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REVIEW

Proton pump inhibitors use and dementia risk: a meta-analysis of cohort studies

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Abstract

Purpose The aim of this study was to explore the relationship between proton pump inhibitors use and the risk of dementia.

Methods A comprehensive literature search was conducted in English and Chinese databases from origination to December 2018. The pooled hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated with a random-effects model. Subgroup analyses and sensitivity analyses were also conducted. Cochran's Q test and the I^2 statistic were used to evaluate the heterogeneity. Publication bias was assessed by Begg's test and Egger's test.

Results Six studies were included, which contained a total of 166,146 participants. The overall result demonstrated a significant increase in dementia risk with proton pump inhibitors use (HR = 1.29, 95% CI = 1.12–1.49). In subgroup analyses, a significant association was detected between proton pump inhibitors use and the risk of dementia in Europe (HR = 1.46, 95% CI = 1.23–1.73) and among participants aged ≥ 65 years (HR = 1.39, 95% CI = 1.17–1.65). For the factor follow-up time ≥ 5 years, the pooled HR was 1.28 (95% CI = 1.12–1.46), demonstrating a 1.28-fold increase in the risk of dementia among proton pump inhibitors users. In the case of regional impact, participants from Europe showed an overall pooled HR estimate of 1.46 (95% CI = 1.23–1.73). There was no evidence of publication bias.

Conclusions The overall result of this meta-analysis supports the hypothesis that proton pump inhibitors increase the risk of dementia. Furthermore, high-quality cohort studies are needed to confirm these findings.

Keywords Proton pump inhibitors · Dementia · Meta-analysis · Risk

Introduction

Dementia is a general term for the progressive deterioration in activities, thinking, memory, and behavior of daily living and it is not a normal part of the elderly population. Nearly 50 million people have dementia, with around 10 million new patients every year, and about 60% living in low-income and middle-income countries in the world [1]. Due to the aging of the global population, the prevalence of dementia will increase to more than 80 million cases worldwide by 2040 [2, 3]. According to research by Alzheimer's Disease International (ADI), southern Asia and eastern Asia will see dementia growth rates over double in the coming 20 years, North Africa and the Middle East will see increases of 125%, and Latin America can expect a 134–146% rise [4]. It is estimated that Asia accounts for 59% of the number of cases worldwide [5]. In 2010, the costs of treating dementia worldwide is estimated at $604 billion dollars [6]. The total social cost of dementia worldwide is estimated at $818 billion, equivalent to 1.1% of the global gross domestic

Yun Zhang and Mingming Liang contributed equally to this work.

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product (GDP) in 2015 [1]. Dementia was listed as one of the main reasons for the increase in disability-adjusted life years in 2015 [7]. In addition, dementia has a huge psychological, physiological, and socio-economic impact, not only on dementia patients, but also on their families, careers, and society as a whole. Therefore, the prevention of dementia among people at increased risk (e.g., the elderly) can help to alleviate the burden of dementia cases and the medical system.

Many factors are associated with the risk of dementia. Some studies found that the use of proton pump inhibitors (PPIs) may be a risk for dementia. PPIs are mainly used to treat gastroesophageal reflux disease (GERD), peptic ulcer disease (PUD), esophagitis, and to prevent and treat nonsteroidal anti-inflammatory drug (NSAID)-related ulcers [8]. In the United States, about one in five of the elderly reported using PPIs in 2011 [9], and these drugs are frequently used over a long period of time [10]. PPIs use may reduce cognitive ability, as a result of the increase of amyloid-beta (Aβ) levels in the brain of mice by affecting the enzymes β- and γ-secretases [11] or by regulating the degradation of Aβ by lysosomes in microglia [11–15]. PPIs were also identified to induce the production of Aβ [16]. Furthermore, it has been shown to lead to vitamin B-12 deficiency, which has been shown to result in cognitive impairment, but this leads to some cognitive disorders that will disappear with adequate treatment; therefore, this hypothesis needs to be further explored [17–19].

