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Emulating a target trial of proton pump inhibitors and dementia risk using claims data

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Abbreviations

AD = Alzheimer's disease; ATC = Anatomical therapeutic chemical classification; DDD = Defined daily dose; H2RA = Histamine 2 receptor antagonist; ICD = International classification of diseases, PPI = proton pump inhibitors; RCT= randomized clinical trial; VaD = Vascular dementia

Abstract

Background:

Understanding the adverse effects of proton pump inhibitors (PPIs) is important due to their widespread use, but the available evidence for an increased dementia risk among patients taking PPIs is inconclusive. The present study aimed to estimate the causal effect of PPIs on the risk of dementia by target trial emulation and time-varying exposure modeling.

Methods:

Using claims data of 2,698,176 insured people of a large German statutory health insurer, we conceptualized a target trial in which individuals aged 40 years and older were classified as PPI initiators or non-initiators between 2008 and 2018, and followed until diagnosis of dementia, death, loss to follow-up or end of study. Incidence of dementia (ICD-10 codes F00, F01, F03, F05.1, G30, G31.0, G31.1, G31.9, and F02.8+G31.82) was defined applying a 1-year lag window. We used weighted Cox models to estimate the effect of PPI initiation vs. non-initiation on

dementia risk and weighted pooled logistic regression to estimate the effect of time-varying use vs. non-use.

Results:
29,746 PPI initiators (4.4%) and 26,830 non-initiators (1.3%) were diagnosed with dementia. Comparing PPI initiation with no initiation, the hazard ratio (HR) for dementia was 1.54 (95% confidence interval [CI]: 1.51-1.58). The HR for time-dependent PPI use vs. non-use was 1.56 (95% CI: 1.50-1.63). Differentiated subtypes, including unspecified dementia, Alzheimer's disease (AD), and vascular dementia (VaD), showed increased risk by PPI initiation and time-varying PPI use.

Conclusions:
This study suggests that PPI initiation and time-varying PPI use may increase overall dementia risk.

Keywords: dementia, proton pump inhibitors, cognitive impairment, Gastroesophageal reflux disease

Introduction

The effect of proton pump inhibitors (PPIs) as a gastric acid suppressant is well established, and they are frequently used to treat disorders characterized by excessive gastric acid production[1]. In recent years, however, observational studies examining the association between PPI intake and risk of dementia have yielded conflicting results[2-6] pointing out the necessity of randomized clinical trials (RCTs) to establish more robust causal evidence. While prospective RCTs are the standard criterion of causal inference[7], performing RCTs to evaluate the effects of PPI intake on dementia risk is infeasible and costly given the long prodromal phase of dementia[8,9]. The issue of attrition by loss to follow-up is also challenging in RCTs with long-term follow-up[7,8].

Given that previous observational studies on the relationship between PPI use and dementia risk have shown contradictory results[2-6], systematic reviews have not achieved consensus either[10-12]. While Wang et al. (2021) reported no association between dementia risk and the use of PPI with a hazard ratio (HR) of 0.98 (95% confidence interval [CI]: 0.85-1.13) and high heterogeneity (I^2 =

98.5%) in the largest meta-analysis[12], recent observational studies conducted in Spain and Taiwan reported an increased risk of dementia in PPI users[2,6]. In addition, a recent Swedish study added a possible underlying mechanism between PPI use and dementia risk, explaining that PPIs may cause cholinergic dysfunction, which is known as a driving force of dementia[13].

Several reasons might have caused discrepancies in previous studies. In many studies, all individuals who took PPIs during the study period were included without information on dose or duration, which could have introduced exposure misclassification and thus attenuated the effect estimate[14-16]. PPI intake was often assessed in proximity to onset of dementia without proper consideration of the prodromal phase of dementia[4,17], which could have introduced reverse causation, because changes in PPI intake could have taken place due to the symptoms of undiagnosed dementia[8]. Although some studies avoided those limitations, few studies have considered potential bias from time-varying confounding[3,18].

Some of the aforementioned limitations can be avoided by conducting an observational study that mimics a clinical trial using clear inclusion criteria, enrollment period, active treatment phases, and long-term follow-up[19,20]. In this study, we specified the protocol of a target trial to estimate the effects of PPI initiation and time-varying PPI use on the risk of dementia using claims data from a large health insurer in Bavaria, Germany[20,21].

