 2013), may especially increase the risk for vertigo, dizziness and balance problems (VDB). A high proportion of older adults are exposed to AS medications at the population level (43%) (Nishtala et al., 2014) and in older adults with VDB in the primary care setting (48%) potentially causing unnecessary VDB in these populations (Phillips et al., 2018).

With a prevalence of 35% in older adults and up to 85% in those ≥80 years old (Agrawal et al., 2009), VDB prevalence increases with age (Colledge et al., 1994; Tinetti et al., 2000) and are frequent complaints in the adult population (Agrawal et al., 2009). VDB are important risk factors for postural instability (O'Loughlin et al., 1993), limitations in mobility (Jonsson et al., 2004), injuries and fractures (Agrawal et al., 2009), and restrictions of social participation (Bronstein et al., 2010), and consequently contribute to disability (Mueller et al., 2014), nursing care (Cigolle et al., 2007) and falls (Agrawal et al., 2009; Fernandez et al., 2015; Iwasaki and Yamasoba 2015). Aging proprioceptive, somatosensory or vestibular systems (Iwasaki and Yamasoba 2015) may contribute to VDB, however AS medication is one modifiable risk factor in older age that needs to be considered.

In addition, older age increases both the sensitivity to AS side effects and the risk for chronic diseases necessitating medication (Holt et al., 2010). Increased susceptibility to functional impairment with polypharmacy can be seen in older age (Huizer-Pajkos et al., 2016). This has also been acknowledged in current recommendations for pharmacotherapy in older adults (Holt et al., 2010) and for prevention of falls which include a thorough medication review (Browne et al., 2014). To date, there is little information to which extent AS medications contribute to VDB in the old, and if these medications may prompt vertiginous symptoms. With the goal of inevitably minimizing or eliminating burdening medications in the old, patients can benefit from doctors or prescribers reviewing the AS burden of their current prescriptions (Bell et al., 2012).

The Drug Burden Index (DBI) was developed in 2007 to measure the cumulative burden of AS medications and can be used worldwide (Hilmer et al., 2007; Kouladjian et al., 2014; Nishtala et al., 2014). High DBI scores have been associated with functional impairment in USA, Australia, Finland and UK populations (Nishtala et al., 2014). This pharmacological equation is recommended as a tool that, if validated in other populations, will provide an evidence-based guide for prescribing in older people (Hilmer et al., 2007; Nishtala et al., 2014). The cumulative burden of AS medications, operationalized using the DBI, has not been used in Germany. There is a need for this risk assessment tool to be evaluated, especially in those with VDB, as these medications could be triggering symptoms.

The objective of this study was to examine exposure to AS medications in the general older population using the DBI and to analyze the association of AS burden with VDB (primary outcome) and falls (secondary outcome) in this group.

2. Methods

2.1 Study Design and Participants

Data in our study 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 this study. For a flow-chart of the study sample, see Appendix Figure A**.**

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.

2.2 Outcome Measures

Presence of VDB, as well as falls, was assessed using standardized questions from the balance section of the National Health and Nutrition Examination Survey (NHANES) questionnaire (2005). 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. 12-month prevalence of falls was defined by answering “Yes” to the question, “Have you fallen in the last 12 months?” For all analyses, 12-month prevalence of VDB and falls was used.

2.3 Exposure Measure

The DBI was used to measure cumulative exposure to AS medications in our study.
We identified AS medication according to:

- relevant published DBI and AS medication lists (Ailabouni et al., 2017; Byrne et al., 2018; Duran et al., 2013; Hilmer et al., 2009; O'Connell et al., 2018; Wouters et al., 2017)
- potentially inappropriate medications with AS effects from the German PRISCUS List (Holt et al., 2010)

- licensed product information collected in this study including Anatomical Therapeutic Chemical Classification System (ATC-Codes)
- defined daily dosage (DDD) according to the German Institute of Medical Documentation and Information (DIMDI) (2015) to ensure these medications are available and prescribed in the German market.

If the DDD could not be clearly determined from the German DIMDI list, the ATC Code was not included in the DBI calculation (n=7 ATC-Codes, n=18 participants, [G04CA52 (n=8 participants), N02AA59 (n=1 participant), N02AX62 (n=1 participant), N05CP08 (n=4 participants), N05CP30 (n= 1 participant), N05CP51 (n=2 participants), R05DA59 (n=1 participant)]). The final list of possible AS medications, using the fourth level of ATC-Codes which identifies the chemical/pharmacologica/therapeurtic subgroup properties, used for DBI calculation in this study was determined upon review and consensus from a clinical pharmacologist and a neurotologist with expertise in geriatric and vestibular rehabilitation and reported in Appendix Table A.