Four meta-analyses that examined the association between PPIs use and dementia risk previously showed no statistically significant association between PPI use and the risk of dementia (relative risk [RR] = 1.17, 95% confidence interval [CI] = 0.89–1.55; RR = 1.08, 95% CI = 0.82–1.43; RR = 1.01, 95% CI = 0.78–1.32; hazard ratio [HR] = 1.04, 95% CI = 0.92–1.15), respectively [20–23]. However, in more recent years, new studies have demonstrated that the use of PPIs may be associated with increased risk of dementia. Considering the lack of consensus, the objective of this study was to perform a systematic review and meta-analysis on PPIs use and dementia risk.

Methods

Literature search

The MOOSE (Meta-analysis Of Observational Studies in Epidemiology) checklist was followed for conducting and reporting meta-analysis data [24]. Ethical approval was not necessary for this meta-analysis.

PICO question

In human subjects, does having used PPIs (compared to no use) increase the risk of dementia (P: human subjects; I (indicator): using PPIs; C: not using proton pump inhibitors; O: dementia)?

A systematic literature search was performed independently by two of the reviewers (Y.Z. and M.L.). PubMed, Web of Science, Cochrane Library, CNKI (China National Knowledge Infrastructure), CBM (China Biomedical Database), and Wanfang Data were searched from origination to December 2018. The search strategy was based on different combinations of words for each database. For the PubMed database, the following combination was used: (PPIs OR PPI OR proton pump inhibitors OR lansoprazole OR dexlansoprazole OR esomeprazole OR pantoprazole OR omeprazole OR rabeprazole) AND (dementia OR vascular dementia OR Alzheimer disease). Language limitations included the English and Chinese languages. No restriction was set for date or publication status. Furthermore, reference lists of retrieved articles were reviewed to identify other eligible studies.

Study selection

The same two authors (Y.Z. and M.L.) independently screened the titles and abstracts of the primary studies that were identified in the electronic search. The following inclusion criteria were set for this study: (1) studies on human subjects; (2) the study evaluated any exposure to PPIs and the risk of dementia; (3) clear definition of dementia and PPIs use; (4) description of how confounders were controlled in the analysis (adjustments); (5) any type of dementia was the outcome of interest; (6) studies must have reported an estimated measure of effect size (RR, HR, or odds ratio [OR]) and its associated 95% CI, or provided calculable data; (7) cohort study.

The following exclusion criteria were set: (1) included an animal experimental model; (2) studies were systematic review articles, letters, meta-analyses, comments, and case reports; (3) a duplicated study; (4) studies where it was impossible to retrieve or calculate data of interest; (5) not meeting the inclusion criteria.

Data extraction

Two reviewers (Y.Z. and M.L.) independently collected the following data (Tables 1 and 2): author names, year of publication, country of examination, sample characteristics (gender, age), intervention, number of participants, definition of PPIs use and dementia, period of follow-up, HR and its 95% CIs, and parameters for adjustment. In case of disagreement in the data extraction process, a third reviewer (C.Y.) was required to resolve the disparity.

Quality assessment

The Newcastle-Ottawa scale was used for cohort studies to assess quality by two reviewers (Y.Z. and M.M.)

