Aus dem Lehrstuhl für Epidemiologie
Medizinische Fakultät der Universität Augsburg am Universitätsklinikum Augsburg
vormals Lehrstuhl für Epidemiologie am universitären Zentrum für Gesundheitswissenschaften
am Klinikum Augsburg (UNIKA-T)
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Long-term Use of Proton Pump Inhibitor and Dementia Risk

Dissertation
zum Erwerb des Doktorgrades der Humanbiologie
an der Medizinischen Fakultät der
Ludwig-Maximilians-Universität München

vorgelegt von
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aus
Incheon, South Korea

2023

Mit Genehmigung der Medizinischen Fakultät der

Ludwig-Maximilians-Universität zu München

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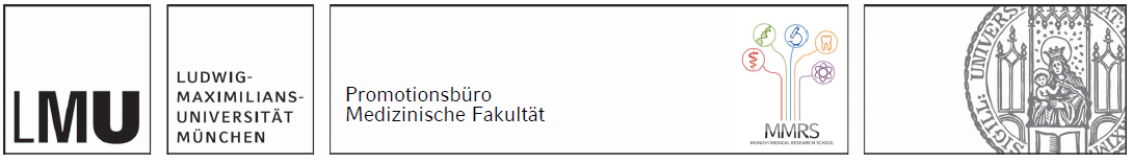

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I hereby declare, that the submitted thesis entitled:

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I further declare that the submitted thesis or parts thereof have not been presented as part of an examination degree to any other university.

Germering, 23.06.2023
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Nayeon Ahn
Signature doctoral candidate

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List of abbreviations

AD	Alzheimer's disease
AOK Bayern	Allgemeine Ortskrankenkasse Bayern (Health insurance provider)
ATC	Anatomical therapeutic chemical
DDD	Defined daily dose
FTD	Frontotemporal dementia
GERD	Gastroesophageal reflux disease
H2RA	Histamine 2-receptor antagonist
ICD	International classification of diseases
ITT	Intention-to-treat
LBD	Lewy body dementia
MRI	Magnetic resonance imaging
NAI	Nuremberg age inventory
PPI	Proton pump inhibitor
SHIP	Study of Health in Pomerania
VaD	Vascular dementia
VLMT	Verbal learning and memory test

List of publications

1. **Ahn N**, Frenzel S, Wittfeld K, Bülow R, Völzke H, Lerch MM, Chenot JF, Schminke U, Nolde M, Amann U, Meisinger C, Linseisen J, Baumeister SE, Grabe HJ, Rückert-Eheberg IM. **Lack of association between proton pump inhibitor use and brain aging: a cross-sectional Study**. *European Journal of Clinical Pharmacology* 2021, 77(7):1039-1048. https://doi.org/10.1007/s00228-020-03068-8

2. **Ahn N**, Nolde M, Günter A, Güntner F, Gerlach R, Tauscher M, Amann U, Linseisen J, Meisinger C, Rückert-Eheberg IM, Baumeister SE. **Emulating a target trial of proton pump inhibitors and dementia risk using claims data.** *European Journal of Neurology* 2022, 29(5):1335-1343. https://doi.org/10.1111/ene.15284

1. Author's contribution to the publications

1.1 Contribution to Publication I

The doctoral candidate searched the literature autonomously, created an analysis plan, and performed all statistical analyses for the publication. She independently interpreted the analysis results. The doctoral candidate also prepared the draft of the manuscript, including creating all tables, graphics, and the accompanying material (supplements). She circulated the draft manuscript among the co-authors and revised the manuscript according to their comments.

Besides, she selected a target journal and managed the whole process of the submission, including communication with the editorial board of the journal. She edited the manuscript reflecting reviewers' comments during the peer review process. Throughout the process, she consulted with her supervisors and received guidance and feedback from them.

1.2 Contribution to Publication II

The doctoral candidate searched the literature and conceptualized the study. She wrote a study protocol and registered it at the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (EUPAS 31571). She carried out all statistical analyses, interpreted the results, and created all tables, graphics, and the accompanying material (supplements).

The doctoral candidate prepared the draft of the manuscript independently. She took charge of the quality assurance of the publication (according to the STROBE statement). She modified the draft manuscript according to the comments of all co-authors. She, as a corresponding author, took responsibility for the submission of the manuscript and communication with the editorial board. She responded to reviewers' comments and performed further analyses during the review process. She was advised and supported in each step by her doctoral supervisors.

