Original Investigation

Association of Proton Pump Inhibitors With Risk of Dementia
A Pharmacoepidemiological Claims Data Analysis

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IMPORTANCE Medications that influence the risk of dementia in the elderly can be relevant for dementia prevention. Proton pump inhibitors (PPIs) are widely used for the treatment of gastrointestinal diseases but have also been shown to be potentially involved in cognitive decline.

OBJECTIVE To examine the association between the use of PPIs and the risk of incident dementia in the elderly.

DESIGN, SETTING, AND PARTICIPANTS We conducted a prospective cohort study using observational data from 2004 to 2011, derived from the largest German statutory health insurer, Allgemeine Ortskrankenkassen (AOK). Data on inpatient and outpatient diagnoses (coded by the German modification of the *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision*) and drug prescriptions (categorized according to the Anatomical Therapeutic Chemical Classification System) were available on a quarterly basis. Data analysis was performed from August to November 2015.

EXPOSURES Prescription of omeprazole, pantoprazole, lansoprazole, esomeprazole, or rabeprazole.

MAIN OUTCOMES AND MEASURES The main outcome was a diagnosis of incident dementia coded by the German modification of the *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision*. The association between PPI use and dementia was analyzed using time-dependent Cox regression. The model was adjusted for potential confounding factors, including age, sex, comorbidities, and polypharmacy.

RESULTS A total of 73 679 participants 75 years of age or older and free of dementia at baseline were analyzed. The patients receiving regular PPI medication (n = 2950; mean [SD] age, 83.8 [5.4] years; 77.9% female) had a significantly increased risk of incident dementia compared with the patients not receiving PPI medication (n = 70 729; mean [SD] age, 83.0 [5.6] years; 73.6% female) (hazard ratio, 1.44 [95% CI, 1.36-1.52]; $P < .001$).

CONCLUSIONS AND RELEVANCE The avoidance of PPI medication may prevent the development of dementia. This finding is supported by recent pharmacoepidemiological analyses on primary data and is in line with mouse models in which the use of PPIs increased the levels of β-amyloid in the brains of mice. Randomized, prospective clinical trials are needed to examine this connection in more detail.

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Proton pump inhibitors (PPIs) are indicated for the treatment of gastroesophageal reflux disease and peptic ulcers.[1,2] The use of PPIs has increased tremendously, especially among the elderly.[3,4] Proton pump inhibitors are among the most frequently used classes of drugs.[5,6] Within the last 10 years, the prescription rate of PPIs increased 4-fold in Germany[7]; in 2013, 3.178 billion defined daily doses were prescribed.[7] Observational studies[8,9] have shown that about 40% to 60% of all PPI prescriptions were considered to be detected as inappropriate, without adequate documentation for a gastrointestinal diagnosis. There is evidence that PPI use might affect cognition. Lam et al[10] report a significant association of previous and current PPI use with vitamin B_{12} deficiency in a population-based sample. Vitamin B_{12} deficiency has been shown to be associated with cognitive decline.[11] In another study,[12] PPIs were observed to enhance β-amyloid (Aβ) levels in the brains of mice by affecting the enzymes β- and γ-secretase. Modulation of the degradation of Aβ by lysosomes in microglia could be another functional aspect of the enrichment of Aβ levels by PPIs.[13-16]

We analyzed detailed data from a prospective, longitudinal, multicenter cohort study of elderly primary care patients, the German Study on Aging, Cognition and Dementia in Primary Care Patients (AgeCoDe),[17] including 3327 community-dwelling persons 75 years of age or older. Follow-up assessments in the AgeCoDe study[17] were conducted every 18 months. The interviews included detailed neuropsychological testing and a detailed recording of medical history and medication. Taking into account a large number of potential confounding factors such as age, sex, educational level, apolipoprotein E4 (ApoE4) allele status, depression, diabetes, stroke, ischemic heart disease, and polypharmacy, we detected a significant association between PPI use and incident dementia in the AgeCoDe study[17] (hazard ratio [HR], 1.38 [95% CI, 1.04-1.83]). In the present study, we used a large longitudinal data set from routine claims data to investigate the influence of PPI use on the risk of incident dementia and, thus, confirm our previous findings.

Key Points

Question: Is there an association between the use of proton pump inhibitors (PPIs) and the occurrence of dementia in the elderly?