Table 1 Characteristics of the studies included

Author	Year	Follow-up time (years)	Country	Age (years)	Intervention	Number of participants	Percentage of females (case/comparator)	HR (95% CI)	Definition and ascertainment of PPIs use	Definition and ascertainment of dementia
Haenisch et al. [25]	2015	6	Germany	≥ 75	O, E, L, P, R, D	3076 (713 PPI users; 2363 non-users)	68.7/64.0	1.38 (1.04–1.83)	At least one use of any PPIs during follow-up period. Information on PPIs used was obtained by interview during follow-up.	MMSE
Gray et al. [26]	2018	7.5	Northwest USA	≥ 65	O, P, E, L, R	3484 (402 PPI users; 3082 non-users)	64.7/58.7	1.13 (0.82–1.56)	Information was collected at interviews every 2 years about self-reported current medication use, including use of OTC medications.	CASI
Tai et al. [27]	2017	8.44	China	≥ 40	O, P, L	15,726 (7863 PPI users; 7863 non-users)	41.2/40.7	1.22 (1.05–1.42)	Outpatient pharmacy prescription database.	ICD-9-CM
Gomm et al. [28]	2016	8	Germany	≥ 75	O, E, L, P, R	73,679 (2950 PPI users; 70,729 non-users)	77.9/73.6	1.44 (1.36–1.52)	Pharmaceutical database of the insurer.	Dementia is defined by the presence of diagnostic codes of dementia in at least 2 of 6 quarters of an 18-month interval
Herghelegiu et al. [29]	2016	3	Romania	≥ 65	O, P, E, L	148 (74 PPI users; 74 non-users)	77.02/66.21	3.67 (2.23–19.15)	PPIs defined as more than 6 months of continuous or nearly continuous administration of any PPI per year for the previous 3 years or more.	MMSE, CDT
Hwang et al. [30]	2018	7	Korea	> 40	n.a.	70,033 (1947 PPI users; 68,086 non-users)	37.2/43.8	0.99 (0.7–1.39)	Outpatient pharmacy prescription database.	ICD-10

D:dexlansoprazole; E:esomeprazole; L: lansoprazole; O:omeprazole; P:pantoprazole; R:rabeprazole

Table 2 Meta-analysis results of the subgroup analysis

	No. of studies	Pooled effect estimate		Test of homogeneity		
		HR[a]	(95% CI[b])	Q-value (d.f.[c])	*p*-Value	I^2 (%)
All studies	6	**1.29**	**1.12–1.49**	12.89(5)	0.024	61.2
Cohort study	6	**1.29**	**1.12–1.49**	12.89(5)	0.024	61.2
Follow-up (years)						
≥ 5	5	**1.28**	**1.12–1.46**	9.77(4)	0.044	59.1
< 5	1	**3.67**	**2.23–19.15**	–	–	–
Study locations						
North America	1	1.13	0.82–1.56	–	–	–
Asia	2	1.17	0.98–1.38	1.19(1)	0.275	16.2
Europe	3	**1.46**	**1.23–1.73**	2.99(2)	0.224	33.2
Age (years)						
≥ 65	4	**1.39**	**1.17–1.65**	5.13(3)	0.162	41.5
≥ 40	6	**1.29**	**1.12–1.49**	12.89(5)	0.024	61.2
Adjusted for confounders						
Sex	5	**1.29**	**1.12–1.50**	8.95(4)	0.062	55.3
Depression	3	**1.42**	**1.31–1.53**	2.18(2)	0.336	8.2
Diabetes	5	**1.31**	**1.08–1.59**	9.46(4)	0.050	57.7
Hypertension	3	**1.29**	**1.12–1.50**	5.18(2)	0.075	61.4

[a] Hazard ratio

[b] Confidence interval

[c] Degrees of freedom

The meaning of the items in blodface was $p < 0.05$

independently [31]. A study with a score ≥ 7 is considered as a high-quality study. Disagreements were resolved through discussion. Funnel plots were constructed to assess the risk of publication bias across series for all outcome measures.

Statistical analyses

In this meta-analysis, in order to estimate the association between PPIs use and the risk of dementia, the method of inverse variance was used, combining the results using DerSimonian and Laird's random-effects model [32]. The analysis was performed using the summary measure pooled HR. For each measure, a pooled estimate of 95% CI was calculated. Statistical heterogeneity was tested using the Cochran Q statistic (considered significant when $p < 0.10$) and was quantified with the I^2 index (ranging from 0% to 100%). Heterogeneity was divided into low (I^2: < 25%), modest (I^2: 25.1–50%), and high (I^2: > 50%) [33]. Subgroup analysis were stratified by years of follow-up (≥ 5 years and < 5 years), study location (Asia, Europe, or North America), and age of participants (≥ 65 years). In addition, some studies found diabetes, hypertension, and depression as key risk factors for dementia and Alzheimer's disease [34–37]; therefore, we performed a subgroup analysis of these adjustment factors. Publication bias was evaluated using Begg's test [38] and Egger's test [39]. Sensitivity analyses were conducted by excluding studies one by one and analyzing the homogeneity and effect size for the rest of the studies. All *p*-values were two-tailed and $p < 0.05$ was considered statistically significant. Stata (version 14.0; StataCorp, College Station, TX) was used for all statistical analyses.