Participants were asked to bring all ingested medication and supplement packages to the study center. The mode of prescription (prescribed, recommended, over-the-counter), mode of ingestion (regularly or as needed), dosage and frequency of ingestion for each regularly taken (at least every other day) preparation were recorded regarding the last seven days before the interview. This information was collected using a database-supported computer software where ATC-Codes and a unique numerical medication identifier bar code printed on the medication package (PZN), or product name are recorded (Instrument for data based assessment of medication, IDOM) (Mühlberger N 2003). 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.

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 minimum recommended daily dose. Then, all individual AS medication DBI scores for each participant were summed for the total DBI score using the following formula (Gnjidic et al., 2009):

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

where D denotes the prescribed daily dose of any AS medication, and $\boldsymbol{\delta}$ is the minimum recommended daily dose of the individual drug according to DIMDI (2015). The DBI includes all regularly taken AS medications. If a medication was classified as having both anticholinergic and sedative effects, it was only included once in the DBI calculation (Best et al., 2013; Hilmer et al., 2007). A DBI >0 demonstrates AS burden. The higher the DBI score, the more AS burden the participant has.

2.4 Measures: Covariates

Sociodemographic characteristics such as age, sex, education and marital status were considered as covariates. Age was defined as age at reference date (July 1, 2014), with corresponding age groups defined as 65-69, 70-74, 75-79 and ≥80 years old in order to capture an older to oldest old adult population. Education levels were defined according to the German school system; the standard educational level corresponds to 9 years of schooling, medium educational level to 10 years of schooling and high educational level to 12 or 13 years of schooling, required to enter a university (Maier et al., 2013). The information on education was acquired from the baseline S4 survey where participants' highest level of school qualification was reported. Marital status was categorized as single, married, divorced, and widowed.

Information on physical activity, morbidity, self-rated health, and alcohol consumption was collected by self-report in the interview. Physical activity was assessed with two separate questions concerning leisure time physical activity in winter and in summer (including biking) and was categorized into inactive: ('No activity' or 'Less than 1 hour of activity per week in either summer or winter'), and active: ('Regularly 1-2 hours of activity per week' or 'Regularly more than 2 hours of activity per week') (Meisinger et al., 2005). Self-rated health was measured with a single-item question: "How would you rate your current health status?" and was categorized into good ('very good' and 'good') and bad ('rather bad' and 'bad'). Alcohol consumption was calculated by self-reported amount of alcoholic drinks in the last week (weekend and weekday) and categorized into no (i.e. 0 g/day), moderate (for men: >0 to <40 g/day, for women: >0 to <20 g/day) and high alcohol consumption (for men: ≥40 g/day, for women: ≥20 g/day) (Pabst et al., 2015). Angina pectoris was defined as pain after exercise retrosternally, in the left arm, and in the left side of the chest and was categorized according to Rose et al (Rose et al., 1982). Dementia was defined by intake of anti-dementia medication (ATC N06DA, N06DX, or N06BX). Parkinson's disease was defined if participants were taking anti-Parkinson's medication (ATC N04). These are important possible covariates, as they are not fully captured in the DBI. The presence of chronic health conditions was self-reported by the participants in a standardized interview. The participants were asked whether they were ever physician-diagnosed with myocardial infarction, stroke, cancer or diabetes. Diabetes is defined as type 2 diabetes mellitus or self-reported intake of diabetic medication. Depression was measured with the German version of the Brief Patient Health Questionnaire (PHQ-D) (Bernd Löwe 2002; Kroenke et al., 2001). Major depression is defined if 5 or more of the 9 depressive symptom questions were answered with at least 'more than half of the days'. Minor depression was defined if these same criteria were met for 2, 3 or 4 questions. Polypharmacy was defined as 5 or more regularly taken medications prescribed by a doctor. Insomnia was defined in accordance with former MONICA/KORA studies (Helbig et al., 2017; Peters et al., 2011). In short, data on distinctive symptoms of insomnia were collected by asking, "Did you have trouble falling asleep?","Did you have problems with sleeping through the night?", and "Do you feel tired or absolutely whacked during the day because of your sleep problems at night?". Answer choices were "often","sometimes",or "almost never", with yes defined as"often"and no as "some-times/almost never"). To identify clearly defined cases of insomnia, participants were rated as having insomnia, if

they reported having trouble falling asleep and/or difficulty staying asleep in addition to, having daytime tiredness (Helbig et al., 2017).