Findings: In this cohort study including more than 70 000 participants and using longitudinal observational data derived from the German statutory health insurer Allgemeine Ortskrankenkassen (AOK), elderly patients 75 years of age or older receiving PPI medication had a significantly increased risk of incident dementia compared with patients 75 years of age or older not receiving PPI medication.

Meaning: The restricted use of PPIs may help prevent the development of dementia.

Methods

Sample and Study Design

Analyses were conducted on a longitudinal sample of elderly patients from the largest German statutory health insurer, Allgemeine Ortskrankenkassen (AOK). The data include information on age, sex, inpatient and outpatient diagnoses (categorized according to the German modification of the *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* [*ICD-10*] codes), and drug prescriptions (categorized according to the Anatomical-Therapeutic Chemical [ATC] Classification System codes) on a quarterly basis for the years 2004-2011. To compare the results of the present analysis with previous results from the AgeCoDe study,[17] for which follow-up assessments took place every 18 months, we aggregated the data into intervals starting with a 1-year baseline in 2004, followed up by 18-month intervals. Owing to the data structure, the last interval (2011) comprises only 12 months. Data access was legally approved by the Wissenschaftliches Institut der Ortskrankenkassen. The study is based on anonymized administrative claims data that never involved patients directly. Individual patients cannot be identified, and the analyses presented do not affect patients whose anonymized records were used.

Selection Criteria

Inclusion criteria consisted of age at the beginning of the study of 75 years or older, no data inconsistencies, and no dementia or death in the baseline interval. A diagnosis of dementia is defined as documented with one of the following *ICD-10* codes: G30, F00, F01, F03, F05.1, G31.1, G31.82, and G31.9. We considered the dementia diagnosis to be valid (incident dementia) if it was reported in at least 2 of the 6 quarters of an 18-month interval. We did not differentiate between dementia subtypes.

Exposure Assessment

Use of a PPI was defined as at least 1 prescription per quarter of omeprazole, pantoprazole, lansoprazole, esomeprazole, or rabeprazole (ATC codes A02BC01-05). We defined regular PPI use as a PPI prescription in each quarter of an interval, and we defined no use as no prescription in an interval at all. Patients with occasional PPI use (defined as a PPI prescription in 1-5 quarters of an interval) were excluded. We selected patients with either no use or regular use in all intervals for the analysis. Use of a PPI was included in the analysis as a time-dependent variable. The end of an observation was defined as the first occurrence of dementia, death, or the end of the study (year 2011). For the evaluation of the use of a single PPI, we defined the regular use of a single PPI in each quarter of an interval.

Potential Confounding Factors

To address potential bias, we selected a priori a number of potential confounding factors that were plausible factors to modify the risk for incident dementia and that have also been used in the previous analysis of the AgeCoDe study[17] for which information was available. We introduced the following confounding factors into the analysis as covariates: age, sex, polypharmacy (defined as ≥5 drug prescriptions besides the PPI), and the comorbidities of stroke (*ICD-10* codes I63 and I64), depression (*ICD-10* codes F32 and F33), ischemic heart dis-

ease (*ICD-10* codes I20-22, I24, and I25), and diabetes (*ICD-10* codes E10-E14).

Diagnoses were considered present if reported in at least 2 quarters of a 12- or 18-month interval. We selected only patients with valid information on the absence or presence of all comorbidities in all intervals before the censoring.

Statistical Analyses

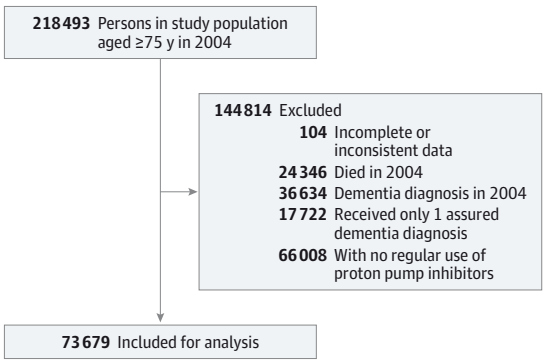
We examined the effect of PPI use vs no use on incident dementia. We applied time-dependent Cox regression models to evaluate the association between PPI use and the risk of incident dementia in the following interval. The dependent variable was the occurrence of incident dementia. The Cox regression model was adjusted for potential confounding factors already mentioned, of which the following were incorporated as time-dependent covariates: polypharmacy and the comorbidities of depression, diabetes, ischemic heart disease, and stroke. In addition, we calculated the hazard ratio (HR) without covariates.

