Received: 7 March 2022 | Revised: 8 August 2022 | Accepted: 25 October 2022

DOI: 10.1111/bcp.15583

META-ANALYSIS

Do proton pump inhibitors increase the risk of dementia? A systematic review, meta-analysis and bias analysis

Nayeon Ahn[1,2] | Michael Nolde[1,2] | Evamaria Krause[3] | Florian Güntner[4] | Alexander Günter[4] | Martin Tauscher[5] | Roman Gerlach[5] | Christa Meisinger[2] | Jakob Linseisen[1,2] | Sebastian-Edgar Baumeister[6] | Ina-Maria Rückert-Eheberg[1,2]

[1]Institute for Medical Information Processing, Biometry, and Epidemiology (IBE), Ludwig Maximilian University of Munich, Munich, Germany

[2]Chair of Epidemiology, University of Augsburg, University Hospital Augsburg, Augsburg, Germany

[3]Medical Library, Augsburg University Library, University of Augsburg, Augsburg, Germany

[4]Bereich Versorgungsmanagement, AOK Bayern, Munich, Germany

[5]Association of Statutory Health Insurance Physicians in Bavaria, Kassenärztliche Vereinigung Bayerns, KVB, Munich, Germany

[6]Institute of Health Services Research in Dentistry, University of Münster, Münster, Germany

Correspondence
Nayeon Ahn, Chair of Epidemiology, c/o University Hospital Augsburg, Stenglinstr. 2, 86156 Augsburg, Germany.
Email: nayeon.ahn@med.uni-augsburg.de

Funding information
This study was supported by the Innovation Committee at the Federal Joint Committee (Gemeinsamer Bundesausschuss, G-BA), the highest decision-making body of the joint self-government of physicians, dentists, hospitals and health insurance funds in Germany (grant no. 01VSF18013). The funding agency played no role in the design, methods, data collections, analysis and preparation of this article.

Aim: Previous studies on the association between proton pump inhibitor (PPI) intake and the increased risk of dementia has shown discrepancies in their conclusions. We aimed to provide updated evidence based on extensive bias assessments and quantitative sensitivity analyses.

Methods: We searched the databases PubMed, EMBASE, SCOPUS, CENTRAL and clinicaltrials.gov for prospective studies that examined an association between PPI use and dementia, up to February 2022. Each study was assessed using the Cochrane risk of bias assessment tools for non-randomized studies of interventions (ROBINS-I) or randomized trials (RoB2). Pooled risk ratios (RRs) and 95% prediction intervals were computed using random-effects models. Sensitivity analyses were adjusted for small-study bias.

Results: We included nine observational studies with 204 108 dementia cases in the primary analysis on the association between PPI use *vs*. non-use and dementia, and the RR was 1.16 (95% CI = 1.00; 1.35). After adjusting for small-study bias by Copas selection model and Rücker's shrinkage procedure, the RR was 1.16 (1.02; 1.32) and 1.15 (1.13; 1.17), respectively. A subgroup analysis of PPI use *vs*. non-use regarding Alzheimer's disease risk yielded an RR of 1.15 (0.89; 1.50). The secondary analysis on the risk of dementia by use of PPI *vs*. histamine-2 receptor antagonist showed an RR of 1.03 (0.66; 1.62).

Conclusion: This meta-analysis provided no clear evidence for an association between PPI intake and the risk of dementia. Due to discrepancies in sensitivity analyses, however, some risk of dementia by PPI use cannot be ruled out. Since an unequivocal conclusion is still pending, further research is warranted.

KEYWORDS
Alzheimer's disease, cognitive impairment, dementia, proton pump inhibitors

Sebastian-Edgar Baumeister and Ina-Maria Rückert-Eheberg are shared last authors.

1 | INTRODUCTION

1.1 | Rationale

Dementia is defined as a condition of progressively declining cognitive and functional abilities. According to a recent study on the global burden of disease,[1] there were 43.8 million individuals with dementia worldwide in 2016, and it is expected that the prevalence will increase to 100 million by 2050. The rising prevalence of dementia is a serious concern for patients and their families and burdens public health. It was reported that dementia had higher health and social care costs than cancer and chronic heart disease combined.[2] Given that the ageing of society is expected to continue, the most efficient way to reduce this burden, besides innovative forms of treatment, is to identify effective preventive measures.

The effect of proton pump inhibitors (PPIs) as gastric acid suppressants has been well established.[3] Due to their treatment success and relatively low incidence of adverse reactions, the use of PPIs has increased enormously worldwide over the last decades.[4] Moreover, PPIs are frequently prescribed without clear indications, and they are available as over-the-counter medications. Patients often start a PPI therapy during their hospitalization and do not discontinue the intake after their discharge.[5]

In recent years, numerous investigations on the adverse effects of PPIs have been conducted and researchers have reached a relatively clear consensus regarding the risk of several side effects.[6,7] Specifically, *Clostridium difficile* infection, bone fracture, major adverse cardiovascular events, chronic kidney disease and dementia have frequently been investigated as adverse effects by PPI use. Among them, all-site fracture and chronic kidney disease showed convincing levels of evidence in the recent systematic umbrella review by Veettil et al.[7] Although plausible pathophysiological pathways of brain deterioration associated with PPI use have been proposed,[6,8] there has not been a consensus based on the available observational studies in human populations.[9–14] While Wang et al.[15] found no evidence for an association between PPI use and dementia risk (pooled hazard ratio [HR] = 0.98, 95% confidence interval [CI] = 0.85; 1.13) in their large meta-analysis, another meta-analysis[16] that excluded cross-sectional studies showed an elevated dementia risk (HR = 1.29, 95% CI = 1.12; 1.49).

To our knowledge, most previous meta-analyses did not pool the different types of effect estimates, that is, meta-analyses of HRs and odds ratios (ORs) were performed separately. Therefore, only a small number of studies was available for each meta-analysis. Despite the contradictory results from previous research, the latest large observational study[9] reported an increased risk of dementia associated with PPI use, and the result has not been included in any quantitative synthesis.