Blood pressure and resting heart rate were measured after the participant was resting in a sitting position for at least 5 minutes and repeated three times at an interval of three minutes per standardized protocol (Ruckert et al., 2015). Hypertension was classified according to the 1999 World Health Organization-International Society of Hypertension Guidelines for the management of hypertension (1999) into six categories: optimal (< 120/80 mmHG), normal (120/80 - 130/85 mmHG), high normal (130/85 - 140/90 mmHG), hypertension grade I (140/90 - 160/100 mmHG), hypertension grade II (160/100 - 180/110 mmHG), and hypertension grade III (≥ 180/110 mmHG). A binary variable for hypertension was created with optimal, normal and high normal blood pressure levels as no hypertension and hypertension grade I, II, and III as hypertension.

2.5 Statistical analysis

Means and standard deviations were reported for continuous variables and absolute and relative percentages for categorical variables. For comparisons between participants with and without VDB, as well as comparisons between older non-participants and participants, explorative t-tests for continuous variables and chi-squared tests for categorical variables were applied. As DBI scores were highly zero-inflated (Appendix Figure B.1, B.2), it was categorized as a binary variable with a cut-off at zero (DBI>0). This cut-off additionally allows for comparison to other studies (Kouladjian et al., 2014; Wouters et al., 2017). A subgroup analysis with DBI as a continuous variable in only those with a DBI >0 to test the dose-relationship, as well as higher DBI cut-off values were included in sensitivity analyses. 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). To increase model interpretability and comparability, potential confounders which are likely to influence the association between DBI>0 and VDB, or DBI>0 and falls, were included in the analyses. Selection of these confounders was based on relevant existing DBI literature (Ailabouni et al., 2017; Byrne et al., 2018; Duran et al., 2013; Hilmer et al., 2009; O'Connell et al., 2018; Wouters et al., 2017). Potential confounders included in logistic regression analyses included age, sex, Parkinson's disease, depression, insomnia and polypharmacy. Additionally, a stratified analysis of younger and older participants can been seen in Appendix Table B.

To check for effect modification, possible interaction terms with age and sex and the main exposure variable DBI were tested. Interaction terms were left if model fit was significantly improved using a Likelihood ratio test. We tested for collinearity using the Variance Inflation Factor (VIF). Goodness of fit for all regression analyses was tested and reported using the Hosmer-Lemeshow test which should be non-significant ($p>0.05$) to declare adequate fit (Lemeshow and Hosmer 1982). We tested for adequate power using chi-square tests for trends, which compare the distribution of a binary variable (No VDB vs. VDB) across levels of an ordered categorical variable (DBI cut-off values) to determine whether the association between the variables follow a trend (significant at $p<0.05$). All participants

with missing information in any covariate were excluded from the multivariable regression model. We used RStudio Version 1.0.136 for all analyses (RStudio 2016). Statistical significance was set at 0.05.

2.6 Sensitivity analyses

The results of our study may be sensitive to the definition of AS burden using the DBI. Small changes in the definition of this burden may lead to different results. In order to test the robustness of our results, three sensitivity analyses were performed using, 1) a higher DBI cut-off value (DBI=0 vs. 0 < DBI ≤ 0.5 vs. DBI >0.5), 2) subgroup analysis of only those with a DBI >0 on a continuous scale including chi-square test for trend, and 3) a model adjusting for 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 (Wouters et al., 2017).

3. Results

3.1 Descriptive characteristics of study participants

Of the 2279 participants in the KORA FF4 study, a subgroup of participants ≥65 years and older were included in the analyses. Thus, data was available for 883 participants (mean age 73.8 years, 48.4% female). VDB was reported in 257 (29.1%) participants during the last 12 months. Table 1 shows the descriptive characteristics of those with and without VDB. 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%). Significantly more participants with VDB were female (p <0.001) and slightly older (p =0.0027) compared to those without. Also, significantly more falls in the last 12 months (p <0.001), depression (p <0.001), insomnia (p <0.001), worse self-rated health (p <0.001) and polypharmacy (p <0.001) were seen in those with VDB.

Table 1. Descriptive characteristics of cases (n=257) and controls (n=626), KORA-FF4 Study (n=883)