All calculations were performed using SAS for Windows 9.3 (SAS Institute Inc). We considered $P < .05$ (2-tailed) to be statistically significant.

Results

The study population consisted of 218 493 persons 75 years of age or older at the beginning of the study period in 2004 (**Figure 1**). Of those 218 493 persons, 144 814 were excluded after quality-control filtering (104 because of incomplete or inconsistent data, 24 346 because they died in 2004, 36 634 because they received a diagnosis of dementia in 2004, 17 722 because they received only 1 assured dementia diagnosis, and 66 008 because they did not regularly use PPIs). We detected 29 510 patients who developed dementia during the study period. Of those 29 510 patients, 9056 (30.7%) received a diagnosis of unspecified dementia only (*ICD-10* code F03), 805 (2.7%) received a diagnosis of Alzheimer disease only (*ICD-10* codes F00 and G30), 1834 (6.2%) received a diagnosis of vascular dementia only (*ICD-10* code F01), 24 (0.1%) received a diagnosis of delirium with dementia only (*ICD-10* code F05.1), 387 (1.3%) received a diagnosis of senile degeneration only (*ICD-10* codes G31.1 and G31.9), and 17 404 (59.0%) received a diagnosis of at least 2 different types of dementia. Because of the large amount of diagnoses of unspecified and mixed dementias, we did not differentiate between the dementia subtypes in the following analyses.

Figure 1. Flowchart of Patients Included for Analysis



Regular PPI use (ie, at least 1 PPI prescription in each quarter of an 18-months interval) was observed for 2950 persons (**Table 1**). Omeprazole, pantoprazole, and esomeprazole were the most prescribed PPIs with regular use among 1340, 659, and 308 patients, respectively (eTable 1 in the Supplement). The data on regular PPI users indicate that there are relatively low numbers of regular users who use additional PPIs (with an average number of quarters per person of 1.0-2.0; eTable 1 in the Supplement). The characteristics of PPI users and nonusers are given in Table 1 for Cox regression with time-dependent covariates. The use of PPIs was associated with a significant increased risk of incident dementia (HR, 1.44 [95% CI, 1.36-1.52]; $P < .001$) (**Table 2**). The occurrence of incident dementia with the use of PPIs was slightly more pronounced in male (HR, 1.52 [95% CI, 1.33-1.74]) rather than female patients (HR, 1.42 [95% CI, 1.33-1.51]). Of the potential confounding factors that were included in the analysis, depression (HR, 1.28 [95% CI, 1.24-1.32]) and stroke (HR, 1.37 [95% CI, 1.29-1.46) showed the highest risk increase for incident dementia. Also, age per year had a considerable effect on risk of dementia (HR, 1.083 [95% CI, 1.081-1.085]). The other factors that were included elevated the risk of dementia only slightly but significantly (HR, 1.15 [95% CI, 1.11-1.18] for female sex; HR, 1.05 [95% CI, 1.02-1.08] for diabetes; and HR, 1.16 [95% CI, 1.13-1.19] for polypharmacy). Data on patients with ischemic heart

Table 1. Characteristics of Proton Pump Inhibitor (PPI) Users and Nonusers for Cox Regression With Time-Dependent Covariates

Characteristic	Incident Dementia,[a] No. (%)		*P* Value[b]
	No PPI Use	PPI Use	
PPI use[c]	70 729 (96.0)	2950 (4.0)	
Age,[d] mean (SD), y	83.0 (5.6)	83.8 (5.4)	<.001
Female sex	52 042 (73.6)	2298 (77.9)	<.001
Depression	9849 (13.9)	592 (20.1)	<.001
Diabetes	23 063 (32.6)	979 (33.2)	.51
Stroke	2661 (3.8)	151 (5.1)	<.001
Ischemic heart disease	26 739 (37.8)	1286 (43.6)	<.001
Polypharmacy[e]	37 565 (53.1)	2316 (78.5)	<.001

[a] Including demented and nondemented patients for a total of 73 679 patients.

[b] Determined by use of the *t* test or the χ^2 test for group comparison.

[c] In at least 1 interval.

[d] At the beginning of the study in 2004.

[e] Defined as the administration of 5 or more drugs.