Material and methods

Study design and participants

This study used administrative claims data from the largest statutory health insurer in Bavaria, Germany (Allgemeine Ortskrankenkassen [AOK] Bayern). The anonymized data contained the insured individuals' demographic and comprehensive health care information, including hospital admissions, outpatient visits, diagnostic codes, and drug prescription details. The International Classification of Diseases (ICD-10) was used to define hospital and ambulatory diagnoses, and drug prescriptions were classified according to the Anatomical Therapeutic Chemical Classification (ATC system). We used data between January 2008 and December 2018. The present study has been approved by the Ethics committee at the Ludwig Maximilians-University of Munich. Since the data were anonymized and produced for research purposes, the requirement for consent from study participants was waived. The study was registered at European network of centres for pharmacoepidemiology and pharmacovigilance (register number: EUPAS31571), where the study protocol was deposited.

We emulated a hypothetical target trial in which eligible individuals received PPIs or no PPI. Eligible individuals were those aged 40 years or older with at least one year of continuously insured records before and after study entry, who did not meet the exclusion criteria (Table 1).

The primary treatment strategy to be compared was an initiation of any PPI (ATC codes A02BC01-06) at baseline and non-initiation. PPI use was assessed using prescriptions dispensed by community pharmacies and applying 365 days of washout period. Information on in-hospital use or over-the-counter (OTC) PPI use was not available. Based on the treatment guideline, patients usually initiate standard-dose therapy for 4-8 weeks (28-56 defined daily doses [DDDs]) and then extend use[22]. Hence, we set a consecutive use of 56 DDDs as a requirement to assign PPI initiators (for details on the DDD computation, see Supplemental Table S1)[23]. The first PPI dispensing date formed the index date for each individual in the PPI initiator group. We assumed consecutive treatment if the initiator filled the next prescription no later than 30 days from the expected dispensing day.

Individuals who were eligible as PPI initiators (n=674,544) were followed-up and compared to non-initiators (Supplemental Figure S1). To minimize the selection bias in the group of non-initiators, we applied the approach of creating a series of trials. Each individual had several trials with different enrollment points, i.e., every quarter of the year from when they became eligible to the end of study participation[24]. All individuals' trials were pooled in the emulated trials of non-initiators, as long as they met the eligibility as study participants but had not yet initiated PPI intake[24]. We then randomly selected three times the number of initiators (n=2,023,632) from the trials of the non-initiators, applying an exposure density sampling method that matches for cohort entry time (a same quarter of the year)[25].

The primary outcome of interest was incident dementia (ICD-10 codes F00, F01, F03, F05.1, G30, G31.0, G31.1, G31.9, and F02.8+G31.82) (Supplemental Table S2)[26]. To ascertain the incidence of dementia, the ICD-10 codes for dementia had to be found at least twice in consecutive quarters. We differentiated unspecified dementia, Alzheimer's disease (AD), and vascular dementia (VaD) for additional subtype analyses.

Confounding factors

We adjusted our analyses for potential confounding factors, considering direct causes of PPI use or dementia or both, excluding possible instrumental variables[27]. Participants' baseline characteristics were measured during the 180 days before, including the index date. Comorbidity was assessed, categorizing obesity, diabetes, hypertension, heart disease, peripheral vascular disease, coagulopathy, chronic pulmonary disease, cancer, depression, abuse of substances or

psychosis, cerebrovascular disease, diseases that may cause dementia, inflammation, infection, or injury of the nervous system assuming that these conditions are risk factors for dementia. These conditions were defined according to a coding algorithm proposed by Quan et al.[28] Concurrent intake of antidiabetics, antihypertensives, statins, clopidogrel, anticholinergics, anti-inflammatory drugs, corticosteroids, antidepressants, and psycholeptics was also included as covariates (Supplemental Table S3).

Statistical analysis

Weighted Cox regression models were used to estimate the effect of PPI initiation versus non-initiation on dementia risk. Entropy balancing was used to adjust for baseline confounding[29,30]. To reduce the potential for reverse causality, we performed additional analyses, where we censored dementia cases occurring during the first one, three, and five years of follow-up, respectively. Based on it, we drew an adjusted cumulative hazard curve that compares the hazard at different times over the observation period.