Variable, n(%)	VDB (n = 257)	No VDB (n=626)	Total (n=883)	p-value
Drug Burden Index (DBI), mean (SD)	0.17 (0.37)	0.08 (0.21)	0.11 (0.27)	<0.001***
DBI >0	71 (27.6%)	96 (15.3%)	167 (18.9%)	<0.001***
DBI categories				
No DBI	186 (72.4%)	530 (84.7%)	716 (81.1%)	<0.001***
0 < DBI ≤ 0.5	43 (16.7%)	71 (11.3%)	114 (12.9%)	
DBI > 0.5	28 (10.9%)	25 (4.0%)	53 (6.0%)	
Female	150 (58.4%)	277 (44.2%)	427 (48.4%)	<0.001***
Age, mean(SD)	74.73 (5.94)	73.41 (5.9)	73.79 (5.94)	0.0027**
Age Groups, 5 year				0.0307*
65-69 years old	64 (24.9%)	189 (30.2%)	253 (28.7%)	
70-74 years old	64 (24.9%)	191 (30.5%)	255 (28.9%)	
75-79 years old	71 (27.6%)	133 (21.2%)	204 (23.1%)	
≥ 80 years old	58 (22.6%)	113 (18.1%)	171 (19.4%)	
Education[a]				0.0482*
Standard (≤ 9 years of schooling)	175 (68.6%)	388 (62%)	563 (63.9%)	
Middle (10 years of schooling)	51 (20%)	126 (20.1%)	177 (20.1%)	
High (12-13 years of schooling)	29 (11.4%)	112 (17.9%)	141 (16%)	
Marital status				0.0025**
married	155 (60.3%)	450 (71.9%)	605 (68.5%)	
unmarried	18 (7.0%)	26 (4.2%)	44 (5.0%)	
divorced	20 (7.8%)	50 (8.0%)	70 (7.9%)	
widowed	64 (24.9%)	100 (16%)	164 (18.6%)	
Falls in the last 12 months	72 (28.0%)	83 (13.3%)	155 (17.6%)	<0.001***
Physically active	124 (48.2%)	335 (53.5%)	459 (52%)	0.1775
Smoking class				0.7193
never	138 (53.7%)	321 (51.3%)	459 (52%)	
former	104 (40.5%)	261 (41.7%)	365 (41.3%)	
smoker	15 (5.8%)	44 (7.0%)	59 (6.7%)	
Alcohol				0.0012**
No alcohol consumption	94 (36.6%)	154 (24.6%)	248 (28.1%)	
Moderate alcohol consumption	123 (47.9%)	341 (54.5%)	464 (52.5%)	

High alcohol consumption	40 (15.6%)	131 (20.9%)	171 (19.4%)	
Hypertension	39 (15.2%)	128 (20.4%)	167 (18.9%)	0.0850
Angina Pectoris[a]	23 (9.0%)	41 (6.6%)	64 (7.3%)	0.2645
Myocardial Infacrtion[d]	16 (6.2%)	43 (6.9%)	59 (6.7%)	0.8241
Diabetes	60 (23.3%)	98 (15.7%)	158 (17.9%)	0.0090**
Cancer	50 (19.5%)	114 (18.2%)	164 (18.6%)	0.7364
Stroke[b]	23 (9.1%)	29 (4.6%)	52 (5.9%)	0.0181*
Dementia[a]	1 (0.4%)	1 (0.2%)	2 (0.2%)	1
Parkinson's Disease[a]	11 (4.3%)	5 (0.8%)	16 (1.8%)	0.0011**
Depression[c]				0.0019**
minor depressive disorder	12 (4.7%)	12 (1.9%)	24 (2.7%)	
major depressive disorder	9 (3.5%)	6 (1.0%)	15 (1.7%)	
Insomnia	34 (13.2%)	28 (4.5%)	62 (7%)	<0.001***
Self-rated Health: bad	109 (42.4%)	119 (19.0%)	228 (25.8%)	<0.001***
Polypharmacy[a]	106 (41.4%)	182 (29.1%)	288 (32.7%)	<0.001***

SD, standard deviation; *** indicates p-value <0.001; ** indicates p-value <0.01, * indicates; p-value <0.05
[a]Variable was available for n=881 participants
[b]Variable was available for n=880 participants
[c]Variable was available for n=882 participants
[d]Variable was available for n=879 participants
Education = Standard (≤9 years), Middle (10 years), and High (12 or 13 years); Physically Active = 'Regularly 1-2 hours of activity per week' or 'Regularly more than 2 hours of activity per week'; Alcohol = no (i.e. 0 g/day), moderate (for men: >0 to <40 g/day, for women: >0 to <20 g/day) and high alcohol consumption (for men: ≥40 g/day, for women: ≥20 g/day); Hypertension = hypertension grade I (140/90 - 160/100 mmHG), hypertension grade II (160/100 - 180/110 mmHG), or hypertension grade III (≥ 180/110 mmHG); Angina Pectoris = Angina pectoris was defined as pain after exercise retrosternally, in the left arm and in the left side of the chest and categorized based on Rose et al. [32]; Myocardial infarction, stroke, cancer = self-reported by participants if physician diagnosed; Diabetes = type 2 diabetes mellitus or self-reported intake of diabetic medication; Dementia = intake of anti-dementia medication (ATC N06DA, N06DX, or N06BX); Parkinson's Disease = intake of anti-Parkinson's medication (ATC N04); Depression = Brief Patient Health Questionnaire, Major depression (5 or more of the 9 depressive symptom questions were answered with at least 'more than half of the days'), Minor depression (same criteria were met for 2, 3 or 4 questions); Insomnia = reported having trouble falling asleep and/or difficulty staying asleep in addition to, having daytime tiredness [39]; Self-rated Health = single-item question: "How would you rate your current health status?", Bad (answer choices 'rather bad' or 'bad'); Polypharmacy = 5 or more regularly taken medications prescribed by a doctor.