2. Introduction

2.1 Background

Proton pump inhibitor (PPI) is regarded as the most effective agent to treat gastric acid-related conditions (1, 2). The approved main indications of PPIs are gastroesophageal reflux disease (GERD), treatment and prophylaxis of gastrointestinal bleeding, treatment of gastric and duodenal ulcers, *Helicobacter pylori* eradication therapy in combination with antibiotics, hypersecretion syndromes such as Zollinger-Ellison syndrome, and Barrett's esophagus (1-4). Since their market launch in 1989, PPIs have superseded former treatment options, such as antacids and histamine-2 receptor antagonists (H2RAs) by far (4). The prescription rates steadily increased and reached the top rank among gastrointestinal medications with about three billion defined daily doses (DDDs) in 2017 in Germany (5). After then, consumption decreased probably because of the growing concern about the potential adverse effects of PPI intake (6).

Contribution to the development of dementia, which is an age-related neurodegenerative disorder, may be one of the possible adverse effects of PPI use (6). The clinical manifestation of dementia is considerably heterogeneous with regard to the clinical expression of neurological features including behavioral and psychiatric symptoms (7). In 2016, dementia was affecting 43.8 million people globally. Additionally, it is predicted that 100 million people will have dementia in 2050 (8). Because dementia is not only ubiquitous but also an onerous disease in society, it is essential to recognize preventable risk factors like the overuse of any specific therapeutic agent.

Since a study has shown an increased risk of dementia in over 75 years-old individuals with long-term PPI use in 2015 (9), research communities, in particular medical practitioners, have paid much attention to investigating whether PPIs deteriorate cognitive functions and even increase dementia risk. However, the studies have reported inconsistent results for the association between PPI use and cognitive deterioration, including dementia risk. While the relationship was not substantiated in several studies (10-13), some research even concluded that PPI administration may be related to a lower risk of dementia (14-16). A similar number of studies also showed an increased dementia risk by PPI treatment (9, 17-19). Such inconsistencies between observational studies have contributed to the doubtfulness of the quality of these studies for clinical decision-making (20, 21). In line with this, the issue of the low evidence level of non-interventional studies regarding the risk-increasing effect of PPI on dementia was pointed out in recent reviews (22, 23).

Although the prospective randomized controlled trial is the standard study design for causal inference (24), conducting it to assess the increased risk of dementia by PPI intake is hardly feasible due to dementia's long prodromal stage (25). To conduct an observational study mitigating the avoidable bias could be the better alternative to achieve consensus on the evidence regarding the relationship between dementia risk and the use of PPI.

In this dissertation, based on two studies, the relation of long-term PPI use with brain aging and dementia risk was examined. For the assessment, various statistical methods were used to minimize possible bias in observational studies, thereby improving the evidence level of the results.

2.2 Dementia

Dementia is a term for describing a group of symptoms affecting memory, thinking, and social functioning that hinder a person's daily life, such as forgetfulness, impaired judgment, language deterioration, and mood changes. It is often regarded as unsuccessful aging (26). Dementia has no broadly accepted definition. Rather, it is described as a syndrome including various symptoms with a wide scope. Despite the diversity of definitions, memory impairment, declined occupational or social function, progress of deterioration, and irreversibility are routinely included in diagnostic criteria (27).

While the relation of dementia with a memory disorder is very common, critical amnesia is not always prominent in dementing disorders. Functional decline, such as poor personal hygiene, difficulty in bill paying, and altered personality, is the clinical marker that separates normal aging from dementia (26, 27). Therefore, the incidence of dementia is recognized by consolidation of an attentively taken anamnesis, physical and mental assessments, and significant findings from neuropsychological examinations. Changes in test results over follow-up intervals also play an important role in the diagnosis (26).

2.2.1 Epidemiology of dementia

The dementia rate is rising rapidly worldwide, particularly in older societies, showing doubled prevalence during the last three decades (8). Consequently, dementia affected 43.8 million people globally in 2016, and it is predicted that 100 million people will live with dementia in 2050 (8). Besides, it was estimated that dementia was the fifth leading cause of death at the global level (28).

The rising dementia rates can be a severe concern to patients and their families and also a burden for the healthcare system because dementia is already causing more costs of social and health care than both cancer and chronic heart disease do (29).

Alzheimer's disease (AD) is known as the most typical dementia subtype occupying 60% of all dementia cases (30). Vascular dementia (VaD) follows, representing approximately 20% of diagnoses (30). Since risk factors, pathophysiology, and symptoms of VaD and AD overlap, they are not easily discriminated. VaD indeed often belongs to the heterogeneous group of clinical disorders resulting from brain damage by hypoxic, hemorrhagic, or ischemic events. (26, 27). Also, cerebrovascular diseases may cause ischemic VaD.

