Proton pump inhibitors and risk of dementia

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Background: Proton pump inhibitors (PPIs) are one of the most commonly prescribed medications. Recent studies have raised a concern over increased risk of dementia among PPIs users but the results of those studies were inconsistent. We conducted this systematic review and meta-analysis to summarize all available data.

Methods: A literature search was performed in MEDLINE and EMBASE database from inception to April 2016. Observational studies that reported risk of dementia among PPIs users compared with non-users were included. Point estimates were extracted from individual studies and pooled risk ratios (RR) with 95% confidence intervals (CI) were calculated using a random-effect, generic inverse variance method.

Results: Four studies were included in the analysis. Pooled RR of dementia among PPIs users compared with non-users was 1.08 (95% CI, 0.82–1.43). Sensitivity analysis including only cohort studies demonstrated a higher risk with pooled RR of 1.44 (95% CI, 1.36–1.52).

Conclusions: Our study demonstrated an increased risk of dementia among PPIs users. Whether this association is causal requires further investigations.

Keywords: Proton pump inhibitors (PPIs); dementia; Alzheimer's disease; systematic review; meta-analysis

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Introduction

Proton pump inhibitors (PPIs) are one of the most commonly prescribed medications in the United States (US) for treatment of several upper gastrointestinal disorders including gastroesophageal reflux and peptic ulcer (1). Over the past decade, the prevalence of the use of PPIs in the US has increased from 4.8% to 8.5% among women and from 3.4% to 7.0% among men (2). PPIs are generally regarded as safe medications with very few adverse effects. However, recent observational studies have suggested that some of its adverse effects, such as acute interstitial nephritis and Clostridium difficile infection, could be more common than previously thought (1,3-5).

Dementia is a disorder of older adults characterized by a decline in one or more cognitive functions (6). Known risk factors for dementia include diabetes mellitus, midlife hypertension, obesity, smoking, depression, physical inactivity, and cognitive inactivity (7). Use of PPIs could potentially be another risk factor for dementia and cognitive decline as demonstrated in recent observational studies even though the results were inconsistent (8-11). To summarize all available evidence and to further characterize this possible association, we conducted this systematic review and meta-analysis.

Methods

Search strategy

Two investigators (Karn Wijarnpreecha and Patompong Ungprasert) independently searched for published studies indexed in MEDLINE and EMBASE database from inception to April 2016 using the search strategy that included the terms for "PPIs" and "dementia" as described in online supplementary data (*Supplementary 1*). No language limitation was applied. A manual search for additional relevant studies using references from retrieved articles was also performed.

Inclusion criteria

The inclusion criteria were as follows: (I) case-control, cross-sectional or cohort studies published as original studies to evaluate the risk of dementia among subjects who used PPIs compared to non-users; (II) odds ratios (OR), risk ratios (RR), hazard ratios (HR) or standardized incidence ratio with 95% confidence intervals (CI) were provided.

Study eligibility was independently determined by the two investigators noted above. Differences in the determination of study eligibility were resolved by mutual consensus. The quality of each study was also independently evaluated by each investigator using Newcastle-Ottawa quality assessment scale (12). This scale evaluated each study in three domains including the selection of the participants, the comparability between the groups and the ascertainment of the exposure for case-control study and the outcome of interest for cohort study. The modified Newcastle-Ottawa scale as described by Herzog *et al*. was used for cross-sectional study (13).

Data extraction

A standardized data collection form was used to extract the following data from each study: title of the study, name of the first author, year of study, year of publication, country of origin, number of participants, demographic data of participants, method used to identify and verify use of PPIs as well as dementia, adjusted effect estimates with 95% CI and covariates that were adjusted in the multivariate analysis.

To ensure the accuracy, this data extraction process was independently performed by all investigators. Any data discrepancy was also resolved by referring back to the original articles.