Results

Study selection

The literature search yielded 610 articles. After screening for duplicates, 422 titles and abstracts were reviewed (Fig. 1). Of these, 416 papers were excluded for the following rea0sons: 297 were not related to PPIs and dementia, 38 were non-human studies, 54 were review articles, 21 were case reports, two were meta-analyses, and four were case–control studies. Finally, a total of six articles, dated between 2015 and 2018 [25–30], fulfilled the selection criteria and were included in this meta-analysis.

Study characteristics and methodological quality

Table 1 summarizes the study characteristics and corresponding HR estimates with 95% CIs. A total of 166,146 participants were included in the six studies. Countries and regions of origin included Northwest USA [26], Germany [25, 28], Taiwan in China [27], Romania [29], and Korea [30]. All risk

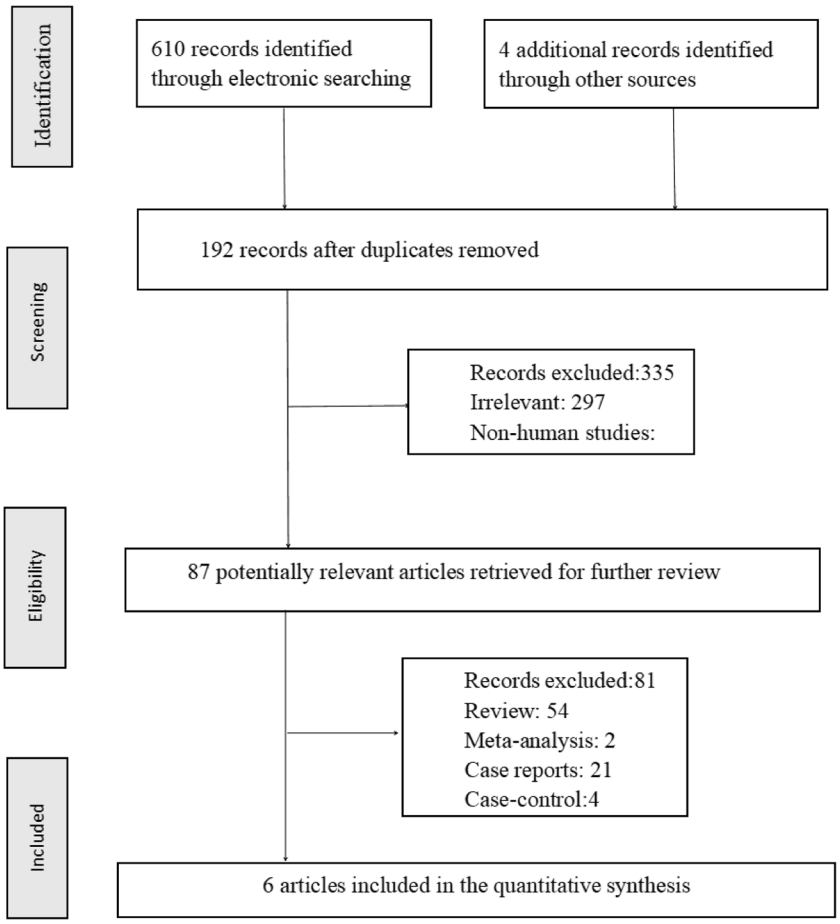

Fig. 1 Flow diagram of the study selection

estimates were adjusted at least for age. Further adjustment for gender was made in five studies [25–28, 30], for diabetes in five studies [25, 26, 28–30], for hypertension in three studies [26, 29, 30], or for depression in three studies [25, 26, 28].