Table 2. Data on Risk of Incident Dementia by PPI Use

	Risk of Incident Dementia					
	Both Sexes		Male Sex		Female Sex	
Risk Factor	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
PPI use calculated[a]						
With potential confounding factors	1.44 (1.36-1.52)	<.001	1.52 (1.33-1.74)	<.001	1.42 (1.33-1.51)	<.001
Without potential confounding factors	1.66 (1.57-1.76)	<.001	1.78 (1.56-2.03)	<.001	1.61 (1.52-1.71)	<.001
Age[b]	1.083 (1.081-1.085)	<.001	1.089 (1.084-1.093)	<.001	1.081 (1.079-1.084)	<.001
Sex[c]	1.15 (1.11-1.18)	<.001				
Depression	1.28 (1.24-1.32)	<.001	1.54 (1.41-1.68)	<.001	1.24 (1.20-1.29)	<.001
Diabetes	1.05 (1.02-1.08)	<.001	1.08 (1.02-1.14)	.01	1.04 (1.01-1.07)	.01
Stroke	1.37 (1.29-1.46)	<.001	1.63 (1.45-1.82)	<.001	1.29 (1.19-1.39)	<.001
Ischemic heart disease	0.93 (0.91-0.95)	<.001	0.91 (0.86-0.96)	<.001	0.94 (0.91-0.96)	<.001
Polypharmacy[d]	1.16 (1.13-1.19)	<.001	1.16 (1.10-1.22)	<.001	1.16 (1.13-1.19)	<.001

Abbreviations: HR, hazard ratio; PPI, proton pump inhibitor.

[a] Use of PPI before the diagnosis of dementia.

[b] At the beginning of the study in 2004.

[c] Male sex as reference.

[d] Defined as the administration of 5 or more drugs.

disease showed a minor reduction in the risk of dementia (HR, 0.93 [95% CI, 0.91-0.95]). Visualization of the association of PPI use and incident dementia as survival function is given in **Figure 2**. Exclusion of all potential confounding factors resulted in a slightly higher HR for the association between PPI use and incident dementia (HR, 1.66 [95% CI, 1.57-1.76]) (Table 2).

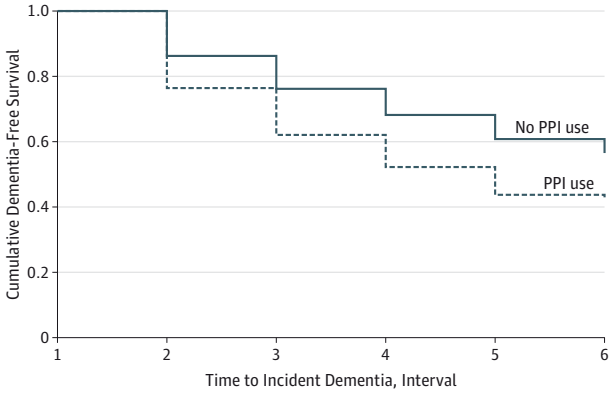
The inclusion in the model of a specific drug class (namely, anticholinergic drugs) that was shown to affect cognitive performance[18] resulted in nearly the same outcomes for PPI use (HR, 1.44 [95% CI, 1.36-1.53]; $P < .001$) and for the other covariates (data not shown). We included anticholinergic drugs with a high anticholinergic activity (levels 3 and 4 according to Chew et al[19]). As expected, anticholinergic drug use itself was a risk factor for incident dementia (HR, 1.80 [95% CI, 1.65-1.96]; $P < .001$).

To examine the effect of the duration of PPI exposure, we analyzed occasional PPI use (defined as a PPI prescription in <6 quarters within an interval). We observed a lower HR for occasional PPI use (HR 1.16, 95% CI 1.13-1.19) (eTable 2 in the Supplement).

For the 3 most prescribed PPIs (omeprazole, pantoprazole, and esomeprazole), we performed subgroup analyses. Including all previous covariates, we detected a similar elevated risk of dementia for omeprazole (HR, 1.51 [95% CI, 1.40-1.64]) and pantoprazole (HR, 1.58 [95% CI, 1.40-1.79]) and a slightly more pronounced risk increase for esomeprazole (HR, 2.12 [95% CI, 1.82-2.47]) (eTable 3 in the Supplement; for sample characteristics of the subgroup analyses, see eTables 4-6 in the Supplement).