Two other common types of dementia are Lewy body dementia (LBD) and frontotemporal dementia (FTD). The prevalence of LBD is uncertain because LBD has similar features as AD and Parkinson's disease, but it is estimated that 10~25% of all dementia cases are LBD (26). FTD is known as a common dementia type in young-onset dementia, and the estimated prevalence is 15-22 per 100,000 with poor life expectancy (31).

2.2.2 Disease course of dementia

The signature syndrome of dementia is progressive amnestic dysfunction, the most frequently observed dementia profile in elderly patients. The cognitive decline in dementia is generally relentless, which means slow-going in early phases, accelerates with the progression of the disease, but can also plateau (26).

Dementia progresses through several phases. The staging scales depend on the typical progression of signs and symptoms through clinical states, variously termed no dementia, prodromal, mild, moderate, and severe dementia by clinical dementia rating (32). The disease develops over 15-25 years from the preclinical to the end-stage (28). Each stage denotes characteristics of decline in memory, linguistic, and social functions, and gaining of abnormalities such as agitation, delusion, and wandering (28). Nevertheless, the time course of each phase varies in each patient. That is, the phases can be relatively shortened or prolonged in an individual compared with other patients. In addition, the duration of the stage is variable in an individual (33). Despite the individual variation, a recent study reported that it takes 3.9 and 5.0 median years from diagnosis to institutionalization and to death, respectively (34).

Once dependence on activities of daily living like personal hygiene is fully established, worsening accelerates (26, 27). When patients have severe memory impairment, they usually have other

accompanying symptoms: aphasia, attentional and reasoning disturbances, apraxia, agnosia, incontinence, and changes of behavior such as wandering (26). Later, patients become slow, and an assessment of cognitive function and communication is not possible anymore (26, 34). Weight loss is generally noticeable. In the late stage, they become cachectic, bedridden, and vulnerable to infectious diseases. After then, the quadriplegic condition can last for months to years until they face death. (34).

If persons have mixed types of dementia, it may result in a faster decline than each apart, with a more severe manifestation of the disease and a higher risk of early institutionalization and mortality (28).

2.2.3 Etiology of dementia

Understanding the etiology of dementia is essential to develop prevention and treatment strategies. Researchers should cautiously interpret both risk and protective factors because the detected harm and benefit may stem from not only known confounding factors but also unknown confounding factors. Nevertheless, some factors have been consistently associated with a greater or smaller risk of developing dementia (26, 27, 35). Dementia has a multifactorial etiology, with several environmental and genetic factors implicated in its development and clinical course (27). However, the extent to which the risk factors affect the development and clinical course of dementia is still largely unknown.

The most decisive risk factor for dementia is age, mainly because the risk of neurodegenerative and cerebrovascular disease increases with getting older (25, 26). A higher prevalence of overall dementia is observed in the female group, especially AD. However, the difference is primarily determined by the longer lifespan of women (27).

The apolipoprotein E4 (APOE) significantly increases the risk of AD and shifts onset age ahead (27). Approximately 40-80% of individuals with Down syndrome develop AD if they reach midlife (36). Various vascular risk factors affect AD risk by indirectly accelerating cerebrovascular pathology and directly influencing the pathology of AD (27).

The major risk factors for VaD are almost the same as the ones for cerebrovascular dysfunction, including hypertension, smoking, high homocysteine level, and metabolic disorders such as obesity, diabetes, and hypercholesterolemia. Other atherosclerotic risk factors and conditions raising brain embolism risk are also significant (37). Amyloid angiopathy in the brain is rare but a key risk factor meaning the deposits of amyloid in the arterial vessels. Another important cause is cerebral autosomal dominant arteriopathy with leukoencephalopathy and subcortical infarction,

which occurs when the thickening of blood vessel walls finally occludes the flow of blood to the brain (27, 38).

Previous studies have suggested that the term “mixed dementia” can stand for the combination of cerebrovascular pathologies and AD (30). Each pathology of pure cerebrovascular disease and pure AD contributes to different levels, which means that the two extremes of the spectrum bring about a continuum of patients (39). Besides, it has been reported that VaD and AD have a common vascular aetiopathogenesis (40). The study also found a neuropathological association between the vascular burden in the necropsied brain and the amyloid/tau proteins among most individuals with dementia (40).

About one-tenth of patients diagnosed with FTD show an autosomal dominant inheritance pattern, and approximately 40 percent of patients have a family history of early-onset dementia (27). Regarding LBD, there is no family history in most cases (27).