1.2 | Objective

We conducted a systematic review and meta-analysis on the question of whether PPI intake (as compared to non-use or intake of histamine-2 receptor antagonists [H2RAs]) is a risk factor for incident dementia (all-cause or Alzheimer's disease), including studies with a prospective design. We performed intensive quality assessments and bias checks of each study using the risk of bias assessment tool for non-randomized studies of interventions (ROBINS-I)[17] that leans on the idea of trial emulation in observational studies and the risk of bias 2 (RoB 2) tool for randomized trials.[18]

2 | METHODS

The study protocol was registered at PROSPERO (Registration: CRD42020197968). This systematic review and meta-analysis was conducted according to the PRISMA 2020 statement: an updated guideline for reporting systematic reviews.[19]

2.1 | Literature search

An experienced medical librarian (E.K.) and two investigators (N.A. and I.R.) developed search strategies and searched PubMed, EMBASE, SCOPUS, the Cochrane Central Register of Controlled Trials (CENTRAL) and clinicaltrials.gov from database inception until 17 February 2022, for studies that investigated the association between PPI intake and the risk of dementia. We tailored search strategies to each database and used controlled vocabulary and specific search fields where available as well as Boolean search methods and free-text terms. Full search strategies are provided in Box S1. We limited the search to human studies and did not use language restrictions. Articles were selected for full-text review based on their titles and abstracts. We performed a hand search for additional articles through the bibliographies of the retrieved publications to increase the yield of potentially relevant articles. All results were downloaded into Citavi 6 (Swiss Academic Software GmbH, Zürich), a bibliographic database manager, and any duplicate citations were removed.

2.2 | Study selection

Two investigators (N.A. and I.R.) independently performed the title and abstract screen, read the full texts of all identified articles to determine whether each study met the predetermined eligibility criteria and collected information assessing the methodological quality of each included study to enter into the structured data extraction forms. Any discrepancies between the investigators were resolved by discussion.

Included studies in this review fulfilled the following criteria: (1) any PPI (ATC code A02BC) use as an exposure variable; (2) incidence of dementia including Alzheimer's disease as a binary outcome; (3) prospective design, that is, cohort, nested case–control, case–cohort and randomized controlled trial (RCT); (4) provision of effect estimates with variances or 95% CIs; (5) articles published in peer-reviewed journals and (6) full text available.

Studies were excluded if the outcome was not an incidence of dementia, for example, numeric score of the mini-mental state examination (MMSE) or if it included mild cognitive impairment.

2.3 | Data extraction and evaluation of study quality

Data were extracted using a standardized data extraction form. Two investigators (N.A. and I.R.) independently checked the data. For each of the eligible studies, the following information was collected: first author's name, publication year, country, participant demographics including age at baseline and sex distribution, dementia diagnostic criteria, adjusted confounding variables, types of PPIs, mean/median duration of follow-up where available, definition of the comparison group (PPI non-use or H2RA [ATC code A02BA] use) and confounder-adjusted effect estimates (HRs, ORs, or risk ratios [RRs]) with 95% CIs (Table 1).

We used the ROBINS-I tool[17] to evaluate the methodological quality of observational studies. The overall risk of bias judgement was categorized into low, moderate, serious, critical or no information according to the judgement of the seven bias domains: (1) bias due to confounding; (2) bias in selection of participants into the study; (3) bias in classification of interventions; (4) bias due to deviations from intended interventions; (5) bias due to missing data; (6) bias in measurement of outcomes and (7) bias in selection of the reported result. In contrast to other quality assessment tools, the ROBINS-I tool considers each observational study as an attempt to emulate a hypothetical randomized trial. Thus, various types of bias in study design, that is, post hoc exclusion of certain participants or inappropriate time points of confounder measurement, become transparent. To evaluate the methodological quality of an RCT, we used the RoB2 tool.[18]

2.4 | Data synthesis and statistical analysis

During the data synthesis for meta-analysis, we further excluded a study,[20] which was assessed as 'critical' in its risk of bias by the ROBINS-I tool according to the recommendation from developers of the tool.[17] If multiple studies were reported on the same dataset, we included the one with the largest number of cases. Therefore, the study by Chen et al.[10] was included in our primary analysis among four Taiwanese studies that had the same data source (Longitudinal Health Insurance Database 2000).[10,21–23] An RCT by Moayyedi et al.[24] was included in the systematic review but not in the meta-analysis due to high risk of bias (Table S2).

Our primary interest was the association between PPI use *vs.* non-use and the risk of dementia. This association has been reported as HRs, ORs or RRs in the literature. Since dementia is not considered as a rare event (10% is often used as a cut-off) in our primary analysis,[25] we derived optimal analytic conversions of ORs and HRs to RRs using the transformation forms for a common outcome that were proposed by VanderWeele.[26] As a sub-analysis, we evaluated the association between PPI use and risk of Alzheimer's disease exclusively. Additionally, we compared the incidence of dementia in PPI users and H2RA users.

The Hartung–Knapp–Sidik–Jonkman random-effects meta-analysis approach with restricted maximum likelihood (REML) variance estimation was used to combine study-specific log RRs with the empirical Bayes estimator for the between-study variance.[27] The 95% CIs from the random-effects model include highly probable values for the mean RR.[28] The 95% prediction interval estimates an interval in which the RR is to be expected in 95% of future studies conducted under similar conditions factoring in the variability of the effect over different settings.[28] Due to the large heterogeneity in our meta-analysis, we report the different properties of a measure of heterogeneity: (1) a percentage of total variability (I^2) and (2) between-study variability (τ^2), which is measured on an outcome scale [0, ∞). The Cochran Q statistic was used to test for heterogeneity.[29] Heterogeneity was additionally examined by estimating the proportion of studies with evidence for a meaningful effect (using thresholds for a mean RR of ≥1.1 and ≥1.2) and the estimated proportion of studies with a protective effect, that is, RR < 1.0.[30]

The random-effects meta-analysis was stratified by study quality (ROBINS-I risk of bias: moderate *vs.* serious), study design (prospective cohort *vs.* nested case–control), geographical region (Asia, Europe or United States), assessed effect (assignment *vs.* starting and adhering), type of outcome data (claims data *vs.* diagnosis protocol), the minimum age at baseline (<65 *vs.* ≥65 years), and study size (number of events <10 000 *vs.* ≥10 000). We did not perform meta-regression to identify sources of heterogeneity because it is recommended only if 10 or more studies are included.[31]