For an age-group analysis, we divided the sample into 3 groups (75-79, 80-84, and ≥85 years). The risk of incident dementia with the use of PPIs gradually decreased with age (HR, 1.69 [95% CI, 1.49-1.92] for 75-79 years; HR, 1.49 [95% CI, 1.35-1.66] for 80-84 years; and HR, 1.32 [95% CI, 1.22-1.43] for ≥85 years) (**Table 3**). Also, the effect of the potential confounding factors such as depression, diabetes, stroke, and polypharmacy decreased with age (Table 3).

Figure 2. Dementia-Free Survival by Use of Proton Pump Inhibitors (PPIs)



Discussion

Dementia is characterized by cumulative cognitive decline and a progressive inability to live independently. Analyses of data from the German statutory health insurance system showed that the prevalence of dementia increases with age.[20] About one-third of Germans who are 90 years of age will have dementia.[20] The global prevalence of dementia will increase from about 35 million people today to more than 80 million people in 2040.[21,22] Besides the substantial burden on patients and their families, dementia also affects health care systems worldwide. Dementia therapies and care have a notable socioeconomic impact. In the year 2010, the estimated worldwide cost of dementia was $604 billion.[23] The largest effect on the reduction of the occurrence of dementia has been reported to be primary prevention (namely, reducing the risk of dementia).[24] Therefore, an effective step for dementia prevention is to detect risk factors for dementia in people at increased risk (ie, the elderly). Often used drugs are of special

Table 3. Data on Risk of Incident Dementia by PPI Use, Age-Group Analysis

	Risk of Incident Dementia					
	75-79 y		80-84 y		≥85 y	
Risk Factor	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
PPI use calulated[a]						
With potential confounding factors	1.69 (1.49-1.92)	<.001	1.49 (1.35-1.66)	<.001	1.32 (1.22-1.43)	<.001
Without potential confounding factors	2.01 (1.78-2.28)	<.001	1.68 (1.51-1.86)	<.001	1.35 (1.25-1.46)	<.001
Age[b]	1.128 (1.109-1.148)	<.001	1.092 (1.076-1.107)	<.001	1.045 (1.040-1.051)	<.001
Sex[c]	1.10 (1.04-1.16)	<.001	1.15 (1.09-1.21)	<.001	1.16 (1.11-1.22)	<.001
Depression	1.44 (1.34-1.54)	<.001	1.35 (1.27-1.43)	<.001	1.15 (1.09-1.21)	<.001
Diabetes	1.16 (1.10-1.22)	<.001	1.04 (0.99-1.08)	.15	0.99 (0.95-1.03)	.45
Stroke	1.78 (1.59-2.00)	<.001	1.37 (1.23-1.54)	<.001	1.15 (1.04-1.27)	.01
Ischemic heart disease	0.94 (0.89-0.99)	.02	0.96 (0.92-1.00)	.07	0.90 (0.87-0.93)	<.001
Polypharmacy[d]	1.27 (1.21-1.34)	<.001	1.21 (1.15-1.26)	<.001	1.05 (1.02-1.09)	.003

Abbreviations: HR, hazard ratio; PPI, proton pump inhibitor.

[a] Use of PPI before the diagnosis of dementia.

[b] At the beginning of the study in 2004.

[c] Male sex as reference.

[d] Defined as the administration of 5 or more drugs.

interest as risk factors for dementia in the elderly, especially data on the consequences of their long-term use.

Our analysis of the AOK data set revealed a significant increased risk of dementia (HR, 1.44 [95% CI, 1.36-1.52]) with the use of PPIs. Thus, the results confirm the findings from our previous study with the AgeCoDe data set (HR, 1.38 [95% CI, 1.04-1.83]).[17] The subgroup analyses for the 3 most often used PPIs (omeprazole, pantoprazole, and esomeprazole) showed similar effect sizes, with a slightly more pronounced risk of dementia by use of esomeprazole. The underlying mechanism by which PPIs might influence the development of dementia is yet to be determined. There is evidence that links PPI intake with cognitive decline. First of all, some PPIs (eg, lansoprazole and omeprazole) have been reported to cross the blood-brain barrier, and so they are able to directly affect the brain.[25,26] Badiola et al[12] showed that PPIs may be able to interact with brain enzymes. They observed increased Aβ levels in an amyloid cell model and in the brains of mice after PPI treatment.[12] They suggest a mechanism of inverse γ-secretase modulation in combination with an augmented β-secretase BACE1 activity that leads to an accumulation of Aβ levels.[12] Aβ peptides are a major pathological sign of dementia in the course of Alzheimer disease.[27]