3.2 Non-participants

Reasons for non-participation (n=622) were dement state (n=8), bad state of health (n=164), distrust of privacy (n=6), not interested (n=74), other (n=296), or no reason (n=74). Of those non-participants who were ≥65 years old (n=353), they were older (77.04 years old vs. 73.79 years old, p <0.001) and had a higher proportion of VDB (39.8% vs. 29.1%, p<0.001) compared to participants in our study, respectively.

3.3 Prevalence of AS burden

In total, AS burden (DBI>0) was present in 18.9% of participants, with men having an overall higher burden. The prevalence of AS burden was greater with increasing age (65-69 years old: 13.0%, 70-74 years old: 16.5%, 75-79 years old: 23.0%, ≥80 years old: 26.3%). In particular, those with VDB and ≥80 years old had a higher prevalence of AS burden compared to those in the same age group without VDB (44.8% vs. 16.8%). Prevalence of AS burden in those with and without VDB stratified by sex and age is illustrated in Figure 1. Further summary statistics of DBI scores stratified by age groups can been seen in Appendix Table C.1 and C.2.

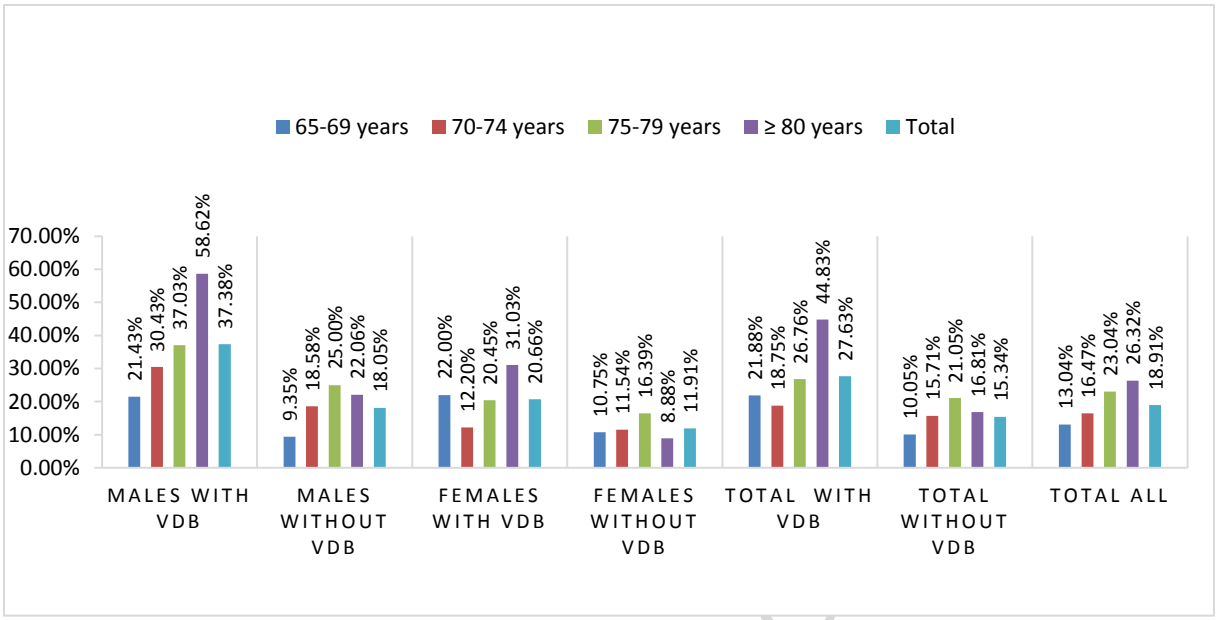

Figure 1. Prevalence of DBI scores >0 in those with and without VDB by sex and age, KORA-FF4 Study (2013-2014)

3.4 VDB model

Results from the adjusted logistic regression analysis for the association of AS burden with VDB are shown in Table 2. After exclusion of all participants with missing values in any of the covariates (n=3), the regression model was based on n=880 participants. Possible confounders such as age, sex, Parkinson's disease, depression, insomnia and polypharmacy were identified to be included in the model. After adjusting for these covariates, AS burden was independently and significantly associated with VDB (AOR: 1.73 [95% CI, 1.16 - 2.56]). Additionally, 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]) were significantly associated with VDB.