We implemented several bias analyses to examine possible effects by small studies and selective publication.[32,33] We assessed publication bias and small-study effects (funnel plot asymmetry) using the regression-based tests proposed by Egger, the trim-and-fill method, and the Copas selection model.[33,34] By using the Rücker regression-based shrinkage estimator, we further examined the presence of a small-study effect, assessed the random-effect estimate adjusted for small-study bias and checked remaining heterogeneity (G^2) after small-study effects were accounted for.[33,34] We further conducted leave-one-out and influence analysis and drew a Baujat plot to detect outliers and recalculate random-effect estimates without influential studies.[35]

Random-effects meta-analysis of observational studies can produce biased estimates of pooled effect sizes if the synthesized individual studies are subject to unmeasured confounding or selection bias.[32] Thus, we further conducted sensitivity analyses for a random-effects meta-analysis restricted to studies with better quality ($n = 2$) because the stratified analysis by study quality showed a possible source of heterogeneity. The approach to sensitivity analysis is a meta-analytic extension of the E-value, a widely used metric quantifying the minimum strength of association that an unmeasured confounder would need to have with the exposure and the outcome on the relative risk scale to fully account for an observed exposure–outcome association beyond the measured covariates.[32] We also used

TABLE 1 Characteristics of observational studies of dementia/Alzheimer's disease and the use of proton pump inhibitors

Author, year, country	Data source	Study design, follow-up	Comparison	No. of study population	Women (%)	Age (mean)
Haenisch et al., 2015, Germany[57]	Study on ageing, cognition and dementia in primary care patients (age-CoDe)	Population cohort study, follow-up: 6 years	PPI use Non-use	713 2363	68.7 64.0	79.6 ± 3.4 79.7 ± 3.6
			PPI use Non-use	673 2238	69.1 64.3	79.6 ± 3.4 79.6 ± 3.6
Gomm et al., 2016, Germany[11]	AOK Germany	Population cohort study, follow-up: 7 years	PPI use Non-use	2950 70 729	77.9 73.6	83.8 ± 5.4 83.0 ± 5.6
Taipale et al., 2017, Finland[14]	Cases: Finnish medication and Alzheimer's disease (MEDALZ) study controls: Finnish nationwide healthcare registries	Nested case–control study, max follow-up: 7 years	PPI use Non-use	113 197 240 379	68.3 63.7	Case: Median 80.8 (IQR: 76.1–84.9)/ control: Median 80.8 (IQR: 76.0–84.8)
Tai et al., 2017, Taiwan[22]	Longitudinal Health Insurance Database 2000 (LHID)	Population cohort study, mean follow-up: 9 years	PPI use Non-use	7863 7863	41.2 40.7	55.7 ± 12.4 55.3 ± 12.2
Gray et al., 2017, USA[12]	Adult changes in thought (ACT) study	Population cohort study, mean follow-up: 7.5 years	PPI use Non-use	402 3082	64.7 58.7	Median 75 (IQR: 70–81) median 74 (IQR: 70–80)
			PPI use Non-use	402 3082	64.7 58.7	Median 75 (IQR: 70–81) 74 (IQR: 70–80)
Hwang et al., 2018, South Korea[51]	National Health Insurance Corporation	Population cohort study, max follow-up: 6 years	PPI use Non-use	1947 68 086	37.2 43.8	Not Reported (min. 60)
Imfeld et al., 2018, UK[13]	Clinical practice research datalink (CPRD)	Nested case–control study, median follow-up: 6.2 years (case), 5.9 years (control)	PPI use Non-use	22 522 29 100	68.5 68.5	80.9 ± 6.7 (overall)
		Nested case–control study, median follow-up: 5.8 years (case), 5.8 years (control)	PPI use Non-use	14 317 16 119	61.1 61.1	82.5 ± 6.6 (overall)
Park et al., 2019, South Korea[60]	National Health Insurance Service-National Sample Cohort (NHIS-NSC) database	Population cohort study, max follow-up: 11 years	PPI use H2RA use	87 562 87 562	43.6 43.0	Not reported (min. 40)
Chen et al., 2020, Taiwan[10]	Longitudinal Health Insurance Database 2000 (LHID)	Population cohort study, max follow-up: 12 years	PPI use Non-use	9348 9348	40.8 40.8	Not reported (min. 65)
Torres-Bondia et al., 2020, Spain[20]	Catalan health sevice (CatSalut) system, Catalan Institute of Health (ICS)	Population cohort study, max follow-up: 14 years	PPI use Non-use	36 360 99 362	39.9 48.1	66.9 ± 11.8 66.8 ± 13.2
Wu et al., 2020, Taiwan[23]	Longitudinal Health Insurance Database 2000 (LHID)	Population cohort study, mean follow-up: 4.0 years	PPI use Non-use	2583 2583	36.2 36.0	55.5 ± 11.5 55.8 ± 12.0
		Population cohort study, mean follow-up: 4.0 years	PPI use H2RA use	2765 2765	35.9 35.9	56.0 ± 11.6 55.7 ± 11.0
Lin et al., 2021, Taiwan[21]	Longitudinal Health Insurance Database 2000 (LHID)	Population cohort study, max follow-up: 10 years	PPI use Non-use	494 6711	NA 42.9	NA 55.0 ± 15.7
			PPI use	494		55.0 ± 15.7 (overall)

(Continues)

TABLE 1 (Continued)

Author, year, country	Data source	Study design, follow-up	Comparison	No. of study population	Women (%)	Age (mean)
		Population cohort study, max follow-up: 10 years	H2RA use	1679	42.9	
Ahn et al., 2022, Germany[9]	AOK Bayern	Population cohort study, median follow-up: 5 years	PPI use Non-use	674 544 2 023 632	55.0 47.0	62.8 ± 13.2 56.9 ± 12.4
			PPI use Non-use	674 544 2 023 632	55.0 47.0	62.8 ± 13.2 56.9 ± 12.4
			PPI use H2RA use	660 635 9457	55.0 55.8	62.7 ± 13.2 64.0 ± 12.7

[a]D:dexlansoprazole; D-L: dexrabeprazole; E:esomeprazole; L: lansoprazole; O:omeprazole; P:pantoprazole; R:rabeprazole.
[b]ROBINS-I tool: risk of bias tool to assess non-randomized studies of interventions.