Statistical analysis

Data analysis was performed using Review Manager 5.3 software from the Cochrane Collaboration (London, UK). Adjusted point estimates and standard errors from individual study were combined by the generic inverse variance method of DerSimonian and Laird, which assigned the weight of each study based on its variance (14). In light of the high likelihood of between study variance because of different study designs and populations, we used a random-effect model rather than a fixed-effect model. Cochran's Q test and I^2 statistic were used to determine the between-study heterogeneity. A value of I^2 of 0% to 25% represents insignificant heterogeneity, more than 25% but less than or equal to 50% represents low heterogeneity, more than 50% but less than or equal to 75% represents moderate heterogeneity, and more than 75% represents high heterogeneity (15).

Results

Our search strategy yielded 1,620 potentially relevant articles (590 articles from Medline and 1,032 articles from EMBASE). After the exclusion of 567 duplicated articles, 1,055 of them underwent title and abstract review. One thousand and thirty three articles were excluded at this stage since they were case reports, letters, review articles or interventional studies, leaving 22 articles for a full-length article review. Twelve of them were excluded since they did not report the outcome of interest while six articles were excluded since they were descriptive studies without comparators. Four articles (two cohort studies, one case-control study, and one cross-sectional study) met the eligibility criteria and were included in the data analysis (8,9,16,17). *Figure 1* outlines the literature review and study selection process. The clinical characteristics and the quality assessment of the included studies are described in *Table 1*.

We found that PPIs users had a small increased risk of dementia compared with non-users with the pooled RR of 1.08 even though without a statistical significance (95% CI, 0.82–1.43). The statistical heterogeneity was high with an

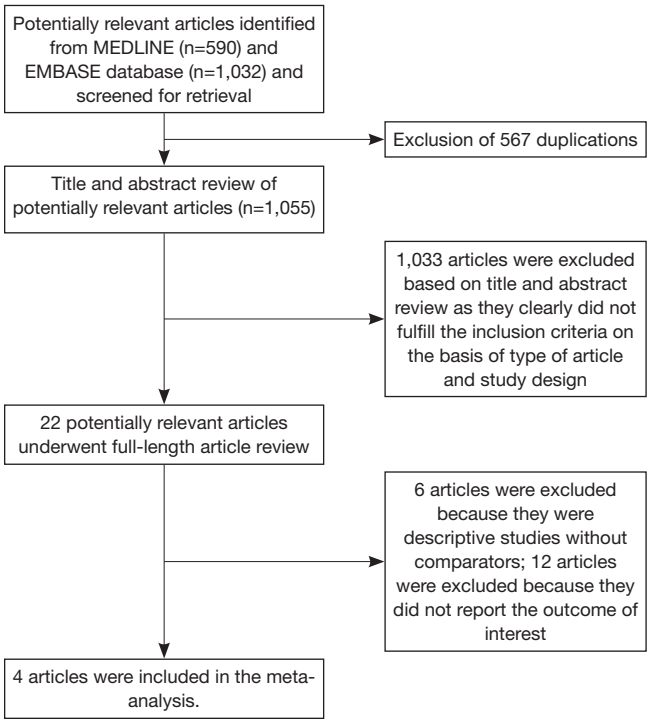

Figure 1 Literature review process.

I^2 of 99%. The forest plot is shown in *Figure 2*. However, sensitivity analysis that included only studies with high quality design (i.e., cohort studies) demonstrated a higher risk of dementia with the pooled RR of 1.44 (95% CI, 1.36–1.52). The statistical heterogeneity was minimal with an I^2 of 0%.

Evaluation for publication bias

We did not perform the evaluation for publication bias as the number of studies included in the meta-analysis was too small.

Discussion

This study is the first systematic review and meta-analysis of published studies assessing the associations of the use of PPIs and risk of dementia. Overall, we found a small increased risk of dementia among PPIs users compared with non-users even though without reaching statistical significance. Nonetheless, sensitivity analysis of only cohort studies demonstrated a higher increased risk (approximately 40%) and achieved statistical significance.

There are few possible explanations for the apparent increased risk of dementia among PPIs users.