Table 2. Multivariable logistic regression of association between Drug Burden Index (DBI) and vertigo, dizziness or balance problems (VDB), KORA-FF4 Study (n=880)

	Adjusted	
Covariables	AOR [95% CI]	p-value
Drug Burden Index (DBI)		
No DBI (ref. group)	1.00	--
DBI>0	1.73 [1.16, 2.56]	0.0068**
Age	1.03 [1.00, 1.05]	0.0439*
Sex		
Male (ref. group)	1.00	--
Female	1.95 [1.43, 2.66]	<0.001***

Depression		
No depressive disorder (ref. group)	1.00	--
Minor depressive disorder	1.77 [0.73, 4.25]	0.1994
Major depressive disorder	1.44 [0.46, 4.79]	0.5338
Polypharmacy		
No Polypharmacy (ref. group)	1.00	--
Polypharmacy	1.27 [0.90, 1.78]	0.1644
Insomnia		
No insomnia (ref. group)	1.00	--
Insomnia	2.53 [1.44, 4.45]	0.0012**
Parkinson's Disease		
No Parkinson's Disease (ref. Group)	1.00	--
Parkinson's Disease	4.06 [1.37, 13.67]	0.0148*

AOR, Adjusted Odds Ratio; CI, Confidence Interval; ref. group, reference group.

*** indicates p-value <0.001; ** indicates p-value <0.01, * indicates; p-value <0.05

Hosmer-Lemeshow Statistic: p=0.6681

3.5 Falls model

When examining the association between AS burden and falls (n=880) no significant association was found in the adjusted model (AOR: 0.80, [95% CI, 0.48 - 1.30]) (Table 3). However, age (AOR: 1.06 [95% CI: 1.03 - 1.09]), female sex (AOR: 1.75 [95% CI: 1.22 – 2.52]), and insomnia (AOR: 2.05 [95% CI: 1.10 – 3.72]) were significant predictors of falls in our study.

Table 3. Multivariable logistic regression of association between Drug Burden Index (DBI) and Falls, KORA-FF4 Study (n=880)

	Adjusted	
Covariables	AOR [95% CI]	p-value
Drug Burden Index (DBI)		
No DBI (ref. group)	1.00	--
DBI>0	0.80 [0.48, 1.30]	0.3887
Age	1.06 [1.03, 1.09]	0.004**
Sex		
Male (ref. group)	1.00	--
Female	1.75 [1.22, 2.52]	0.0026**
Depression		
No depressive disorder (ref. group)	1.00	--
Minor depressive disorder	1.45 [0.52, 3.63]	0.4507
Major depressive disorder	1.06 [0.27, 3.51]	0.9264
Polypharmacy		
No Polypharmacy (ref. group)	1.00	--
Polypharmacy	1.19 [0.79, 1.76]	0.3991
Insomnia		
No insomnia (ref. group)	1.00	--
Insomnia	2.05 [1.10, 3.72]	0.0205*

Parkinson's Disease		
No Parkinson's Disease (ref. group)	1.00	--
Parkinson's Disease	1.69 [0.44, 5.37]	0.3983

AOR, Adjusted Odds Ratio; CI, Confidence Interval; ref. group, reference group.

*** indicates p-value <0.001; ** indicates p-value <0.01, * indicates; p-value <0.05

Hosmer-Lemeshow Statistic: p=0.6772

3.6 Sensitivity analyses

In our sensitivity analyses, the adjusted multiple logistic regression models using higher DBI cut-off categories (DBI=0 vs. 0 < DBI ≤ 0.5 vs. DBI >0.5) (Appendix Table D), and model controlling for all co-morbidities (Appendix Table F), yielded similar results. Most notably, DBI>0.5 (AOR: 2.27, [1.18 – 4.36]) compared to no DBI was positively significantly associated with VDB. In the subgroup analyses of only those with AS burden (n=167) (Appendix Table E), a significant association between AS burden and VDB could not be seen (AOR: 1.90, [0.65 - 5.97]). This indicates for an increase of 1 unit in DBI score, odds of VDB increase however not significant. An increase of 1 may be too extreme, therefore, a chi-square test for trend (p<0.001) testing proportions of VDB in better fitting increments of DBI groups (DBI ≤ 0.5, 0.5 < DBI ≤ 1, DBI > 1) showed a linear increase in the proportion of VDB cases as the DBI category increases by 0.5. For the results of the logistic regression sensitivity analyses, please refer to Appendix Tables D, E and F.

4. Discussion

This study provides evidence that AS burden in the general aging population is high. Prevalence of AS burden (DBI scores >0) was greater with increasing age and was higher in those with VDB. Of particular importance, AS burden was independently and significantly associated with the presence of VDB using multiple DBI cut-off values and most prevalent in the oldest old (≥80 years old: 26.3%). These findings suggest that AS medications used in the calculation of the DBI could contribute to the burden of VDB especially when evaluating AS burden in this age group.