Weighted pooled logistic regression models were used to examine the effect of time-varying PPI use on dementia risk, because PPI intake varied over time[31,32]. Time-varying stabilized inverse probability weights were used to adjust for the time-varying confounding. We constructed a dataset consisting of follow-up intervals of 180 days, calculated updated weights. To additionally adjust for time-varying selection bias, we weighted each individual at each time t by the inverse probability of being censored due to incidence of dementia, death, or end of study participation. This approach provides a conservative estimate of the HR, analogous to analysis in an unblinded RCT, and can be considered as an intention to continuous PPI treatment analysis[31]. Survival curve standardized for baseline covariate distribution and weighted for time-varying confounders was also drawn.

We performed several sensitivity analyses to examine the extent to which observed associations could be due to bias. As the first sensitivity analysis, we fit the same weighted Cox model restricted to individuals who had an ICD code of the approved indications as documented in the official product information (gastroesophageal reflux disease (GERD), *Helicobacter Pylori*-infection, peptic ulcer, esophagitis, Zollinger-Ellison syndrome, and heartburn)[33]. This restriction strategy aims to make patients more homogeneous regarding potential confounding factors and treatment effects[34-36]. We additionally compared PPI initiation to the initiation of an active comparator, histamine 2 receptor antagonists (H2RAs, ATC: A02BA01-08)[36]. Like a PPI initiator, an H2RA initiator was defined as a person who fulfilled consecutive use episodes with at least 56 DDDs.

Lastly, we calculated an E-Value, which indicates the minimum strength of an association that an unmeasured confounder would need to have to account for the observed association between PPI exposure and incidence of dementia[37]. Analyses were performed using R (version 3.6.3).

Results

We identified 674,544 PPI initiators and 2,023,632 non-initiators who met the eligibility criteria in our data set of 6,097,740 individuals. The median follow-up time of PPI initiators and non-initiators was 4.3 (interquartile range (IQR): 2.3-6.8) years and 5.3 (IQR: 3.0-7.5) years, respectively. The median age of the whole study population was 56.0 (IQR: 48.0-68.0) years, and 49% were women. More details on the demographic and clinical characteristics of PPI initiators and non-initiators are provided in Supplemental Table S4. In our dataset, PPI initiators generally had more baseline diseases and medication intake history. After weighting, however, both groups were well balanced on the confounders. (Table 2).

Of 2,698,176 individuals, there were 39,776 cases of dementia in PPI initiators (5.9%) and 31,042 cases in non-initiators (1.5%) (Table 3). With a 1-year lag window application, the incidence of dementia decreased to 29,746 cases (4.4%) in PPI initiators and 26,830 cases (1.3%) in non-initiators. Without application of lag window, the HR for comparing the overall dementia risk in PPI initiators and non-initiators was 1.71 (95% CI: 1.67-1-75). HRs for PPI initiation versus non-initiation slightly decreased after censoring cases that occurred during the first one, three, and five years of follow-up, respectively (Table 3).

While there were more dementia incidence during the first year in PPI initiators (n=10,030, 25% of total cases) than in non-initiators (n=4,212, 14% of total cases) and the adjusted cumulative hazard curves diverged promptly with the start of follow-up (not shown), gradual diverging of curves was observed when 1-year lag window applied (Figure 1), which is pathologically more plausible for dementia.

In the analysis of time-varying PPI use versus non-use that considered time-varying confounding and censoring, increased dementia risk was observed by PPI use (HR: 1.56, 95% CI: 1.50-1.63; 1-year lag window applied) (Table 4). The survival curves standardized for baseline covariates and weighted for time-varying confounders also showed that PPI use had a higher risk of dementia than no PPI use (Supplemental Figure S2).

In the sensitivity analysis restricted to 193,513 initiators and 32,974 non-initiators who had at least one on-label PPI indication, baseline characteristics of both groups were similar even before

weighting, and a better balance was observed after weighting (Supplemental Table S5). Again, we found an increased risk of dementia by PPI initiation versus non-initiation (HR: 1.32; 95% CI: 1.23-1.42, 1-year lag window applied) (Table 4).

On the other hand, the comparison of 660,635 PPI initiators and 9,457 H2RA initiators identified 28,803 and 585 dementia cases in each group with no difference concerning the risk of dementia (HR: 0.93; 95% CI: 0.85-1.01; 1-year lag window applied). The demographic and clinical characteristics of the groups are provided in the Supplemental Table S6).