First, *in vitro* studies have demonstrated that PPIs could interfere with the degradation of amyloid beta (Aβ) peptide, one of the pathological hallmarks of Alzheimer's disease (18). Fibrillar Aβ clearance by microglia is pH-dependent and induced by acidification of lysosomes. PPIs are known to have inhibitory effect on V-ATPase proton pump that is pivotal for acidification. Thus, use of PPIs might reduce the rate Aβ degradation, resulting in increased Aβ levels (19-21). Second, PPIs might act as an inverse γ-secretase modulator by increasing the activity of the β-secretase BACE1, resulting in accumulation of Aβ (22). Third, use of PPIs has been shown to be associated with vitamin B12 deficiency as a result of suboptimal GI absorption (23). Vitamin B12 deficiency is known to negatively affect cognitive function as a result of impaired DNA synthesis, methylation, and homocysteine neurotoxicity (24,25).

Although most of the included studies were of high quality as reflected by the high-quality assessment scores, this meta-analysis had some limitations. Therefore, the results should be interpreted with caution.

First, we could not perform the evaluation for publication bias as the number of included studies was too small. Thus, publication bias in favor of positive studies might have been present. Second, two studies included in this meta-analysis were medical registry-based studies which could raise a concern over coding inaccuracy and incompleteness. Third, the included studies were conducted exclusively in European countries. Therefore, our results might not be generalizable to other ethnic groups. Fourth, the statistical heterogeneity in this study was high. We suspect that the difference in study designs was responsible for this heterogeneity as the I^2 dropped dramatically with the sensitivity analysis that included only cohort studies. Fifth, this is a meta-analysis of observational studies that could only demonstrate an association but could not establish causality. Therefore, we cannot conclude that PPIs use does increase the risk of dementia as this association could be a result of confounding.

Conclusions

In summary, this meta-analysis demonstrated an increased risk of dementia among PPIs users. Nonetheless, there are some limitations in methodology and the results should be

Table 1 Main characteristics of the studies included in this meta-analysis of the association between PPIs and dementia

Study	de Souto Barreto *et al*. (17)	Gomm *et al*. (8)	Haenisch *et al*. (9)	Booker *et al.* (16)
Country	France	Germany	Germany	Germany
Study design	Cross-sectional study	Prospective cohort study	Prospective cohort study	Case-control study
Year	2013	2016	2015	2016
Number of participants	6,275 (2,379 PPI users; 3,905 non-users)	73,679 (2,950 PPI users; 70,729 non-users)	3,076 (713 PPI-users; 2,363 non-users)	23,912 (11,956 dementia; 11,956 non-dementia)
Recruitment of participants	This cross-sectional survey was conducted in 175 nursing homes in south-western France	Sample of patients ≥75 years who were free of dementia at baseline were randomly selected from the largest German statutory health insurer database	Participants ≥75 years who were free of dementia at baseline were recruited from six study centers in Germany	Patients aged 70–90 with dementia and age, sex and primary care physician-matched controls without dementia were randomly selected from the disease analyzer database which covered representative sample of primary care physician practices across Germany
Mean age of participants in years (case/comparator)	86.7/85.5	83.8/83.0	79.6/79.7	80.4/80.4
Percentage of female (case/comparator)	72.2/74.5	77.9/73.6	68.7/64.0	61.0/61.0
Definition and ascertainment of PPIs use	Current use of any PPIs during the time of survey. Data on drug use were obtained from prescription history provided by nursing home staffs	At least one prescription per quarter of any PPIs. The prescription data were derived from pharmaceutical database of the insurer	At least one use of any PPIs during follow up period. Information on PPIs used was obtained by interview during follow up visit	Current use of any PPIs at the time of diagnosis of dementia
Definition and ascertainment of dementia	Dementia is defined by presence of diagnosis of dementia in the medical records of participants. These data were provided by nursing home staffs	Dementia is defined by presence of diagnostic codes of dementia in at least 2 of 6 quarters of 18-month interval	Diagnosis of dementia was made according to DSM-IV criteria during follow up visit by an experienced geriatrician or geriatric psychiatrist	Dementia is defined by presence of diagnostic codes of dementia in the database
Confounder adjustment	Age, ADL score, number of disease, number of medications, hospitalization, pain, peptic ulcer, stroke, taking calcium, antithrombotic agents, NSAIDs, aspirin, clopidogrel, glucocorticoids and duration of stay in nursing homes	Age, sex, stroke, depression, heart disease, diabetes and polypharmacy	Age, sex, education, the Apolipoprotein E4 allele status, polypharmacy, depression, diabetes, ischemic heart disease, stroke	Age, sex, type of health insurance, comorbidities, diabetes, hypertension, obesity, hyperlipidemia, history of stroke, Parkinson's disease, coronary heart disease, mild cognitive impairment, mental and behavioral disease due to alcohol, intracranial injury, and use of several medications, statins, PPIs, antihypertensive drugs
Quality assessment (Newcastle-Ottawa scale)	Selection: 4; comparability: 1; outcome: 3	Selection: 4; comparability: 2; outcome: 3	Selection: 4; comparability: 2; outcome: 3	Selection: 3; comparability: 2; outcome: 3