The characteristics of the studies are summarized in Table 1, with adjusted covariates of each study given in Supplementary Table 1. Supplementary Table 2 shows our view on every item of bias risk for the included studies, and most of which were "low risk".

Overall meta-analysis

A forest plot of HR estimates with 95% CIs from individual studies and the overall meta-analysis are shown in Fig. 2. In the overall meta-analysis, PPIs use was significantly associated with increased risk of dementia, and the overall pooled HR was 1.29 (95% CI = 1.12–1.49) with a high heterogeneity ($p_{\text{for heterogeneity}} = 0.024$; $I^2 = 61.2\%$).

Subgroup analyses

Subgroup analyses found that, when the follow-up time was ≥ 5 years, the pooled HR was 1.28 (95% CI = 1.12–1.46; $p_{\text{for heterogeneity}} = 0.044$; $I^2 = 59.1\%$) [25–28, 30], and when the follow-up time was < 5 years, the HR was 3.67 (95% CI = 2.23–19.15) [29]. In the case of regional impact, participants from Europe showed an overall pooled HR estimate of 1.46 (95% CI = 1.23–1.73; $p_{\text{for heterogeneity}} = 0.224$; $I^2 = 33.2\%$) [25, 28, 29]. On the other hand, participants from Asia and North America did not have a significant association between PPIs use and dementia, HR = 1.17 (95% CI = 0.98–1.38; $p_{\text{for heterogeneity}} = 0.275$; $I^2 = 16.2\%$) [27, 30] and HR = 1.13 (95% CI = 0.82–1.56) [26], respectively. In addition, the overall pooled HR estimate of studies for participants whose age was ≥ 65 years was 1.39 (95% CI = 1.17–1.65) with moderate heterogeneity ($p_{\text{for heterogeneity}} = 0.162$; $I^2 = 41.5\%$) [25, 26, 28, 29], and the overall pooled HR estimate of studies for participants whose age was ≥ 40 years was 1.29 (95% CI = 1.12–1.49; $p_{\text{for heterogeneity}} = 0.024$; $I^2 = 61.2\%$) [25–30]. For the adjusted confounders, when adjusted for sex, depression, diabetes, and hypertension, the overall pooled results indicated that PPIs use was significantly associated with increased risk of dementia (sex: HR = 1.29, 95% CI = 1.12–1.50; $p_{\text{for heterogeneity}} = 0.062$; $I^2 = 55.3\%$; depression: HR = 1.42, 95% CI = 1.31–1.53; $p_{\text{for heterogeneity}} = 0.336$; $I^2 = 8.2\%$; diabetes: HR =1.31, 95% CI = 1.08–1.59; $p_{\text{for heterogeneity}} = 0.050$; $I^2 = 57.7\%$;