TABLE 1 (Continued)

Author, year, country	Outcome, no. of cases	PPI[a]	Effect estimate (95% CI)	Controlled covariates	ROBINS-I risk of bias judgement[b]	ROBINS-I aim of study
Haenisch et al., 2015, Germany[57]	Dementia, 431	O,E, L,P, R,D	HR 1.36 (1.03–1.81)	Age, sex, education, ApoE4, depression, diabetes, stroke, ischaemic heart disease, polypharmacy and anticholinergic drug use	Serious	Starting and adhering
	Alzheimer's disease (as subgroup analysis), 260	O,E, L,P, R,D	HR 1.44 (1.01–2.06)	Same as above excluding anticholinergic drug use	Serious	Starting and adhering
Gomm et al., 2016, Germany[11]	Dementia, 29 510	O,E, L,P, R	HR 1.44 (1.36–1.53)	Age, sex, depression, diabetes, stroke, ischaemic heart disease, polypharmacy and anticholinergic drug use	Serious	Starting and adhering
Taipale et al., 2017, Finland[14]	Alzheimer's disease, 70 718	O,E, L,P, R	OR 1.03 (1.00–1.05): 3 years lag-window	Matched: Age, sex and region of residence adjusted: Cardiovascular disease (hypertension, coronary artery disease, chronic heart failure, chronic arrhythmia), diabetes, depression, stroke and number of drugs	Serious	Assignment
Tai et al., 2017, Taiwan[22]	Dementia, 707	NA	HR 1.22	Matched: Age, sex, propensity score and index year	Serious	Assignment

(Continues)

TABLE 1 (Continued)

Author, year, country	Outcome, no. of cases	PPI[a]	Effect estimate (95% CI)	Controlled covariates	ROBINS-I risk of bias judgement[b]	ROBINS-I aim of study
			(1.05–1.42)	Adjusted: Age, sex, urbanization, Charlson's comorbidity index score, Comorbidities (diabetes, hyperlipidaemia, hypertension, depression, ischaemic heart disease, cerebral vascular disease) and medications (anticoagulant agents, antiplatelet agents, antidiabetic agents, antihypertension agents, statin, NSAIDs)		
Gray et al., 2017, USA[12]	Dementia, 827	O,P, E,L, R	HR 1.14 (0.82–1.60): 1 year lag-window	Age, study cohort, sex, education, hypertension, diabetes mellitus, smoking, stroke, coronary heart disease, body mass index, exercise, self-rated health, depression, gait speed, difficulties with activities of daily living, hospitalizations and exposure to nonsteroidal anti-inflammatory medications and anticholinergics	Serious	Starting and adhering
	Alzheimer's disease (as subgroup analysis), 670	O,P, E,L, R	HR 1.15 (0.80–1.67): 1 year lag-window	Same as above	Serious	Starting and adhering
Hwang et al., 2018, South Korea[51]	Dementia, 1297	NA	HR 1.02 (0.65–1.60): 3 year lag-window	Age, sex, BMI, smoking status, alcohol drinking, physical activity, type 2 diabetes, hypertension, hyperlipidaemia, aspirin use, NSAIDs use, socioeconomic status by quartiles of insurance premium and Charlson comorbidity index score	Serious	Assignment
Imfeld et al., 2018, UK[13]	Alzheimer‘s disease, 25 811	O,E, L,P, R	OR 0.85 (0.82–0.89)	BMI, smoking status, Charlson comorbidity index score, recent use of SSRIs/SNRIs and concomitant use of histamine-2 receptor antagonists	Serious	Assignment
	Vascular dementia, 15 218	O,E, L,P, R	OR 0.90 (0.85–0.95)	Same as above	Serious	Assignment
Park et al., 2019, South Korea[60]	Dementia, 6223	O,E, L,P, R,D	IRR 1.01 (0.96–1.06): 1 year lag-window	Matched: Propensity score (age, gender, insurance type, polypharmacy, previously used medication) Adjusted: Propensity score, (antidepressant, antipsychotics and benzodiazepine) and comorbidities (stroke, depression and diabetes) Medications (antidepressant, antipsychotics, anticholinesterase and Z-drug) and	Serious	Assignment

(Continues)

TABLE 1 (Continued)

Author, year, country	Outcome, no. of cases	PPI[a]	Effect estimate (95% CI)	Controlled covariates	ROBINS-I risk of bias judgement[b]	ROBINS-I aim of study
				comorbidities (ischaemic heart disease, stroke, depression and diabetes)		
Chen et al., 2020, Taiwan[10]	Dementia, 3720	O,E, L,P, R	HR 1.42 (1.07–1.84): 1 year lag-window	Matched for sex, age, index year, and Charlson comorbidity index, adjusted for sex, age, index year, Charlson comorbidity index, numbers of annual outpatient visits and use of co-medications, including non-steroidal anti-inflammatory drugs and aspirin, and use of H2RAs	Moderate	Starting and adhering
Torres-Bondia et al., 2020, Spain[20]	Alzheimer's dementia (as subgroup analysis), 1125	O,E, L,P, R	OR 1.06 (0.93–1.21): 5 year lag-window	Age, sex, hypertension, diabetes, dyslipidaemia	Critical	Assignment
Wu et al., 2020, Taiwan[23]	Dementia, 130	O,E, L,P, R,D, D-L	HR 0.72 (0.51–1.03)	Propensity score matching: Age, sex, comorbidity (hypertension, diabetes, coronary artery disease, hyperlipidaemia, gout, stroke, asthma, chronic renal failure, depression) Adjusted: Annual ambulatory visit times, depression, peptic ulcer and gastroesophageal reflux disease	Serious	Assignment
	Dementia, 140	O,E, L,P, R,D, D-L	HR 0.82 (0.58–1.17)	Same as above	Serious	Assignment
Lin et al., 2021, Taiwan[21]	Dementia, 347	O,E, L,P, R,D	HR 1.836 (1.345–2.507)	Matched: Age, sex and index Date adjusted: Age, sex, hypertension, stroke, hyperlipidaemia, atherosclerosis, alcohol abuse, depression and use of drug (anti-Parkinson, antithrombotics, antipsychotics, benzodiazepines, antidepressants, antiarrhythmics, statins)	Serious	Assignment
	Dementia, 176	O,E, L,P, R,D	HR 1.462 (1.038–2.057)	Same as above	Serious	Assignment
Ahn et al., 2022, Germany[9]	Dementia, 56 576	O,E, L,P, R,D	HR 1.56 (1.50–1.63): 1 year lag-window	Age, sex, nationality, hospital admission history, history of obesity, diabetes, hypertension, heart disease, peripheral vascular disease, coagulopathy, chronic pulmonary disease, cancer, depression, abuse of substances, diseases that may causing dementia, cerebrovascular disease,	Moderate	Starting and adhering