E-value analysis for the primary analysis suggested that an unobserved confounder would need to be associated with PPI initiation and dementia risk with a relative risk (RR) of 2.45, above and beyond the adjusted confounders, to explain the observed HR of 1.54. An unobserved confounder would need to be related with a RR of 2.39 with PPI initiation and dementia to shift the lower CI limit (i.e., 1.51) to the null.

There were no notable differences in risks of dementia subtypes associated with PPI initiation and time-dependent use (Table 5).

Discussion

The present study is the first to emulate a hypothetical randomized trial of PPI use and incident dementia, suggesting that PPI initiation increases the risk of dementia. Even after the long lag-window application for controlling reverse causality[8,9], the increased risk of dementia by PPI initiation and its long-term use was observed. An analysis of time-dependent PPI intake adjusted for time-varying confounding and censoring further supported an increased risk of dementia.

We also found a positive association between PPI initiation and dementia risk in the extreme restriction analysis limited to persons with on-label indications for PPI prescription to make treatment groups more comparable concerning potential confounding[35,36]. In this analysis, there was overlap in pretreatment demographic and clinical characteristics of PPI initiators and non-initiators (Supplemental Table S5), and thereby our finding is strengthened. Besides, our finding is consist with the result of a recent study that compared dementia risk by PPI intake versus no-intake in patients with upper gastrointestinal disease (HR: 1.89, 95%CI: 1.38-2.58, P <.001)[6].

We further performed an analysis for comparing the dementia risk in PPI and H2RA initiators. Although no difference in the risk of dementia between PPI initiators and H2RA initiators was observed, our finding was consistent with studies that reported no difference in the dementia risk between PPI users and H2RA users: (1) Park et al (2019) (incidence rate ratio: 1.01, 95% CI: 0.96-1.06)[38], (2) Wu et al (2020): (HR: 0.82, 0.58-1.17)[4]. There are few studies on the risk of

dementia by H2RA use versus non-use. Nevertheless, several studies reported an increased risk of dementia by H2RA use versus non-use: (1) Hwang et al (2018) (HR: 1.3, 1.13-1.51)[39], (2) Lin et al (2021) (HR: 1.36, 1.10-1.68)[6], (3) Chen et al (2021) (HR: 1.84, 1.49-2.20)[2], and (4) Boustani et al (2007) (odds ratio: 2.42, 1.17-5.04)[40]. Thus, it is questionable whether H2RA is a valid active comparator since its positive safety profile is not established [41,42].

A previous meta-analysis by Zhang et al.[11] suggested that PPI use elevates the risk of dementia (HR: 1.29; 95% CI: 1.12–1.49). A strength of this analysis is that no cross-sectional studies were included. Therefore, the bias by reverse causation or long latent period of dementia could be minimized compared to other systematic reviews that included cross-sectional studies in their meta-analyses[10,12,43].

While Khan et al.[10] performed a meta-analysis including five further studies compared to the meta-analysis by Zhang et al., all the additionally included studies found no association between PPI use and dementia risk. However, they included relatively older study populations (mean or median age over 80 years). In these older study participants, a lack of association between PPI use and dementia might have resulted from competing risk by death, i.e., they were at greater risk of dying earlier than being diagnosed with dementia[8]. Likewise, although the latest review by Wang et al.[12] contained the largest number of study participants, cross-sectional studies were included in the quantitative synthesis. This meta-analysis did not provide subgroup analysis stratified by study quality or study design.

The effect of a frequently prescribed medication is often of interest in health care studies. However, estimating a medication's effect can be challenging because it requires enrollment of participants without prevalent disease and long-term follow-up[19,20]. To the best of our knowledge, only one RCT was performed regarding dementia risk by PPI use, and it reported no association between pantoprazole use and dementia risk[44]. However, the main objective for pantoprazole randomization was to determine whether pantoprazole use reduces the risk of gastrointestinal tract complications in participants receiving antithrombotic therapy. Dementia was one among several secondary outcomes that were additionally observed. Furthermore, this trial had only a median of 3-years follow-up time with a very small number of reported dementia cases (n=101, 0.6%), and the assured washout period was 30 days. To overcome the challenges in conducting RCTs, we took advantage of the rich data from a large insurer, mitigating several limitations of previous observational studies on this topic[19].