Another explanation for the enrichment of Aβ by PPIs might involve a modulation of degradation of Aβ by lysosomes in microglia.[13] Fibrillar Aβ clearance by microglia is pH-dependent, and this process is induced by acidification of lysosomes. Vacuolar-type H^+-adenosine triphosphatase (V-ATPase) proton pumps mediate this acidification,[14] and PPIs have inhibitory properties at V-ATPases.[15] As a result, PPIs may contribute to the inhibition of acidification, reduced Aβ degradation, and enhanced Aβ levels.[16] A further hint of a possible involvement of PPIs in cognition is given in a study by Lam et al,[10] in which an association of previous and current PPI use with the presence of vitamin B_{12} deficiency is reported (odds ratio, 1.65 [95% CI, 1.58-1.73]). Poor vitamin B_{12} status has been described as negatively affecting cognition and promoting neurological damage, probably owing to impaired DNA synthesis, methylation, and homocysteine neurotoxicity.[28,29]

For the claims data analysis, we were able to include almost all of the potential confounding factors that have also been included in the analysis of the AgeCoDe study.[17] The 2 exceptions are the ApoE4 allele status and educational level, variables for which we lack claims data. Of the included covariates, age per year, stroke, depression, diabetes, and polypharmacy all significantly elevated the risk of dementia. This is in line with the results of the data analysis of the AgeCoDe study,[17] in which age per year, stroke, depression, and diabetes were significantly associated with risk of dementia, while polypharmacy contributed to an elevated risk of dementia that failed to be statistically significant. Female sex was slightly but significantly associated with an increased risk of dementia in the claims data analysis; in the data analysis of the AgeCoDe study,[17] there was no clear sex-specific signal for incident dementia.

The HRs in our study were very similar to those in the data analysis of the AgeCoDe study[17] for age per year (1.083 [95% CI, 1.081-1.085] vs 1.12 [95% CI, 1.10-1.15]) and polypharmacy (1.16 [95% CI, 1.13-1.19] vs 1.14 [95% CI, 0.92-1.42]). The increased risk of dementia with regard to the comorbidities of stroke and diabetes was less pronounced (by 25%-50%) in the claims data analysis. For depression, the value for the HR was 1.0 higher in the data analysis of the AgeCoDe study[17] compared with the claims data analysis. This might be explained by the comprehensive and detailed neuropsychological assessments performed for the AgeCoDe study,[17] whereas the diagnosis of depression can be overlooked during a routine general practitioner visit, a situation that is reflected in the AOK data. The covariate ischemic heart disease was not significantly associated with dementia in the data analysis of the AgeCoDe study[17] but showed a HR of 0.93 (95% CI, 0.91-0.95) in the claims data analysis. This effect might be attributed to the concomitant treatment with antihypertensive medication. Population-based studies have shown that antihypertensive drugs such as calcium channel blockers and renin-

angiotensin system blockers can be beneficial in preventing cognitive decline and dementia in the elderly.[30]

The age-group analysis revealed that the risk of incident dementia with the use of PPIs gradually decreased with age, with the highest HR in the age-group of 75 to 79 years. The same was true for potential confounding factors such as depression and stroke, which also showed lower effect sizes with increasing age. This might reflect the decreasing influence of external and internal factors on dementia progression with age, possibly owing to an already initiated disease process.

To address the possibility that regular PPI users might have a higher chance of receiving a diagnosis of dementia owing to an increased use of the health care system, we defined the percentage of quarterly data entries during the whole study period (2004-2011) as a proxy variable for use of the health care system in general. We observed an average percentage of 94% and 93% of quarterly data entries for regular PPI users and nonregular PPI users, respectively. Thus, both groups regularly use the health care system, with the differences between the groups being negligible and not likely to have caused a more likely dementia diagnosis for PPI users.

Our study has several strengths. The sample of patients is a population-based sample and covers longitudinal data from 2004 to 2011 extracted from the largest German mandatory public health insurer, the AOK. The AOK comprises one-third of the German population and as much as 50% of the elderly population.[31] This allowed us to perform the analysis in a real-life setting in an unselected patient population. Health claims data cover the total population, including people who live in institutions such as assisted living or nursing homes. In addition, selection bias or recall bias was avoided because of the use of routine database records.