PPIs, proton pump inhibitors; ADL, activities of daily living; NSAIDs, nonsteroidal anti-inflammatory drugs; DSM, diagnostic and statistical manual of mental disorders.

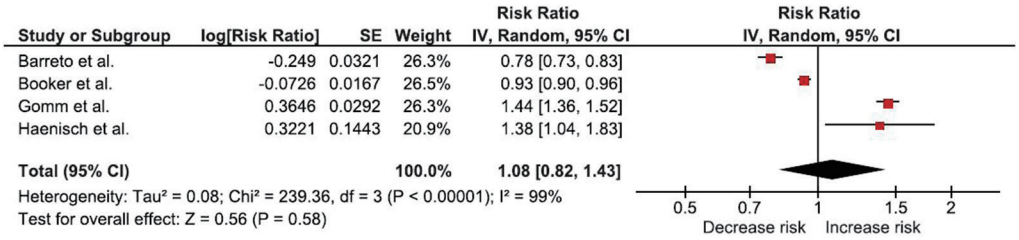

Figure 2 Forest plot of the included studies of the associations between proton pump inhibitors (PPIs) and risk of dementia. CI, confidence intervals.

interpreted with caution.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Supplementary 1

Search strategy

Database: Ovid MEDLINE

(I)	exp proton pump inhibitor/
(II)	proton pump inhibitor.mp.
(III)	proton pump antagonist.mp.
(IV)	prton-translocating atpases.mp.
(V)	proton pump.mp.
(VI)	ppi.mp.
(VII)	ppis.mp.
(VIII)	lansoprazole.mp.
(IX)	dexlansoprazole.mp.
(X)	kapidex.mp.
(XI)	prevacid.mp.
(XII)	omeprazole.mp.
(XIII)	esomeprazole.mp.
(XIV)	nexium.mp.
(XV)	prilosec.mp.
(XVI)	pantoprazole.mp.
(XVII)	protonix.mp.
(XVIII)	rabeprazole.mp.
(XIX)	aciphex.mp.
(XX)	dexrabeprazole.mp.
(XXI)	Pariet.mp.
(XXII)	(I) or (II) or (III) or (IV) or (V) or (VI) or (VII) or (VIII) or (IX) or (X) or (XI) or (XII) or (XIII) or (XIV) or (XV) or (XVI) or (XVII) or (XVIII) or (XIX) or (XX) or (XXI)
(XXIII)	dementia.mp. or exp dementia/
(XXIV)	vascular dementia.mp or exp vascular dementia/
(XXV)	exp multi-infarct/
(XXVI)	Alzheimer disease.mp. Or exp Alzheimer disease/
(XXVII)	cognitive decline.mp.
(XXVIII)	cognitive impairment.mp.
(XXIX)	(XXIII) or (XXIV) or (XXV) or (XXVI) or (XXVII) or (XXVIII)
(XXX)	(XXII) and (XXIX)