The association between PPI initiation and its time-dependent use and dementia risk was also seen in our subtype analysis. In our data, unspecified dementia was most frequently observed,

followed by VaD and AD, while it has been reported that AD is the most common type of dementia, consisting of about 60% of dementia cases[45]. Although 6% of individuals diagnosed with dementia had ICD-10 codes of both AD and VaD in our dataset, mixed dementia is not considered in the ICD-10 coding system. Therefore, we repeated the same analysis applying the different subtype classifications, including mixed dementia (Supplemental Figure S3-S4), and no notable change in the result was observed (Supplemental Table S7). In the ICD-11, the latest version of the ICD to be adopted from 2022, the code 6D80.2 is available with a description "Alzheimer disease dementia, mixed type, with cerebrovascular disease"[46]. This new code would be beneficial for better classification of subtypes in future studies using claims data, given dementia is often associated with several mixed pathologies[45].

Dementia includes a set of diseases with common clinical symptoms, and several plausible pathophysiological mechanisms of brain deterioration that PPIs may be involved, such as increased amyloid-β plaques, increased tau protein formation, and vitamin B12 deficiency[47]. Furthermore, a recent study showed how PPIs could inhibit the activity of the core-cholinergic enzyme, with potencies that lie far below their in vivo plasma and cerebrospinal fluid concentration in humans even at low dosages[13]. This finding is significant because degeneration of the cholinergic neuronal network is a paramount feature of neurodegenerative diseases that commonly lead to the manifestation of cognitive impairment[48]. Our finding, together with this discovered mechanism, warrants further pathophysiological studies on PPIs in relation to the incidence of dementia.

Despite the use of rigorous statistical approaches to mitigate bias in the design of nonrandomized studies, there could be residual confounding. Limited information on lifestyle factors such as obesity and alcohol abuse was available solely as relevant ICD-10 codes. We did not have socioeconomic status or data on genetic risk such as education level or family history of dementia.

In our additional analysis to examine bias by unmeasured confounding, we obtained an E-Value of 2.45, which indicates that an unmeasured confounder associated with both PPI initiation and incidence of dementia would have to have an effect as large as 2.45 beyond the measured confounders, to explain away the estimate. For instance, although an association of saturated fat intake with risk of AD (RR: 1.87, 95% CI: 1.09-3.20) has been reported, we could not take this confounder into account due to a lack of dietary information in our data[49]. Occupational factors such as shift work were not assessed either, while previous studies have shown shift work could increase the risks of dementia (HR range: 1.12-2.43)[50]. Although each unmeasured dementia risk

factor is not presumed to have an RR larger than the calculated E-Value, the observed effect estimate could be smaller if the analysis is additionally adjusted for lifestyle-relevant factors.

Regarding the exposure measurement, PPI use was assessed using prescriptions dispensed by community pharmacies. Information on in-hospital use and use as OTC drug were not available in the data source. Thus, some PPI users might have been included in the non-initiator group. While exposure to PPIs might be underestimated due to OTC use, PPIs might also be overestimated when prescribed “on-demand”. Moreover, we had no information on patient compliance. Overall, the combined influence of sources of exposure measurement error is expected to be independent of the outcome of interest and therefore attenuated towards the null. Classifying different subtypes of dementia in our dataset was also difficult as many individuals were diagnosed with multiple types of dementia. This study did not evaluate the effects of individual PPI agents because of the complexity of dispensing episodes, e.g., switching between different PPI agents, prescriptions of different agents at the same time, or within very short intervals in one patient.

Conclusion

The present study showed a positive association between PPI use and dementia risk in the general population. Our study contributes to achieving a consensus on estimating the effect of PPI use on dementia risk by mitigating typical biases occurring in observational studies. However, due to the complexities of dementia subtype classification, studies taking clear criteria into account for diagnosis are needed to determine the causation between PPI use and dementia subtypes.

Author contributions

NA: study design, statistical analysis, interpretation of data, writing and revising the manuscript; MN: statistical analysis, acquisition and interpretation of data and critical review of manuscript, AG: acquisition and interpretation of data and critical review of manuscript; FG: acquisition and interpretation of data and critical review of manuscript; RG: interpretation of data and critical review of manuscript; MT: interpretation of data and critical review of manuscript; UA: interpretation of data and critical review of manuscript; JL: interpretation of data and critical review of manuscript; CM: interpretation of data and critical review of manuscript; IR: interpretation of data and critical review of manuscript; SB: study design, acquisition and interpretation of data, critical review of manuscript and revising the manuscript.

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Conflict of interests

The authors declare no competing interests.

Data availability statement

The data that support the findings of this study are available from AOK Bayern by contractual agreement.