TABLE 1 (Continued)

Author, year, country	Outcome, no. of cases	PPI[a]	Effect estimate (95% CI)	Controlled covariates	ROBINS-I risk of bias judgement[b]	ROBINS-I aim of study
				inflammation, infection or injury of the nervous system, Use of medication: Antidiabetics, antihypertensives, statins, clopidogrel, anticholinergics, anti-inflammatory drugs, corticosteroids, antidepressants and psycholeptics		
	Alzheimer's disease (as subgroup analysis), 9032	O,E, L,P, R,D	HR 1.32 (1.23–1.42): 1 year lag-window	Same as above	Moderate	Starting and adhering
	Dementia, 29 388	O,E, L,P, R,D	HR 0.93 (0.85–1.01): 1 year lag-window	Same as above	Moderate	Assignment

[a]D:dexlansoprazole; D-L: dexrabeprazole; E:esomeprazole; L: lansoprazole; O:omeprazole; P:pantoprazole; R:rabeprazole.
[b]ROBINS-I tool: risk of bias tool to assess non-randomized studies of interventions.

an upper–lower bounding factor approach to selection bias to determine the strength of selection on the relative risk scale that would be necessary to explain away the mean relative risk.[32,36]

To assess whether the exclusion of the study with critical risk of bias altered the results of the meta-analyses, we re-performed the meta-analyses, including all eligible studies with any level of risk of bias.

We performed the analysis using R (version 4.1.0, Foundation for Statistical Computing, Vienna, Austria) using the E-value, meta, metaphor, metasens, MetaUtility and dmetar packages.

3 | RESULTS

3.1 | Systematic review and qualitative assessment

Our search strategy identified 3162 articles of which 1237 were excluded as duplicate publications and a further 1888 were excluded after the title and abstract review (Figure 1). A manual search of the bibliographies identified no other relevant publications. The remaining 39 articles underwent a full-text review, after which 25 were excluded for the reasons described in Figure 1. Studies with cross-sectional/case–control design[37–39] and a study that compared the risk of dementia in short-term PPI users and long-term PPI users[40] did not fit our protocol. Eight studies did not present dementia as an outcome but only reported a combined outcome of dementia plus mild cognitive impairment or cognitive function.[41–48] Another study that provided effect estimates without variances or 95% CIs[49] and one that used PPIs as comparator to assess cognitive decline[50] were not incorporated in our systematic review.

For the 14 eligible studies, we assessed the risk of bias using the ROBINS-I tool for observational studies and RoB 2 tool for an RCT. Details of the assessments are provided in Tables S1 and S2, respectively. We excluded a Spanish observational study and the RCT that were judged to have critical/high risk of bias from our quantitative synthesis. In total, nine cohorts from eight publications were included in the primary analysis to compare the risk of all-cause dementia in PPI users and non-users. Five cohorts from five publications were incorporated in a sub-analysis restricted to Alzheimer's disease. Three cohorts from three publications were included in the secondary analysis to compare the risk of dementia in PPI and H2RA users.

A total of 3 302 778 individuals were included in our primary analysis. There were 839 940 PPI users and 2 462 838 non-users. Overall, 204 108 (6.2%) individuals were diagnosed with dementia showing discrepancies in incidence rates between studies. The studies by Hwang et al.[51] and Ahn et al.[9] presented low incidence rates of 1.9% and 2.1%, respectively. However, other studies showed dementia as a common outcome (incidence rate range = 19.9%–50.0%). Among the nine included cohorts, two were conducted in Asia, six in Europe and one in the United States. The quality of the studies assessed by the ROBINS-I tool was moderate for two studies and serious for seven studies. The age ranges of study participants were presented in different ways across the studies, that is, mean, median or