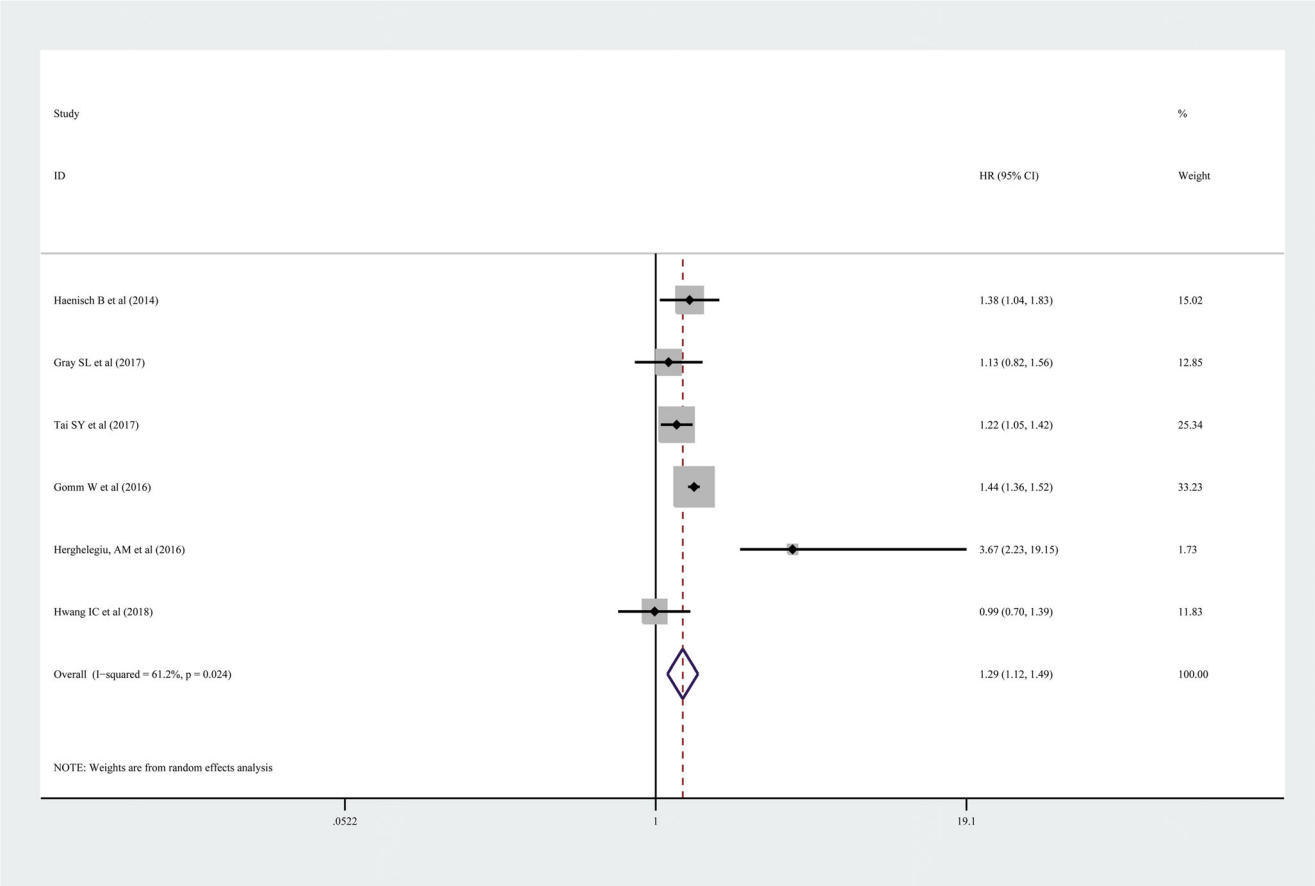

Fig. 2 Forest plot of the overall meta-analysis of proton pump inhibitors (PPIs) use and dementia risk

hypertension: HR = 1.29, 95% CI = 1.12–1.50; $p_{\text{for heterogeneity}} = 0.075$; $I^2 = 61.4\%$), respectively. These details are shown in Table 2.

Sensitivity analyses

Sensitive analyses showed that the study by Gomm et al. [28] had great influence on the pooled result. However, insignificant variation was found in combined HRs by excluding this study (HR = 1.22; 95% CI = 1.03–1.45; $p_{\text{for heterogeneity}} = 0.171$; $I^2 = 37.5\%$), confirming the stability of the present results.

Publication bias

In this meta-analysis, no publication bias was found using Begg's test ($p = 0.573$) and Egger's test ($p = 0.484$) (Fig. 3).