Exposure to AS medications using the DBI in older populations ranges from 20-79% (Kouladjian et al., 2014) in the literature. Prevalence estimates of DBI scores in the oldest old are limited. In our study, 26.3% of those aged ≥80 years were exposed to AS medications. Similarly, in the GeMS (Geriatric Multidisciplinary Strategy for the Good Care of the Elderly) population based study of 339 community-dwelling participants aged ≥75 years, 38% of participants were exposed to AS medications using the DBI (Lonnroos et al., 2012). In addition, in 2,172 community-resident Medicare recipients aged 70-79 years in the Health ABC study, 34% were exposed to AS medications using the DBI (Hilmer et al., 2009). Variability in prevalence can be contributed to the different medications and dosages used to define medications used in the DBI definition, as well as the fact that our sample does not include those who were unable to come to the study center. Thus, we may have underestimated the prevalence of AS burden using the DBI in our study. However, keeping these details in mind, 26.3% is still quite high in those aged ≥80 years in our study and the association of AS burden with VDB using the DBI in the oldest old is alarming. This emphasizes the importance of publishing and updating country-specific lists of AS medications to facilitate an easily calculated DBI score. These results also highlight the importance of monitoring medications like anticholinergic and sedatives in older age groups, specifically those with VDB symptoms, since they are a possible contributing factor which should be avoided (Fleck 2000; van Vugt et al., 2017).

In our study, age, sex, insomnia, Parkinson's disease and AS burden increased the risk of VDB. Despite several evidence based recommendations and guidelines for avoiding the use of certain AS medications or reducing polypharmacy when possible in older adults such as the German PRISCUS List (Holt et al., 2010), American Geriatrics Society Updated Beers Criteria (2015), or the STOPP/START criteria (Gallagher et al., 2008), our study shows this is still a current issue which needs attention. Not only are AS medications risky for older people regarding negative side-effects, but they are particularly precarious for those with VDB due to their potential central and peripheral effects (Bell et al., 2012; Mintzer and Burns 2000). Therefore, prescribing AS medications for older patients, especially those with pre-existing VDB symptoms, should be carefully evaluated in health care.

Similar studies investigated the association between AS burden and VDB presenting comparable results. In a cross-sectional survey on community dwelling older men enrolled in The Concord Health and Ageing in Men Project in Sydney, Australia, DBI scores were associated with balance difficulty ($P < 0.01$) (Gnjidic et al., 2009). Likewise, anticholinergic drug burden was independently associated with greater difficulties in balance (AOR: 3.2, 95% CI: 1.5-6.9) and mobility (AOR: 3.6, 95% CI: 1.6-8.0) in

932 moderately to severely disabled community-resident women aged 65 years or older from the Women's Health and Aging Study I (Cao et al., 2008). Data on adverse drug reactions analyzed from the Pharmacovigilance Regional Center (Calabria, Italy) in 2012 suggested that some anti-epileptic drugs, benzodiazepines, and anti-hypertensives may cause vertigo or dizziness as an adverse effect (Chimirri et al., 2013). Chimirri et al. also stresses that although vertigo and dizziness symptoms may not be life threatening, these symptoms could be an indirect cause of other serious adverse events like falls and subsequent fractures or traumas, particularly in fragile patients (Chimirri et al., 2013). Our findings are important because VDB could contribute to disability (Mueller et al., 2014) or physical functioning problems in geriatric risk management (Kersten and Wyller 2014). Our study did not find an association between AS burden and falls. The small number of participants with falls in our dataset could explain this. However, since AS burden is associated with VDB and VDB and older age are predictors of falls (Agrawal et al., 2009; Fernandez et al., 2015), monitoring AS medications, for example using the DBI as a prescribing tool, could help reduce VDB symptoms and in-turn contribute to the reduction of disability, falls and physical functioning problems in older adults.