There are significant lifestyle-related risk factors, such as consumption of alcohol, smoking habits (41), lack of physical and mental activities (42), and a diet high in saturated fat (43). Traumatic brain injury increases the risk of dementia as well (27, 44). In addition, bad air quality, exposure to toxic heavy metals, and occupation-related exposures were discussed as environmental risk factors in previous studies (41). On the other hand, mental activities in middle age (e.g., training new skills) (45), physical activity (46), and a healthy diet including antioxidants (47), are regarded as possible protective factors.

Recent research suggested that up to a third of dementia cases can be preventable by lifestyle modification (35). Prevention is always better than treating diseases, and it is especially important in the field of dementia since currently no interventions to cure the disease are available (35).

2.3 Utilization and pharmacology of proton pump inhibitors (PPIs)

PPIs are the most successful options to treat gastric acid-related conditions by excess production of gastric acid and are one of the most frequently prescribed drugs overall (1, 4). The name refers to their mechanism of action as they irreversibly block the highly specialized proton pump-transport system (i.e., H^+, K^+-ATPase) in the gastric parietal cells, thus inhibiting the secretion of hydrochloric acid in the stomach lumen (48). The pharmacodynamics is described in more detail below.

The approved main indications of PPIs are given above. Omeprazole is the firstly introduced PPI to the market. Since then pantoprazole, lansoprazole, rabeprazole, esomeprazole and dexlansoprazole followed. The pharmacokinetics and pharmacodynamics of each PPI are slightly different, even though they share the core structures (49). Despite no proven differences in therapeutic efficiency between the specific agents at equivalent doses (49), it has been reported that different types of PPIs are preferred country by country, probably because of various drug approval processes, pharma contracts, or healthcare systems. While pantoprazole dominated others in a German study (5), omeprazole was more frequently used in the UK (12) and Spain (50). Combined use was most often observed in Finland (13).

In the stomach, parietal cells secret gastric acid if there is stimulation by the gastrin, vagus nerve, and histamine. Therefore, many drugs target the parietal cells to hinder the secretion of acid. The gastric proton pump and the histamine type 2 (H2) receptor are the main functional targets in the parietal cell (51).

In 1977, H2RA was introduced to the market and remarkably increased the successful treatment rates in patients with peptic ulcer disease (52). The increase of intracellular cyclic AMP concentration and the activation of protein kinase A (PKA) are the results of the binding of histamine to the H2 receptor (51). PKA activation affects the proton pump transport to the plasma membrane (48). However, H2RA showed limited healing effects on GERD due to its limited capability to control PH in the stomach (52).

For better achievement of PH control, the acid-secreting enzyme was selected as a new target (52). PPI was introduced to the market for the first time in 1989, directly targeting the gastric proton pump. It contributed to faster symptom relief and healing of the lesions (51). PPI is activated by acid since it is a prodrug (48, 52). Once it is activated, it inhibits the proton pump by covalent bonds with cysteine (48). To form bicarbonate (HCO_3^-) and H^+, carbonic anhydrase assists the reaction of H_2O and CO_2. After then, the gastric proton pump uptakes H^+ into the lumen of the stomach (51). Via simple diffusion, Cl^- moves from parietal cells into the lumen of the stomach (51). To form hydrochloric acid (HCl), water combines with H^+ and Cl^- in the stomach lumen, and the produced bicarbonate is released into the bloodstream (48, 51). The inhibitory activity of PPI can last longer through the dynamics of covalent binding (48).

2.4 Scientific challenges

Results from an observational study are usually considered as a lower grade of evidence since the randomized controlled trial can minimize both known and unknown confounding factors by random selection of study participants (24, 25). However, it is not always feasible to examine all exposures in randomized controlled trials because of ethical and practical issues. Besides, generalizability cannot be achieved when the study participants are not representing the population where the findings should be applicable, for example, the selection of only the elderly or the comorbid individuals (25). The common scientific challenges in the examination of the correlation between PPI use and the risk of dementia are described in the following paragraphs.

Researchers should very carefully address the confounding because it is a frequently observed systematic error in observational studies. When a variable is associated with both the exposure (i.e., PPI use) and outcome (i.e., dementia risk), confounding occurs, and it affects the result of the study (53). Confounding can be reduced by randomization, matching, stratification, restriction, or adjustment for possible confounders in regression models (54). Nevertheless, residual confounding is often possible because we still do not know the causal pathway sufficiently, and known confounders can be misclassified.

Selection bias is derived from the selection of study participants based on factors affecting the outcome of the study (54). It could be related to confounding in that several variables can have unequal associations with PPI use and dementia risk in the exposed and unexposed groups (53, 54). While confounding is typically addressed when analyzing the gathered data, selection bias could be effectively reducible at the stage of including patients in a study (54).