Discussion

This meta-analysis of six cohort studies found that the use of PPIs was a risk factor for dementia (HR = 1.29; 95% CI = 1.12–1.49). This finding is inconsistent with previous meta-analyses of PPIs use and dementia [20–23]. One explanation is due to the different inclusion criteria of three meta-analyses [20, 21, 23] and we also added some new studies. In this meta-analysis, we only included cohort studies; the reasons for this are as follows. First, case–control studies were less conclusive than cohort studies and might introduce selection and recall biases. Second, in cohort studies, the timing of exposure factors and diseases is clear, so the ability to demonstrate causality is strong. Third, we only included cohort studies, which ensured that the quality of the included studies was high. In addition, in this study, we stratified age of participants, follow-up time, study location, and adjustment of potential confounders, in order to obtain clearer meta-analysis results about cohort studies. In addition, a meta-analysis with cohort studies found that there was no statistical association between PPIs use and increased risk of dementia [22]. This meta-analysis included the study of Goldstein et al. [40], but we did not include this study due to their outcome of interest being the total mild cognitive impairment or dementia. Mild cognitive impairment is not a type of dementia and the study of Song et al. [23] also included the study of Goldstein et al. [40]. Because our inclusion criteria were different, we only included the study where

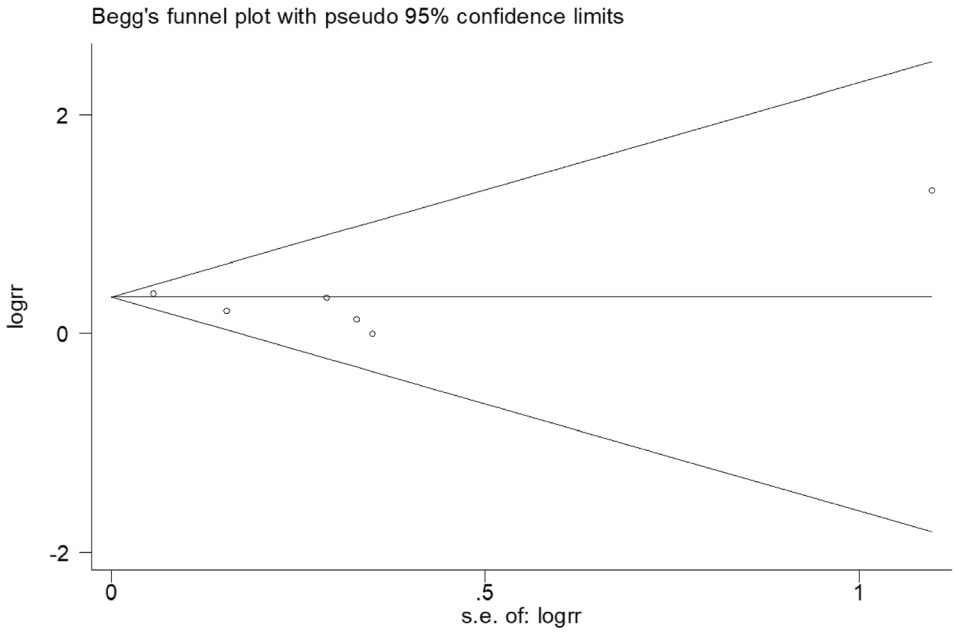

Fig. 3 Funnel plot for publication bias in the studies investigating risk of dementia associated with proton pump inhibitor (PPI) use

s.e = standard error

the outcome was dementia. Furthermore, we included the study of Hwang et al. [30] but not the meta-analysis of Li et al. [22], and we included the study of Herghelegiu et al. [29] but not the meta-analysis of Song et al. [23].

Some case–control studies found that PPIs use is associated with increased risk of dementia [41–43], but a nested case–control study found no clinically significant association between PPIs use and risk of Alzheimer's disease [44].

The Newcastle-Ottawa scale was used to assess the quality of included studies. Some studies showed very important differences in the probability of quality or bias in studies, usually leading to very close ratings across studies. We have produced a table containing more detail regarding the risk of bias assessment. Sensitivity analysis demonstrated that the study of Gomm et al. [28] contributed greatly to the variability among all studies. The study of Gomm et al. [28] has the following strengths: the sample of patients was large and health claims data cover the total population, and selection bias or recall bias was avoided. However, there are some limitations that have to be taken into account. Other risk factors for dementia (e.g., ApoE4 allele carrier or lower educational level) could not be integrated into the analysis. In addition, because they analyzed claims data with a high rate of diagnoses of unspecified and mixed dementia, they were not able to differentiate between different dementia etiologies.