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Figure 1. Cumulative hazard curve adjusted for baseline covariates

Table 1. Study design of the emulated trial using claims data

	A hypothetical clinical controlled trial	Emulated trial using claims data
Eligibility criteria	- Adult individuals (≥40 years at baseline) - The duration of the enrollment period is determined based on the required sample size and recruitment period. - No prescription of PPI in the previous 365 days - No prior history of dementia	Same, except that only participants with at least one year of continuously insured records before and after study entry are eligible.
Treatment strategies	Two treatment strategies are considered: (1) Receive continuous PPI treatment of 56 DDDs or more at baseline and remain on PPI during the follow-up (2) No initiation of PPI use during the follow-up.	Same, except that an individual in initiator group is allowed to stop taking PPI depending on medical condition.
Randomized assignment	Individuals will be randomly assigned to either strategy at baseline without blinding.	Individuals are assumed to be randomly assigned at baseline within levels of age, sex, German nationality, hospitalizations in the year preceding cohort entry, history of obesity, diabetes, hypertension, heart disease, peripheral vascular disease, coagulopathy, chronic pulmonary disease, cancer, depression, abuse of substances or phychosis, diseases may causing dementia, cerebrovascular disease, inflammation, infection or injury of the nervous system, use of medication (antidiabetics, antihypertensives, statins, clopidogrel, anticholinergics, anti-inflammatory drugs, corticosteroids, antidepressants and psycholeptics).

Start/end of follow-up	Follow-up starts at treatment assignment and ends at first occurrence of an outcome, death, loss to follow-up or administrative end of the study, whichever comes first.	Same
Outcome	Diagnosis of dementia.	Same (two records in consecutive quarters needed)
Analysis plan	Intention-to-treat analysis	Intention-to-treat analysis with adjustment for baseline covariates

Table 2. Comparison of baseline confounders for initiators of PPIs and non-initiators before/after weighting

	Unweighted population			**Weighted population**		
	PPI Initiators 674,544	**Non-initiators** 2,023,632	**SD**	**PPI Initiators** 674,544	**Non-initiators** 2,022,950	**SD**
Age (years)	62.8 (13.2)	56.9 (12.4)	0.463	58.4 (12.9)	58.3 (12.9)	<0.001
Women (n, %)	370,897 (55.0)	951,709 (47.0)	0.160	330,591 (49.0)	991,675 (49.0)	<0.001
German nationality (n, %)	577,458 (85.6)	1,525,175 (75.4)	0.261	525,651 (77.9)	1,576,366 (77.9)	<0.001
Hospitalizations in the year preceding cohort entry	53,202 (7.9)	11,968 (0.6)	0.368	16,381 (2.4)	48,515 (2.4)	0.002
Obesity	107,752 (16.0)	94,233 (4.7)	0.379	50,651 (7.5)	151,728 (7.5)	<0.001
Diabetes	153,848 (22.8)	136,341 (6.7)	0.465	72,842 (10.8)	218,465 (10.8)	<0.001
Hypertension	356,005 (52.8)	336,079 (16.6)	0.821	173,652 (25.7)	520,346 (25.7)	<0.001
Heart disease	152,897 (22.7)	107,072 (5.3)	0.518	65,355 (9.7)	195,601 (9.7)	0.001
Peripheral vascular disease	74,725 (11.1)	48,837 (2.4)	0.351	31,138 (4.6)	93,036 (4.6)	0.001
Coagulopathy	17,765 (2.6)	9,801 (0.5)	0.174	6,899 (1.0)	20,570 (1.0)	0.001
Chronic pulmonary disease	135,390 (20.1)	106,621 (5.3)	0.456	60,914 (9.0)	182,277 (9.0)	0.001
Cancer	65,582 (9.7)	42,338 (2.1)	0.328	27,151 (4.0)	81,323 (4.0)	<0.001