Misclassification of PPI use or incident dementia causes bias in a study. It is particularly problematic if the misclassification is differential. It means that an inaccurate classification of PPI intake and incidence of dementia more frequently occurs in one group compared with another. As a result, the observed effect can be either inflated or reduced. If an erroneous classification randomly occurs in both groups, it is regarded as non-differential misclassification, and generally attenuates the association.

Generalizability (i.e., external validity) is related to what extent the finding of a study is applicable also in various settings beyond the setting of the study (54, 55). A high level of internal validity is a prerequisite to achieving generalizability, which means that no systematic error exists.

As described earlier, observational studies have reported discrepant results on an association between dementia risk and PPI intake. Even meta-analyses do not reach a consensus (56, 57). Many

of the observational studies are prone to confounding. A common source of bias is the inclusion of prevalent users of PPIs and patients with prevalent dementia, which might have resulted in immortal time and other time-related biases. Also, there are often selection bias issues by excluding cancer records or including too old individuals (25).

2.5 Research aims

This dissertation aims to evaluate whether the use of PPI increases dementia risk by using comprehensive data as well as advanced pharmaco-epidemiological study designs and methods. This was done by conducting two separate studies, and each aim is presented below:

- Publication I: To investigate the link of PPI use to cognitive function, brain volumes, and estimated brain age by using data from a population-based cohort study.

- Publication II: To evaluate the effect of long-term intake of PPI on the incidence of dementia by using big claims data and applying advanced methods to limit confounding.

2.6 Description of the analyses and contribution to the scientific evidence

2.6.1 Publication I

The first publication examined whether PPI intake is associated with brain aging, including verbal learning and memory function, estimated brain age, and brain volume as outcomes. The analysis datasets were available from the Study of Health in Pomerania (SHIP), which includes two separate cohorts of adults between 2008 and 2012.

The design of this study included SHIP-2 and SHIP-Trend since the individuals from those two groups were encouraged to take the whole-body MRI examination, which included brain MRI scans. In total, 3,746 individuals participated in whole-body MRI (58). Among them, 3,310 subjects aged between 21 and 89 underwent brain MRI scans. We excluded individuals who had MRI scans with critical movement artifacts (i.e., failed quality control) or had missing information on confounders. In the end, the analytic cohort for analyzing MRI-derived outcomes comprised 2,653 participants. 788 subjects were from SHIP-2, and 1,865 were from SHIP-Trend. For both cohorts, two different cognitive skill tests were conducted, respectively. 1,569 participants from SHIP-2 and 4,142 from SHIP-Trend went through the examination.

The study participants of SHIP were assumed to be representative of the general population of Pomerania, a northeastern region of Germany. However, not every participant underwent a brain MRI scan. Thus, we tested whether missing-completely-at random (MCAR) assumption was plausible, which means we computed inverse probability weight (IPW) for participating in the brain MRI by fitting a multivariable logistic regression model. The calculated IPW was further used to reduce selection bias resulting from the non-random carrying out of the brain MRI.

We controlled possible confounders by including them in the regression model to calculate the weight. In this study, sociodemographic status, such as income and education level, and behavioral factors including smoking habits and alcohol consumption, were available, as well as comorbidity and medication use. A broad range of data on confounding was available thanks to the nature of the population-based cohort study.

After adjustment for multiple confounders, a relation between PPI use and brain volumes was not obtained. Also, the estimated brain age was not different across the user group and non-user group. Although age slightly modified the effect of PPI intake on right hippocampal volume, there was no significant link between them.

However, we found inconsistent results from the comparison of verbal learning and memory tests. PPI users presented lower scores for the Verbal learning and memory test (VMLT), even though effect sizes were not large (Cohen's d was 0.13 and 0.17 for prompt memory and delayed recall, respectively). On the other hand, the two groups showed no difference in the results when the Nuremberg age inventory (NAI) was used to assess verbal memory function. The different complexity of the tests might have caused the discrepancy in the results of VLMT and NAI, that is, the different number of words and the test process. During the NAI test, study subjects had to only recognize the distractor words rather than actively recall the given words. Because two verbal learning and memory assessments presented discrepancies in results, it is also examined whether the left hippocampus's size, which is positively associated with verbal memory (59, 60), showed a difference. However, no evidence was found that the groups differed in the left hippocampal volumes.

The lack of explicit agreement between the test results warrants further research. Montreal Cognitive Assessment (MoCA) and Mini-Mental State Examination (MMSE) are indeed more frequently chosen to assess general cognitive functions (61-63). Our findings, therefore, suggest that employing the above-mentioned examinations that include assessment of visuospatial processing, attention, executive functions, language, orientation, recall, and abstraction, could be advantageous for the general evaluation of declined cognitive functions and dementia risk.