On the other hand, there are also limitations that have to be taken into account when interpreting the results. Residual confounding in claims data is a concern that cannot be ruled out completely. However, we have adjusted our analysis by including several potential confounding factors, such as age, sex, comorbidities, and polypharmacy. Other risk factors for dementia (eg, ApoE4 allele carrier or lower educational level) could not be integrated into the analysis because the AOK claims data lack genetic information or detailed sociodemographic parameters. Because we analyzed claims data with a high rate of diagnoses of unspecified and mixed dementia, we were not able to differentiate between different dementia etiologies, such as dementia in the course of Alzheimer disease or vascular dementia. However, because we found in the analysis of the data from the AgeCoDe study[17] only subtle differences between the results of patients with all different types of dementia and the results of patients with dementia in the course of Alzheimer disease, and because mixed dementia forms outweigh pure dementia forms,[32,33] this fact should not be a major limitation in the present analysis.

Conclusions

We analyzed a large longitudinal German claims data set and confirmed the results of our previous analysis on a smaller primary data set that PPI use is associated with an increased risk of incident dementia. Thus, the avoidance of PPI medication may contribute to the prevention of dementia. The present study can only provide a statistical association between PPI use and risk of dementia. The possible underlying causal biological mechanism has to be explored in future studies. To evaluate and establish direct cause and effect relationships between PPI use and incident dementia in the elderly, randomized, prospective clinical trials are needed.

ARTICLE INFORMATION

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Author Contributions: Drs Gomm and Haenisch had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Drs Gomm and von Holt contributed equally to this work.
Study concept and design: Haenisch.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Gomm, von Holt, Maier, Haenisch.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Gomm, von Holt, Haenisch.
Administrative, technical, or material support: Gomm, von Holt, Thomé, Fink.
Study supervision: Broich, Maier, Doblhammer, Haenisch.

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REFERENCES

1. Katz PO, Gerson LB, Vela MF. Guidelines for the diagnosis and management of gastroesophageal reflux disease. *Am J Gastroenterol*. 2013;108(3):308-328.

2. Londong W, Barth H, Dammann HG, et al. Dose-related healing of duodenal ulcer with the proton pump inhibitor lansoprazole. *Aliment Pharmacol Ther*. 1991;5(3):245-254.

3. Hollingworth S, Duncan EL, Martin JH. Marked increase in proton pump inhibitors use in Australia. *Pharmacoepidemiol Drug Saf*. 2010;19(10):1019-1024.

4. Forgacs I, Loganayagam A. Overprescribing proton pump inhibitors. *BMJ*. 2008;336(7634):2-3.

5. Cai S, García Rodríguez LA, Massó-González EL, Hernández-Díaz S. Uncomplicated peptic ulcer in the UK: trends from 1997 to 2005. *Aliment Pharmacol Ther*. 2009;30(10):1039-1048.

6. Mazer-Amirshahi M, Mullins PM, van den Anker J, Meltzer A, Pines JM. Rising rates of proton pump inhibitor prescribing in US emergency departments. *Am J Emerg Med*. 2014;32(6):618-622.

7. Schwabe U, Paffrath D, eds. *Arzneiverordnungs-Report 2014: Aktuelle Daten, Kosten, Trends und Kommentare*. Berlin, Germany: Springer; 2014.

8. Pasina L, Nobili A, Tettamanti M, et al; REPOSI Investigators. Prevalence and appropriateness of drug prescriptions for peptic ulcer and gastro-esophageal reflux disease in a cohort of hospitalized elderly. *Eur J Intern Med*. 2011;22(2):205-210.

9. Heidelbaugh JJ, Goldberg KL, Inadomi JM. Magnitude and economic effect of overuse of antisecretory therapy in the ambulatory care setting. *Am J Manag Care*. 2010;16(9):e228-e234.

10. Lam JR, Schneider JL, Zhao W, Corley DA. Proton pump inhibitor and histamine 2 receptor antagonist use and vitamin B_{12} deficiency. *JAMA*. 2013;310(22):2435-2442.

11. Vogiatzoglou A, Smith AD, Nurk E, et al. Cognitive function in an elderly population: interaction between vitamin B12 status, depression, and apolipoprotein E ε4: the Hordaland Homocysteine Study. *Psychosom Med*. 2013;75(1):20-29.

12. Badiola N, Alcalde V, Pujol A, et al. The proton-pump inhibitor lansoprazole enhances amyloid beta production. *PLoS One*. 2013;8(3):e58837.