According to the preclinical findings, there is a strong correlation between PPIs use and dementia risk. In vitro studies have shown that PPIs can interfere with the degradation of Aβ peptide, which is one of the pathological characteristics of Alzheimer's disease [45]. The fibrin Aβ clearance by microglia is dependent on pH and caused by lysosomal acidification. PPIs inhibit V-ATPase proton pump, which is the key to acidification. Therefore, the use of PPIs may reduce the rate of Aβ degradation, leading to an increase in Aβ levels [12, 14, 15]. Some studies have reported that PPIs can cross the blood–brain barrier [46, 47]. In addition, PPIs may act as an inverse γ-secretase modulator by increasing the activity of β-secretase BACE1, leading to the accumulation of Aβ [11]. Besides, vitamin B-12 deficiency is usually associated with cognitive impairment, possibly due to brain atrophy and white-matter damage associated with B-12 deficiency [48]. Köbe et al. found that low vitamin B-12 levels are associated with poor memory performance, partly due to a decrease in the microstructural integrity of the hippocampus [49]. Smith et al. found that there is a continuous inverse relationship between serum B12 and dementia [50]. Dharmarajan et al. found that PPIs use can lead to a decrease in vitamin B-12 levels in the elderly [51]. In conclusion, long-term use of PPIs may promote Aβ deposition in the brain and reduce serum vitamin B-12 levels, affecting cognitive function and leading to increased risk of dementia.

The advantages of this meta-analysis are as follows. First, this meta-analysis included a large sample size. A total of 166,146 participants were included in the six studies. Second, there is no evidence of publication bias. Third, we stratified the age of participants, follow-up time, study location, and adjustment of potential confounders. Finally, the studies that we included are from three continents and with high-quality research.

In addition, there some limitations that also need to be considered. First, there is substantial heterogeneity among our studies, but it was reduced among groups in relation to study location and age by stratified analysis, and studies

included different ethnicities and genders, which could lead to a further source of heterogeneity, and we cannot analyze them due to the small number of studies. Second, pooled HR estimates had a bias because of the use of different HR indicators (HR or OR) as the same effect measures. Nearly 50 million people have dementia in the world [1], so the incidence of dementia was very low (< 0.1%), even though among the elderly, the proportion of people with dementia in the population aged 60 years and over is 5–8%. In addition, because the included studies are all cohort studies, these measured effects produce a similar HR estimate, and the bias was very low. Third, in the subgroup analysis, there was not enough information to explore the relationship between PPIs doses and dementia. Fourth, we were unable to further explore the relationship of PPIs with different sub-types of dementia, due to the fact that the limitation of original researches included in our analysis did not analyze different sub-types of dementia. Finally, we only included cohort studies and the number of cohort studies is relatively limited, so the inherent biases and selection bias cannot be avoided. Therefore, the results of this study should be treated with caution.

The findings from this study have important clinical or practical implications. We have found that people using PPIs aged ≥ 65 years and living in Europe to be vulnerable to dementia. In view of the existing health burden of dementia, prolonged administration of PPIs should be avoided. Routine geriatric care practices should include active screening for long-term use of PPIs and reevaluation of medication after appropriate investigations and diagnosis. Therefore, prevention of dementia among people at increased risk (e.g., the elderly) can help to alleviate the burden of dementia cases and the medical system.

Conclusion

In this meta-analysis, the results support that proton pump inhibitors (PPIs) use increases the risk of dementia. In order to better understand the mechanisms, we will need well-designed cohort studies with large sample sizes, long follow-up periods, and a reliable method to adjust for standardized confounders and perform subgroup analyses.

Author contributions Yun Zhang and Mingming Liang conceived and designed the study, with substantial contributions from Chenyu Sun, Tingting Shi, Min Min, Evelyn J. Song, Ce Cheng, and Yehuan Sun. Yun Zhang and Mingming Liang collected, analyzed, and interpreted the data and drafted the manuscript. All authors revised it critically for important intellectual content and approved the final manuscript.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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