The nature of the cross-sectional analysis did not allow us to draw causal associations. Still, we were able to present how to examine the effect of PPI intake on brain age/brain volumes calculated based on MRI scans. Given that reduced brain volumes can act as proxies for prevalent dementia (62, 64-66), we adopted quantitative approaches to investigate brain volumes and their association with the use of PPI, and the findings add further evidence to the current literature.

2.6.2 Publication II

We conducted the second publication with a retrospective, weighted cohort study design using large German claims data from AOK Bayern (Allgemeine Ortskrankenkassen Bayern) including about 6.1 million adults between 2008 and 2018. In other words, we followed an exposed group (PPI initiators) and a comparison group (non-initiators) to assess whether they would be diagnosed with dementia. We emulated a target trial by benefiting from a health insurer's large data and mitigating unresolved methodological issues in previously conducted observational studies regarding the study question.

A target trial emulation, which is proposed in recent studies (67-69), is used to transfer methodological strategies from clinical studies to our data in order to avoid bias that typically arises in observational studies. Intention-to-treat (ITT) analysis was conducted in which eligible individuals who started PPI treatment or had no PPI. To assess the long-term PPI use effect, a marginal structural model was used.

The entropy balancing was employed to control baseline confounders (70, 71). Additionally, we performed a series of sensitivity analyses to assess possible residual confounding. Firstly, we restricted analysis samples to persons who had documented International classification of diseases (ICD)-10 codes of the officially approved indications (peptic ulcer, GERD, esophagitis, heartburn, *Helicobacter Pylori*-infection, and Zollinger-Ellison syndrome) (72). The aim of the restricting method is to increase the homogeneity of the effects of medication intake and potential confounding factors in study subjects (73-75). Secondly, a comparison between the initiation of PPI and an active comparator, H2RAs (Anatomical therapeutic chemical [ATC] code: A02BA01-08), was performed (73). Lastly, despite careful statistical methods to minimize bias in non-randomized studies, residual confounding is possible. We calculated E-value, to assess the bias stemming from unmeasured confounding. E-value implies the minimum strength of the association that an unmeasured confounder would need to explain away the observed association between PPI use and dementia risk (76).

We created a series of trials for each non-initiator to avoid selection bias. By doing so, a single person shared trials starting at various time points (i.e., each quarter) (77). All individual trials of

non-initiators were pooled in the emulated trial if they were meeting the eligibility criteria but had not yet received PPI treatment. After that, we selected three times the number of PPI initiators from the pooled trials using an exposure density sampling approach, which indicates a match for the time of cohort entry (78).

Regarding the measurement of exposure, we investigated PPI use based on the prescription records dispensed in community pharmacies. Prescription drug records are made for all outpatient dispensing which were reimbursable by the health insurance provider. Each record included the date of prescription, central pharmaceutical number, and date of dispensing. Further information on the generic and trade name, strength, prescribed quantity, formulation, ATC code, and DDD was available through the link of the central pharmaceutical number to a drug reference database (79, 80).

The outcome of interest in this study was an incidence of dementia. Dementia is referred to as a slowly progressing disease and encompasses a spectrum of psychological symptoms from mild depression to a combination of cognitive impairment and functional impairment. Reversion from cognitive impairment with no dementia to normal cognitive status for age is also possible (25, 81). We checked whether at least two ICD-10 codes for dementia were found in consecutive quarters to confirm the incidence of dementia.

As the population of study II was from AOK Bayern, which is the largest health insurer in the federal state of Bavaria in Germany, the question of whether the study population has generalizability for the Bavarian population is redundant. We would be able to apply our findings to other regions of Germany and countries similar to Germany, but may not to countries with different ethnic proportions and different lifestyle aspects such as smoking and dietary habits.

The present study suggests that PPI initiation increases the dementia risk (hazard ratio [HR]: 1.54, 95% confidence interval [CI]: 1.51-1.56). Even with an application of long lag windows to control reverse causality (25, 82), the elevated dementia risk by the initiation of PPI was observed with the HR of 1.45 (95% CI 1.41-1.50) and 1.38 (95% CI 1.32 -1.44) applying 3- and 5-years lag windows, respectively. The analysis of time-varying PPI use adjusted for time-dependent confounders and censoring strengthened the evidence that long-term use of PPI increases the risk of dementia (HR: 1.56, 95% CI: 1.50-1.63).