13. Majumdar A, Cruz D, Asamoah N, et al. Activation of microglia acidifies lysosomes and leads to degradation of Alzheimer amyloid fibrils. *Mol Biol Cell*. 2007;18(4):1490-1496.

14. Pillay CS, Elliott E, Dennison C. Endolysosomal proteolysis and its regulation. *Biochem J*. 2002;363(pt 3):417-429.

15. Mattsson JP, Väänänen K, Wallmark B, Lorentzon P. Omeprazole and bafilomycin, two proton pump inhibitors: differentiation of their effects on gastric, kidney and bone H^+-translocating ATPases. *Biochim Biophys Acta*. 1991;1065(2):261-268.

16. Fallahzadeh MK, Borhani Haghighi A, Namazi MR. Proton pump inhibitors: predisposers to Alzheimer disease? *J Clin Pharm Ther*. 2010;35(2):125-126.

17. Haenisch B, von Holt K, Wiese B, et al. Risk of dementia in elderly patients with the use of proton pump inhibitors. *Eur Arch Psychiatry Clin Neurosci*. 2015;265(5):419-428.

18. Jessen F, Kaduszkiewicz H, Daerr M, et al. Anticholinergic drug use and risk for dementia: target for dementia prevention. *Eur Arch Psychiatry Clin Neurosci*. 2010;260(suppl 2):S111-S115.

19. Chew ML, Mulsant BH, Pollock BG, et al. Anticholinergic activity of 107 medications commonly used by older adults. *J Am Geriatr Soc*. 2008;56(7):1333-1341.

20. Ziegler U, Doblhammer G. Prevalence and incidence of dementia in Germany—a study based on data from the public sick funds in 2002 [in German]. *Gesundheitswesen*. 2009;71(5):281-290.

21. Ferri CP, Prince M, Brayne C, et al; Alzheimer's Disease International. Global prevalence of dementia: a Delphi consensus study. *Lancet*. 2005;366(9503):2112-2117.

22. Reitz C, Brayne C, Mayeux R. Epidemiology of Alzheimer disease. *Nat Rev Neurol*. 2011;7(3):137-152.

23. Wimo A, Jönsson L, Bond J, Prince M, Winblad B; Alzheimer Disease International. The worldwide economic impact of dementia 2010. *Alzheimers Dement*. 2013;9(1):1-11.

24. Wu YT, Fratiglioni L, Matthews FE, et al. Dementia in western Europe: epidemiological evidence and implications for policy making. *Lancet Neurol*. 2016;15(1):116-124.

25. Cheng FC, Ho YF, Hung LC, Chen CF, Tsai TH. Determination and pharmacokinetic profile of omeprazole in rat blood, brain and bile by microdialysis and high-performance liquid chromatography. *J Chromatogr A*. 2002;949(1-2):35-42.

26. Rojo LE, Alzate-Morales J, Saavedra IN, Davies P, Maccioni RB. Selective interaction of lansoprazole and astemizole with tau polymers: potential new clinical use in diagnosis of Alzheimer's disease. *J Alzheimers Dis*. 2010;19(2):573-589.

27. Querfurth HW, LaFerla FM. Alzheimer's disease. *N Engl J Med*. 2010;362(4):329-344.

28. O'Leary F, Allman-Farinelli M, Samman S. Vitamin B_{12} status, cognitive decline and dementia: a systematic review of prospective cohort studies. *Br J Nutr*. 2012;108(11):1948-1961.

29. Reynolds E. Vitamin B12, folic acid, and the nervous system. *Lancet Neurol*. 2006;5(11):949-960.

30. Rouch L, Cestac P, Hanon O, et al. Antihypertensive drugs, prevention of cognitive decline and dementia: a systematic review of observational studies, randomized controlled trials and meta-analyses, with discussion of potential mechanisms. *CNS Drugs*. 2015;29(2):113-130.

31. Doblhammer G, Fink A, Fritze T. Short-term trends in dementia prevalence in Germany between the years 2007 and 2009. *Alzheimers Dement*. 2015;11(3):291-299.

32. Schneider JA, Arvanitakis Z, Bang W, Bennett DA. Mixed brain pathologies account for most dementia cases in community-dwelling older persons. *Neurology*. 2007;69(24):2197-2204.

33. Heneka MT, Fink A, Doblhammer G. Effect of pioglitazone medication on the incidence of dementia. *Ann Neurol*. 2015;78(2):284-294.