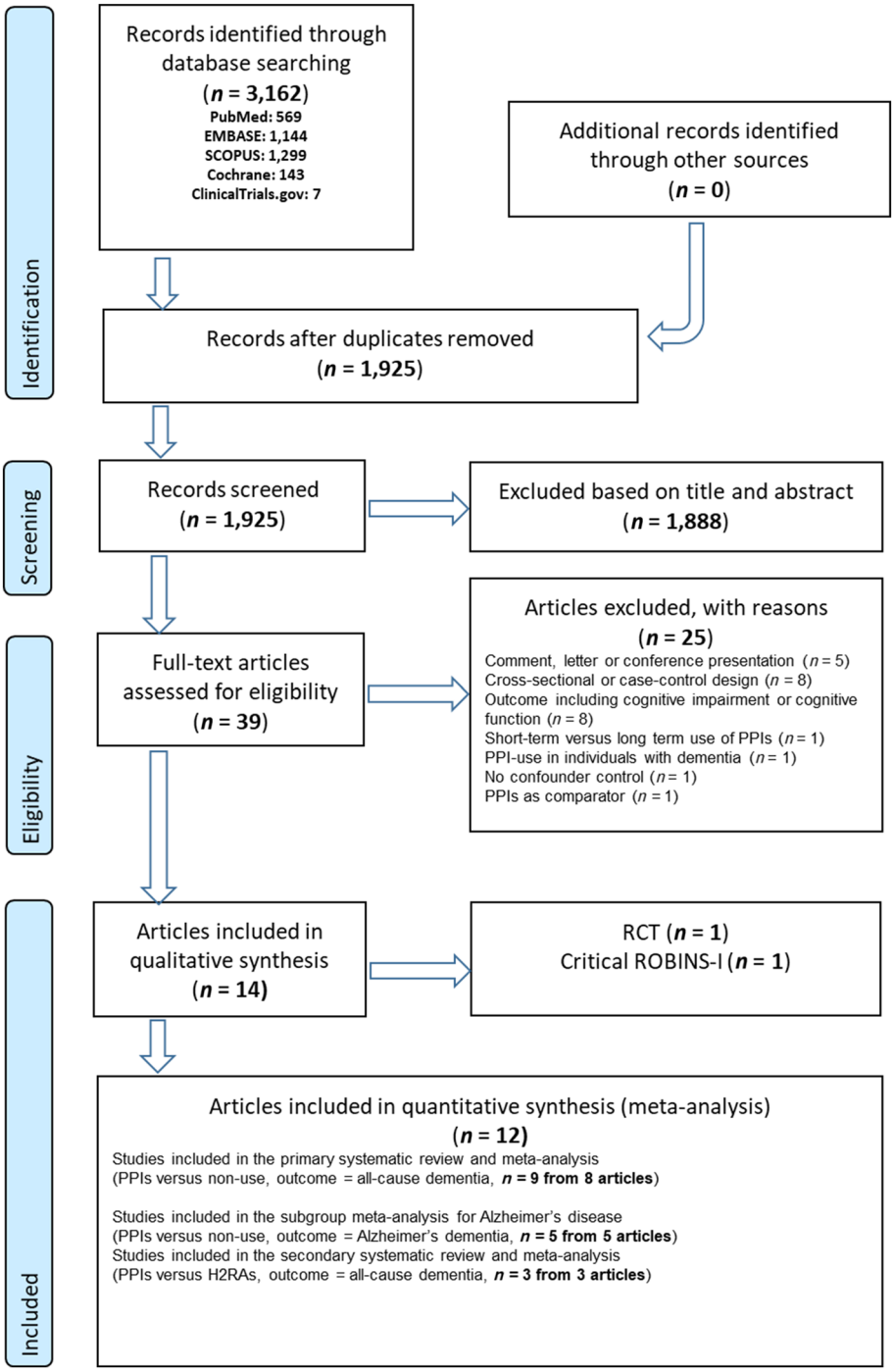

FIGURE 1 Flowchart of studies selected for systematic review and meta-analysis

minimum. Detailed characteristics of the included studies are shown in Table 1.

3.2 | Meta-analysis

The primary meta-analysis provided no evidence for an association of PPI intake *vs.* non-intake and all-cause dementia (RR = 1.16; 95% CI = 1.00; 1.35) (Figure 2). There was substantial heterogeneity between the studies (Cochran Q test $P < .0001$, $I^2 = 99\%$). Based on the point and τ^2 estimates from the random-effects model, we estimated that 61.6% (95% CI = 54.5%; 68.8%) and 42.0% (95% CI = 36.8%; 47.2%) of all effect estimates would have RRs above 1.1 and 1.2, respectively. We further estimated that 20.1% (5.6%; 34.6%) of all studies would have RRs smaller than 1.0. The 95% prediction interval for the RR was 0.72–1.86; this additionally suggests, with high probability, that a new RR estimated from the population will include 1. When the meta-analysis was stratified by study quality, study design, geographic region, assessed effect, type of outcome data, the minimum age at baseline and study size, we found a difference in the

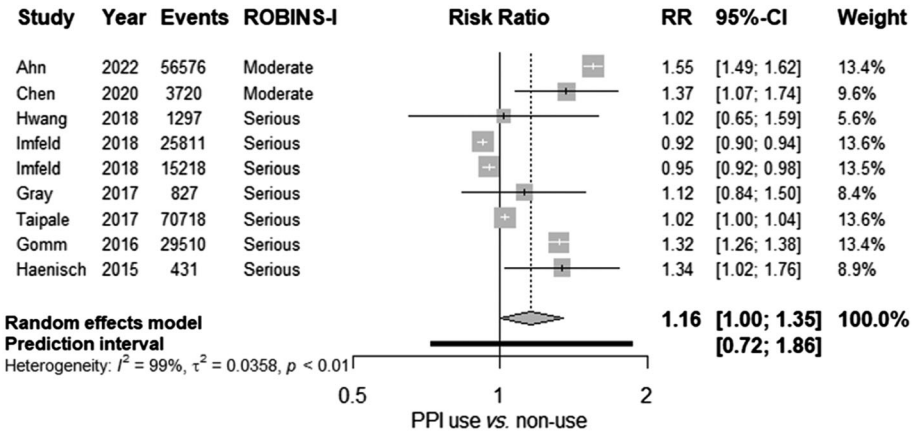

FIGURE 2 Forest plot from random-effects meta-analysis of studies on the risk of dementia and the use of proton pump inhibitors compared to non-use. Study-risk ratios (RRs) are represented by squares (with their 95% confidence interval [CI] as error bars).RRs were combined using a Hartung–Knapp–Sidik–Jonkman random-effects model, yielding a mean RR and its 95% confidence interval and 95% prediction interval. Two-sided *P*-value for between-study heterogeneity based on Cochran Q statistic.

TABLE 2 Subgroup meta-analyses of PPI intake and dementia

Subgroup	No. of studies	RR (95% CI)	I^2 (%)	τ^2	P^b
Study quality (ROBINS-I)[a]					<0.0001
Moderate	2	1.54 (1.12–2.13)	2.9	0.0002	
Serious	7	1.07 (0.93–1.24)	97.4	0.0217	
Study design					<0.0001
Prospective cohort	6	1.36 (1.19–1.55)	84.7	0.0094	
Nested case–control	3	0.96 (0.84–1.10)	96.4	0.0029	
Geographic region					0.8158
Asia	2	1.26 (0.23–6.76)	22.1	0.0095	
Europe	6	1.15 (0.92–1.45)	99.2	0.0460	
United States	1	1.15 (0.92–1.45)	–	–	
Assessed effect					<0.0001
Assignment effect	4	0.97 (0.89–1.05)	94.6	0.0028	
Starting and adhering effect	5	1.38 (1.20–1.58)	86.9	0.0083	
Type of outcome data					<0.0001
Claims data	4	1.39 (1.14–1.70)	89.9	0.0096	
By diagnosis protocol	5	0.99 (0.87–1.14)	93.6	0.0054	
Minimum age at baseline (years)					0.6993
<65	3	1.20 (0.65–2.24)	99.4	0.0597	
≥65	6	1.13 (0.93–1.37)	97.8	0.0306	
Number of events					0.3719
<10 000	4	1.25 (1.03–1.53)	0.0	0.0000	
≥10 000	5	1.13 (0.85–1.50)	99.4	0.0512	

[a]ROBINS-I tool: risk of bias tool to assess non-randomized studies of interventions.
[b]Two-sided *P*-value was calculated using Q test for subgroup differences.

result with regard to study quality, study design, assessed effect and type of outcome data (all Cochran Q *P*-values < 0.0001) (Table 2).