The risk-increasing effect of PPI initiation on dementia was also found in the extreme restriction analysis, where the study subjects were limited to those with officially approved indications for PPI prescriptions to set the treatment and comparator groups more homogenous on confounders

(73-75). An overlap in clinical characteristics and pretreatment demographics of non-initiators and PPI initiators was observed in this analysis; thereby the findings are further supported.

The adverse effect of frequently taken medications is constantly of interest in medical research. However, an estimation of a medication effect is challenging because it takes much effort to enroll the participants without prevalent diseases and follow them up for a long time (69, 83). So far, there is only one randomized controlled trial regarding the risk-increasing effect of PPI intake on dementia. It presented that pantoprazole use did not increase the dementia risk (84). However, the trial was conducted for a short follow-up period including a small sample size; i.e., three years of follow-up and 101 reported dementia cases. Furthermore, thirty days of washout period was applied, which is relatively short. We took advantage of the large data provided by a health insurer to reduce unresolved issues of previously performed non-interventional studies and to overcome the aforementioned challenges in implementing randomized controlled trials to address this study question (83).

Dementia comprises a series of diseases, including common clinical symptoms. Vitamin B12 deficiency and an increase of tau protein formation and amyloid-β plaques may be the conceivable pathophysiological pathways of brain decline where PPI use is involved (85). Furthermore, one of the recent studies reported how PPIs are able to hinder the action of the core-cholinergic enzyme even with a low dose of exposure (86). This novel finding is meaningful since the deterioration in the network of cholinergic neurons is a core feature of neurodegenerative disorders that usually result in cognitive decline (87). Our findings, supported by the newly discovered mechanism, warrant further pathophysiological investigations of the PPI effect on the incidence of dementia.

3. Summary

Dementia is an age-related neurodegenerative disorder that affected 43.8 million people globally in 2016. In addition, it is expected that the prevalence will continue to increase to 100 million by 2050. Since dementia is ubiquitous and an onerous disease in society, it is essential to recognize preventable risk factors like the overuse of any specific therapeutic agent. Since an increase in dementia risk by Proton pump inhibitor (PPI) intake was reported in 2015, many studies have presented inconsistent evidence for the effect of PPI use on brain aging, including dementia risk and cognitive deterioration. Therefore, this dissertation aimed to investigate whether the PPI treatment is related to brain aging using comprehensive data and advanced pharmaco-epidemiological study designs and methods.

In Study I, we conducted a cross-sectional investigation of the brain-aging effect of PPI use in the population-based study. In the primary analysis, there were 2,653 individuals took part in brain magnetic resonance imaging scans. In the secondary analysis, the Verbal Learning and Memory Test (VLMT) and the Nuremberg Age Inventory (NAI) were employed to evaluate cognitive function. No clear evidence was found that PPI intake was associated with estimated brain age or brain volumes. While we observed declined immediate and delayed recall in PPI users when VLMT was used, no difference in the results was found using NAI.

In study II, we conducted a prospective observational study including 2,698,176 subjects insured by a German health insurance provider. We designed the study emulating a target trial for individuals aged at least 40 years. Study participants were assigned to the PPI initiator group or non-initiator group from 2008 to 2018. 1.3% of non-initiators and 4.4% of PPI initiators were diagnosed with dementia. We observed an increased dementia risk in both initiation and time-dependent effect analyses with risk estimates of 1.54 (95% CI: 1.51-1.58) and 1.56 (95% CI: 1.50 -1.63), respectively.

Although the results of the first study aiming at exploring the effect of PPI on cognitive function, brain volume, and brain aging, did not show clear associations, the results of the second study gave a strong indication for a risk-increasing effect of PPI use for a later incidence of dementia. By applying advanced methods, the latter findings provided a higher level of evidence regarding the association between PPI use and dementia risk.

In summary, the presented results extend the current knowledge of the relationship between PPI use and dementia risk. Besides, the study design with advanced methodologies and a large sample size demonstrated how to mitigate the avoidable bias in non-interventional studies when conducting randomized controlled trials is not feasible.

4. Zusammenfassung

Demenz ist eine altersbedingte neurodegenerative Erkrankung, von der im Jahr 2016 weltweit 43,8 Millionen Menschen betroffen waren. Darüber hinaus wird erwartet, dass die Prävalenz bis zum Jahr 2050 auf 100 Millionen steigen wird. Da Demenz eine häufige und belastende Krankheit in alternden Gesellschaften ist, ist die Identifizierung von vermeidbaren Risikofaktoren, wie etwa Arzneimittelwirkstoffe, wichtig. Seit 2015 über ein erhöhtes Demenzrisiko durch die Einnahme von Protonenpumpen-Inhibitoren (PPI) berichtet wurde, haben Studien widersprüchliche Ergebnisse zu Assoziationen zwischen der Einnahme von PPIs und der Alterung des Gehirns und des Risikos für kognitivem Störungen und Demenz vorgelegt. Daher zielt diese Dissertation darauf ab, anhand umfassender Daten und fortschrittlicher pharmako-epidemiologischer Studiendesigns und Methoden zu untersuchen, ob die PPI-Dauereinnahme das Risiko für Gehirnalterung und Demenz erhöht.