Depression	152,131 (22.6)	115,990 (5.7)	0.497	67,334 (10.0)	201,667 (10.0)	<0.001
Abuse of substances or psychosis	16,000 (2.4)	16,251 (0.8)	0.126	8,069 (1.2)	24,229 (1.2)	<0.001
Diseases may cause dementia	92,855 (13.8)	88,348 (4.4)	0.332	45,602 (6.8)	136,645 (6.8)	<0.001
Cerebrovascular disease	75,552 (11.2)	47,363 (2.3)	0.358	30,968 (4.6)	92,482 (4.6)	0.001
Inflammation, infection or injury in nervous system	18,310 (2.7)	13,813 (0.7)	0.158	8,097 (1.2)	24,328 (1.2)	<0.001
Antihypertensive drugs	375,188 (55.6)	340,175 (16.8)	0.883	179,549 (26.6)	537,916 (26.6)	0.001
Anti-inflammatory drugs	334,716 (49.6)	200,353 (9.9)	0.965	134,087 (19.9)	401,659 (19.9)	0.001
Statins	137,488 (20.4)	101,273 (5.0)	0.475	59,915 (8.9)	179,495 (8.9)	<0.001
Antidiabetic drugs	92,826 (13.8)	82,959 (4.1)	0.344	44,106 (6.5)	132,280 (6.5)	<0.001
Antidepressants	68,568 (10.2)	45,502 (2.2)	0.333	28,642 (4.2)	85,637 (4.2)	0.001
Psycholeptics	62,812 (9.3)	38,919 (1.9)	0.325	25,530 (3.8)	76,389 (3.8)	<0.001
Corticosteroids	57,267 (8.5)	21,817 (1.1)	0.353	19,800 (2.9)	58,938 (2.9)	0.001
Anticholinergics	44,144 (6.5)	30,722 (1.5)	0.258	18,768 (2.8)	56,151 (2.8)	<0.001
Clopidogrel	21,259 (3.2)	6,220 (0.3)	0.219	6,867 (1.0)	20,246 (1.0)	0.002

PPI, proton pump inhibitor; SD, standardized difference

Data are mean (standard deviation) or n (percentages)

Table 3. Effect of PPI initiation on overall dementia risk

	Number of events in PPI initiators	Number of events in non-initiators	HR (95% CI)	*P*
No lag window	39,776	31,042	1.71 (1.67-1.75)	<2e-16
1-year lag window applied	29,746	26,830	1.54 (1.51-1.58)	<2e-16
3-year lag window applied	15,840	17,173	1.45 (1.41-1.50)	<2e-16
5-year lag window applied	6,651	8,581	1.38 (1.32-1.44)	<2e-16

CI, confidence interval; HR, hazard ratio; PPI, proton pump inhibitor; *P, P*-value.

Hazard ratios (HRs) were adjusted for age, sex, German nationality, hospitalizations in the year preceding cohort entry, history of obesity, diabetes, hypertension, heart disease, peripheral vascular disease, coagulopathy, chronic pulmonary disease, cancer, depression, abuse of substances or psychosis, diseases may cause dementia, cerebrovascular disease, inflammation, infection or

injury of the nervous system, use of antidiabetics, antihypertensives, statins, clopidogrel, anticholinergics, anti-inflammatory drugs, corticosteroids, antidepressants and psycholeptics.

Table 4. Additional analyses for comparison with the effect of PPI initiation on dementia risk using different analysis approaches

	Number of events In PPI initiators	Number of events in non-initiators	HR (95% CI)	*P*
PPI time-varying use vs. non-use†	29,746	26,830	1.56 (1.50-1.63)	2e-16
PPI initiation vs. non-initiation (restricted) ‡	6,996	1,179	1.32 (1.23-1.42)	4.54e-14

CI, confidence interval; HR, hazard ratio; PPI, proton pump inhibitor; *P, P*-value.

Hazard ratios(HRs) were adjusted for age, sex, German nationality, hospitalizations in the year preceding cohort entry, history of obesity, diabetes, hypertension, heart disease, peripheral vascular disease, coagulopathy, chronic pulmonary disease, cancer, depression, abuse of substances, diseases may cause dementia, cerebrovascular disease, inflammation, infection or injury of the nervous system, use of antidiabetics, antihypertensives, statins, clopidogrel, anticholinergics, anti-inflammatory drugs, corticosteroids, antidepressants and psycholeptics.

† Using weighted pooled logistic regression with adjustment for all covariates listed above and follow-up time (180 day-interval) and its square term. A 1-year lag window between exposure and outcome was applied.

‡ PPI initiation effect on dementia risk (within the individuals who had any PPI indication at the baseline. PPI indications included gastroesophageal reflux disease (GERD), *Helicobacter Pylori*-infection, peptic ulcer, esophagitis, Zollinger Ellison-syndrome, and heartburn). A 1-year lag window between exposure and outcome was applied.