In the sub-analysis including 3 109 769 individuals, we did not identify a difference in the risk of Alzheimer's disease between PPI users and non-users (RR = 1.15, 95% CI = 0.89; 1.50) (Figure 3). Likewise, the secondary random-effects meta-analysis of 847 399 participants showed no association between dementia risk and PPI use *vs.* H2RA use (RR = 1.03, 95% CI = 0.66; 1.62) (Figure 4).

3.3 | Sensitivity and bias analysis

We performed several sensitivity and bias analyses for our primary analysis that compared the dementia risk between PPI users and non-users. There was no evidence for publication bias using analysis of funnel plot asymmetry by the Egger test (*P* = .32) (Figure S1). We used the trim-and-fill method, the Copas selection model and Rücker's shrinkage procedure to examine small-study bias (Table S3). The trim-

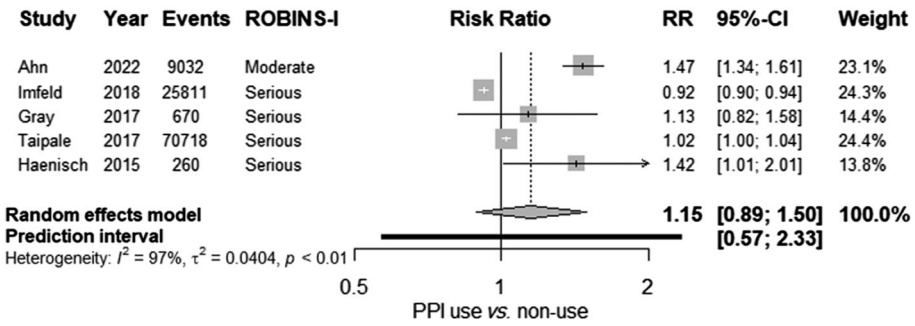

FIGURE 3 Forest plot from random-effects meta-analysis of studies on the risk of Alzheimer's disease and the use of proton pump inhibitors compared to non-use.Study-risk ratios (RRs) are represented by squares (with their 95% confidence interval [CI] as error bars).RRs were combined using a Hartung–Knapp–Sidik–Jonkman random-effects model, yielding a mean RR and its 95% confidence interval and 95% prediction interval. Two-sided *P*-value for between-study heterogeneity based on Cochran Q statistic.

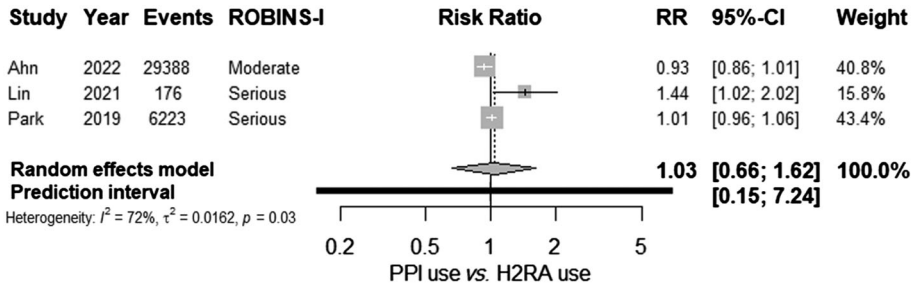

FIGURE 4 Forest plot from random-effects meta-analysis of studies on the risk of dementia and the use of proton pump inhibitors compared to histamine-2 receptor antagonists use.Study-risk ratios (RRs) are represented by squares (with their 95% confidence interval [CI] as error bars). RRs were combined using a Hartung–Knapp–Sidik–Jonkman random-effects model, yielding a mean RR and its 95% confidence interval and 95% prediction interval. Two-sided *P*-value for between-study heterogeneity based on Cochran Q statistic.

and-fill method mirrored five cohorts included in a pooled analysis of nine cohorts. The mean RR and 95% CI from the analysis using the trim-and-fill method agreed with our primary finding, but the results by the Copas selection model (RR = 1.16, 95% CI = 1.02; 1.32) and Rücker's shrinkage procedure (RR = 1.15, 95% CI = 1.13; 1.17) showed discrepancies. The adjusted point estimates by those two methods were comparable, but the 95% CI was much narrower when Rücker's shrinkage procedure was applied. The heterogeneity estimated by Rücker's shrinkage method (G^2) was 97.4%. The plots from the Copas selection model did not show that the estimated treatment effect decreases if the degree of selection increases, nor presented evidence for unexplained selection, as indicated in a plot not crossing the $P = .1$ line (Figure S2). In our leave-one-out analyses (Table S4), we did not find a remarkable difference in effect estimate or heterogeneity by omitting one study at a time. However, the Baujat plot identified that the study by Imfeld et al.[13] had the largest influence on the effect estimate and the study by Ahn et at.[9] made the biggest contribution to overall heterogeneity (Figure S3). In the analysis excluding three detected outliers, the recalculated random-effect showed an increased dementia risk by PPI use (RR = 1.19, 95% CI = 1.03; 1.38) (Figure S4).

We performed additional bias analyses restricted to the studies with moderate risk of bias ($n = 2$), that is, studies of better quality. In the analysis for unobserved confounding, an unobserved confounder would have to be associated with a 2.45-fold increase in the risk of PPI intake and dementia, above and beyond the measured confounders to explain the mean RR of 1.54 (95% CI = 1.12; 2.13). To shift the lower CI limit (i.e., 1.12) to the null, the unobserved confounder would need to be related with an RR of 1.49 with PPI intake and dementia. By calculating the lower bounding factor $\sqrt{(1/1.54)} + \sqrt{(1/1.54 - \sqrt{(1/1.54)})} = 1.78$, we concluded that unaccounted for selection variables would have to be related to PPI use and dementia with a relative risk of 1.78 to produce an observed RR of 1.54 if the true RR were equal to 1.0.

In the last sensitivity analysis, where we repeated meta-analyses including the study with critical risk of bias, no noticeable differences were observed in the risk of overall dementia and Alzheimer's disease, showing an RR of 1.15 (95% CI = 1.00;1.31) and an RR of 1.13 (95% CI = 0.93; 1.38), respectively (Figures S5 and S6).