In Studie I wurde eine Analyse zum Zusammenhang zwischen PPI-Einnahme und Hirnalterung in der Allgemeinbevölkerung (SHIP-Studie) durchgeführt. 2.653 Teilnehmer*innen nahmen an einer Magnetresonanztomographie (MRT) des Gehirns teil und wurden in die Analyse eingeschlossen. Die kognitive Funktion wurde mit dem Verbal Learning and Memory Test (VLMT) und dem Nürnberger Altersinventar (NAI) untersucht. Es wurde keine Assoziationen zwischen der Einnahme von PPIs und den verschiedenen Hirnvolumina bzw. dem geschätzten Hirnalter gefunden. Bei PPI-Einnehmer*innen war der VLMT-Score für unmittelbare und für verzögerte Erinnerung der Test-Wörter niedriger als bei Nichteinnehmer*innen. Die Einnahme von PPIs stand in keinem Zusammenhang mit dem NAI-Score.

In Studie II wurde anhand von Routinedaten von 2.698.176 Versicherten untersucht, ob die Dauereinnahme von PPIs das Risiko für Demenz erhöht. Die Daten enthielten Informationen zu demographischen Merkmalen, stationären und ambulanten Diagnosen sowie Verschreibungen von Medikamenten zwischen Januar 2008 und Dezember 2018. In die Studie wurden Personen ab einem Alter von 40 Jahren ohne bestehende Demenz eingeschlossen.

Bei 4.4% inzidenten PPI-Einnehmer*innen und 1.3% Nicht-Einnehmer*innen wurde im Beobachtungszeitraum eine Demenz diagnostiziert. Wir beobachteten ein erhöhtes Risiko für Demenz sowohl in der Initiationseffektanalyse (Hazard Ratio: 1.54, 95% KI 1.51-1.58) als auch in der zeitabhängigen Dauereinnahme-Effektanalyse (Hazard Ratio:1.56, 95% KI 1.50-1.63), in der 180-Tage-Intervalle betrachtet wurden.

Während die erste Studie keinen eindeutigen Beweis für den Zusammenhang zwischen der PPI-Einnahme und der kognitiven Funktion zeigte, zeigten die Ergebnisse der zweiten Studie einen

starken Hinweis, dass die PPI-Dauereinnahme das Demenzrisiko erhöht. Aufgrund der Verwendung fortschrittlicher Methoden liefert die zweite Studie die Ergebnisse mit einem höheren Evidenzgrad für den Zusammenhang zwischen der PPI-Einnahme und dem Demenzrisiko.

Zusammenfassend erweitern die vorgestellten Ergebnisse den derzeitigen Stand der Wissenschaft über den Zusammenhang zwischen PPI-Einnahme sowie Demenzrisiko. Darüber hinaus zeigten die Studiendesigns mit entsprechenden Methoden und einer großen Stichprobe ausreichend, wie die vermeidbare Verzerrung in Beobachtungsstudien minimiert werden kann, insbesondere wichtig in Situationen, wo randomisierte kontrollierte Studien nicht durchgeführt werden können.

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Acknowledgements

I would like to thank my doctoral supervisor Prof. Dr. Jakob Linseisen for allowing me the opportunity to work with him on this project. I would also like to thank him for the opportunities to participate in many scientific trainings, seminars, and conferences. Most of all, I am grateful for his generous nature and constant willingness to make his knowledge and time available.

Furthermore, I would like to express my appreciation to Prof. Dr. Sebastian E. Baumeister. For all the times I've bothered him with questions about statistics, I would like to thank him for his excellent answers and kind attitude toward me.

In addition, I want to thank Prof. Dr. med. Christa Meisinger for her help and support throughout my time at LMU München, not only as a master's student but also as a doctoral candidate.

I am grateful to my colleagues at the Institute of Epidemiology at LMU München at UNIKA-T Augsburg. It was a great joy to work with them.

I especially appreciate my friends who always had a great interest in my progress and encouraged me over the years.

I thank my family in South Korea for their huge support and unconditional love throughout my life. They encouraged me to keep going and finish the degree.

Finally, special thanks to Tom, who is the unsung hero of this work. Without his constant encouragement and support, I would never have been able to complete this work.