4.1 Strengths and limitations

Our study has some important strengths. It is the first time a large population based sample of older adults in Germany was used for multivariable analysis. Second, as suggested by Wouters et al. (Wouters et al., 2017), in a recent review for future DBI research, we included possible confounders like polypharmacy, neurodegenerative disorders, depression and co-morbidities, researched a vulnerable study group (those with VDB) in Germany, and used consensus lists of AS medications from relevant literature for our DBI calculation. These covariates were included in the final model to reduce possible residual confounding or sensitivity analyses were provided with their inclusion. Adjusting for co-morbidities, as well as using higher DBI cut-off values yielded similar results. Third, potential confounders were selected based on existing DBI literature to ensure interpretability and comparability of results. Additionally, adjustment of diseases and disease-specific medication at the same time would introduce collinearity into the model; therefore we are confident the multivariable adjustment in our analyses yielded meaningful results. Fourth, participants provided comprehensive medication data by bringing all recently ingested medications to the study center where this data was recorded by interviewers. Lastly, we used the DBI in our study which is specifically designed to estimate cumulative anticholinergic and sedative medication effects. The DBI considers dosage and has been validated in many other countries (Kouladjian et al., 2014); however the DBI has not yet been studied in Germany using a vertigo and dizziness study group. Dosage is important since adverse effects could be dose-related. Nonetheless, in our sensitivity analysis a dose-response relationship between DBI scores >0 and risk of VDB was not observed when DBI scores increased by 1 unit, however this could be seen with an increase of DBI score by 0.5, equivalent to taking just 1 more medication at the DDD.

Limitations also need to be considered. Causation cannot be determined from our study design. No universally accepted list of AS medications exists, however we used consensus lists from existing DBI literature (Ailabouni et al., 2017; Byrne et al., 2018; Duran et al., 2013; Hilmer et al., 2009; O'Connell

et al., 2018; Wouters et al., 2017) as a comprehensive approach to create the DBI to be used in a German setting using the fourth level of ATC-Codes. The DBI assumes a linear load of medications; the impact of each anticholinergic and sedative medication is then considered equivalent which could under- or overestimate the true effect of each medication on participants (Kouladjian et al., 2014). Furthermore, we used the DDD in our study when calculating DBI scores in place of the recommended minimum licensed daily dose (MDD) (Hilmer 2018) based on availability of licensed medicinal product information in Germany (2015). The DDD is much higher than the MDD for some drugs but not all (Hilmer 2018), and has been considered as an alternative approach to be used in different populations (Hilmer 2018; Hilmer et al., 2014). This may have led to an underestimation of DBI scores. Also, the DBI excludes the use of topical, inhaled, ophthalmological or not regularly taken medications in our study as these different dosing forms of medications have not been clearly defined (Kouladjian et al., 2014); therefore, possible underestimation of the use of the anticholinergic and sedative medications of interest cannot be disregarded (Best et al., 2013). In addition, our study had non-participants due to a bad health state, interest, privacy and other reasons. When we compared ≥65 year old non-participants who would have been included in our study to those in the study population, we could show that non-participants were on average older and had a higher proportion of VDB. Consequently, the strength of the association between DBI>0 and VDB was most likely underestimated. The outcome measure VDB was based on self-reported scores and could lead to misrepresentation of self-observation. Nevertheless, VDB are complex, often multidimensional, and difficult to handle (Grill et al., 2016); in many cases, VDB goes un- or misdiagnosed in primary care (Kruschinski et al., 2008; Phillips et al., 2018). Hence, self-reported VDB still captures the true picture that participants have suffered from the symptoms, regardless of their specificity. Besides, previous studies have shown that self-report of other health conditions were reliable in this study setting (Meisinger et al., 2000). Lastly, the KORA-FF4 cohort includes community-dwelling older individuals and because those who were not able to make it to the study center were not included in our analysis, we may have underestimated the prevalence of DBI scores as well as its true influence on VDB. This issue of non-participation in one of the KORA baseline health surveys has been investigated in detail before (Holle et al., 2006). It was shown that more persons with worse health were non-participants and that severely impaired persons are less likely to participate in the study.

4.2 Conclusion

In summary, this study indicates the extensive exposure to medications with anticholinergic and sedative effects (AS) in older adults using the Drug Burden Index (DBI) and its association with vertigo, dizziness or balance problems (VDB). Higher AS drug burden was seen most frequently in those aged ≥80 years and in those with VDB. AS burden and age were positively significantly associated with the presence of self-reported VDB. As VDB are among the main reasons for falls we do recommend including the calculation of AS burden as a routine risk assessment in ambulatory medical care.

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Critical revision of the manuscript for important intellectual content: All authors.

Statistical Analysis: Phillips, Strobl.

FIGURE LEGEND

Figure 1. Prevalence of DBI scores >0 in those with and without VDB by sex and age, KORA-FF4 Study (2013-2014)

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Highlights

- Medications with anticholinergic and sedative effects (AS) have unwanted central and peripheral effects on the body like confusion, delirium, or blurred vision, especially in older people.
- Specifically in older adults, AS burden could increase the risk for vertigo, dizziness and balance problems (VDB) and should be minimized or eliminated when possible.

- We estimated AS prevalence, using the DBI, in older people using data from a large population based sample in Germany.
- AS burden increased linearly with age, being the highest in those aged ≥80 years old (oldest old).
- After controlling for confounders, AS burden was significantly and independently associated with VDB compared to no AS burden.