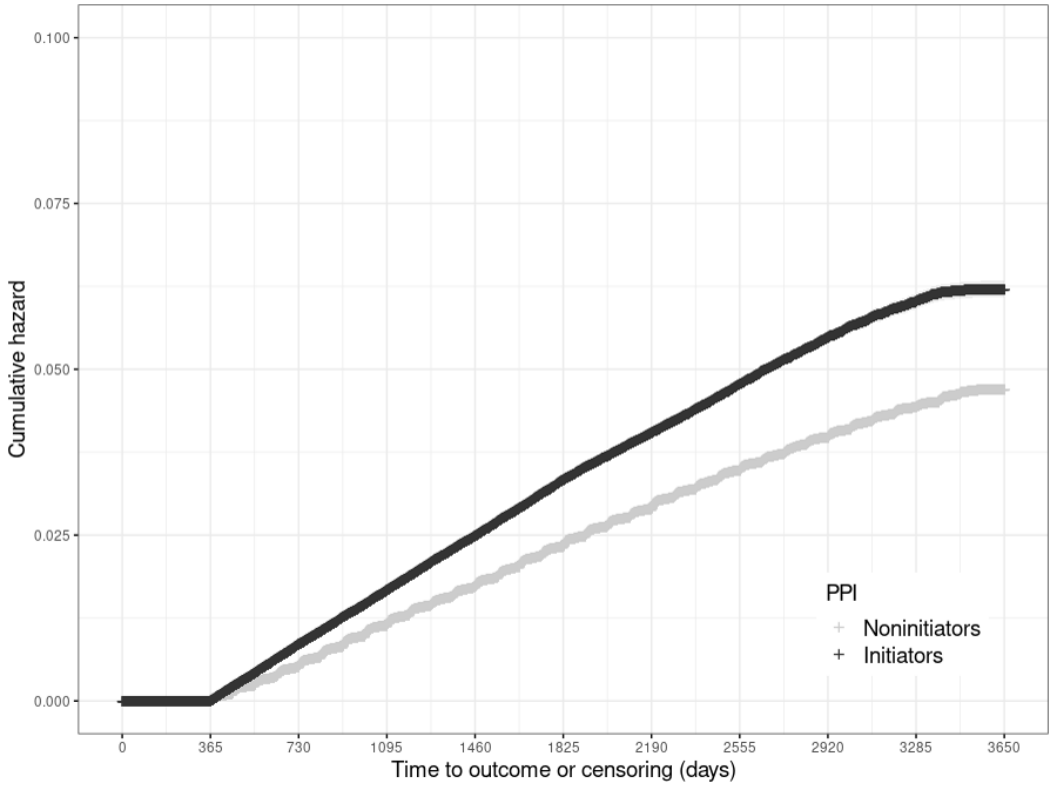
Table 5. Effect of PPI initiation and time-updated use of PPI on the risk of dementia subtypes

	Number of events in PPI initiators	Number of events in non-initiators	Initiation effect†		Time-varying use effect‡	
			HR (95% CI)	*P*	HR (95% CI)	*P*
Unspecified dementia	18,371	16,519	1.55 (1.51-1.59)	<2e-16	1.52 (1.45-1.60)	<2e-16
AD	4,608	4,424	1.52 (1.44-1.61)	<2e-16	1.47 (1.34-1.62)	<2e-16
VaD	6,166	5,223	1.53 (1.45-1.61)	<2e-16	1.70 (1.56-1.85)	<2e-16

AD, alzheimer's disease; CI , confidence interval; HR, hazard ratio; PPI, proton pump inhibitor; *P, P*-value; VaD, vascular dementia hazard ratios(HRs) were adjusted for age, sex, German nationality, hospitalizations in the year preceding cohort entry, history of obesity, diabetes, hypertension, heart disease, peripheral vascular disease, coagulopathy, chronic pulmonary disease, cancer, depression, abuse of substances or psychosis, diseases may cause dementia, cerebrovascular disease, inflammation, infection or injury in nervous system, use of antidiabetics, antihypertensives, statins, clopidogrel, anticholinergics, anti-inflammatory drugs, corticosteroids, antidepressants and psycholeptics.

†A 1-year lag window between exposure and outcome was applied.

‡Using weighted pooled logistic regression with adjustment for all covariates listed above and follow-up time (180 day-interval) and its square term. A 1-year lag window between exposure and outcome was applied.



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