4 | DISCUSSION

The present meta-analysis including 3 302 778 individuals from nine observational cohorts did not indicate that PPI use increases the risk of dementia. PPIs are among the most widely used medications and

are often prescribed to older adults.[4] Therefore, any clinically meaningful effect of PPI intake on dementia risk can bring significant public health implications. Compared to previous systematic reviews and meta-analyses, one recently published claims data study[9] was additionally included in our meta-analysis. To our knowledge, this is the first meta-analysis to include studies with prospective designs assessing the association of PPI use and the incidence of dementia, restricting the outcome to the incidence of dementia rather than additionally including mild cognitive impairment[42,43,46] or deteriorated cognitive function scores.[37] The present systematic review is also the first to apply the ROBINS-I tool.

A previous systematic review and meta-analysis by Zhang et al.[16] summarized six available prospective cohorts on the association of PPI intake and increased dementia risk. This meta-analysis provided a mean HR of 1.29 (1.12; 1.49). However, one study[44] which was included in this meta-analysis had MMSE and clock drawing test (CDT) scores as outcomes instead of a diagnosis of dementia as a binary outcome.

By comparison, a pooled analysis of six different cohorts[52] reported a mean HR of 1.16 (95% CI = 0.86; 1.47). However, the Taiwanese study by Tai et al.,[22] which presented an increased risk of dementia by PPI use, was excluded from this analysis without proper explanation, although it had been included in previous meta-analyses.[16,53] Instead, the authors included the RCT by Moayyedi et al.[24] in their meta-analysis. This RCT was also part of the latest meta-analysis.[15] However, we judged the risk of bias of the RCT as high (Table S2) and did not include it in our quantitative synthesis.

A recent meta-analysis with five studies[54] found a pooled HR of 1.17 (95% CI = 0.91; 1.49). The authors assessed the risk of bias of each study using the risk of bias assessment tool for non-randomized studies (RoBANS).[55] They included the studies with a high risk of confounding in quantitative synthesis, while we used the ROBINS-I tool for the risk of bias judgement and excluded the study with critical risk of bias as the developers of the tool recommended (Table S1).[17]

We did not consider mild cognitive impairment as an outcome of interest based on a meta-analysis that assessed reversion rates from mild cognitive impairment to normal cognition.[56] It showed an overall reversion rate of approximately 18% depending on subject-based factors such as recovery from illness, differing measurements and variations in cut-off scores that were used to diagnose mild cognitive impairment. Therefore, the study by Goldstein et al.[43] was not included in our analysis, although it had frequently been included in previous meta-analyses on this topic. For the same reason, two very recent studies from Israel[46] and the UK[42] were not eligible for our analysis.

Concerns about our meta-analysis include the considerable heterogeneity between studies and small-study bias. Statistical heterogeneity and small-study effect are known as two major issues affecting the validity of meta-analyses.[34] Although heterogeneity in our primary analysis is substantial ($I^2 = 99\%$), it is consistent with the ones from previous meta-analyses by Wang et al. ($I^2 = 98.5\%$),[15] Khan et al. ($I^2 = 96\%$),[53] Desai et al. ($I^2 = 93\%$)[52] and Yoon et al. ($I^2 = 91\%$).[54] If the studies become very large, the sampling error tends to null and I^2 comes close to 1. On the other hand, a description of the underlying between-study variability can best be obtained by estimating the between-study variance, τ^2.[29] In our primary analysis, τ^2 was 0.0358, which was lower than that observed in another big meta-analysis by Khan et al. ($\tau^2 = 0.07$).[53] Other previous meta-analyses did not provide τ^2. When it comes to the quantified heterogeneity by Rücker's method (G^2), it was 97.4%, which means that there is still unexplained variance after adjustment for small-study bias.[34] We assume that the heterogeneity was caused by the large studies that had very different point estimates, and it was confirmed by the Baujat plot for detecting outliers (Figure S3).[9,13] After excluding the outliers that had a substantial influence on the overall result or overall heterogeneity in the influence analysis, the heterogeneity became smaller ($I^2 = 96\%$, $\tau^2 = 0.0149$) (Figure S4).

Due to the substantial heterogeneity, we estimated the metrics proposed by Mathur and VanderWeele.[30] It showed that 61.6% of all true RRs would be larger than 1.1, and 42.0% of all true RRs would be larger than 1.2. In the leave-one-out analysis, no notable changes in heterogeneity or effect estimate were observed (Table S4). Interestingly, the heterogeneity differed remarkably by stratification in the subgroup analysis (Table 2). In particular, τ^2 was close to 0 in subgroups when the studies were stratified by study design (prospective cohort and nested case–control) and assessed effect (assignment effect, starting and adhering effect). More studies are necessary to investigate the source of the heterogeneity.

Concerning the small-study effect, it cannot easily be separated from heterogeneity. Instead, it can be interpreted as a special case of heterogeneity.[33,34] We performed several sensitivity analyses to adjust for small-study bias. We could not see the increased dementia risk by PPI intake (RR = 0.97, 95% CI = 0.82; 1.15) when we used the trim-and-fill method. However, we found an increased risk of dementia by PPI intake when the Copas selection model (RR = 1.16, 95% CI = 1.02; 1.32) and Rücker's shrinkage procedure (RR = 1.15, 95% CI = 1.13; 1.17) adjusted the small-study bias. It is known that the Copas selection model and Rücker's shrinkage method perform better with regard to the properties of parameter estimation.[33] Therefore, these discrepancies deserve to capture more attention. In fact, we could observe an increased risk of dementia by PPI use when we restricted the analysis to the studies with better quality (ROBINS-I: moderate), better study design (prospective cohort study) or effect of long-term use of PPIs (starting and adhering effect) (Table 2). Besides, an influence analysis that was used to recalculate the random-effect estimate excluding the outliers presented an increased dementia risk by PPI use (Figure S4).

The limitations of our meta-analysis derive from the design and analytic methods of each non-randomized observational study. Bias arises from the selection of participants if enrolment is influenced by the exposure and the outcome of interest. For example, some studies did not clearly show whether the exposure to PPI was new use.[11,13,14,57] Therefore, we could not rule out prevalent user bias that could have attenuated true effect sizes. Individuals were often excluded instead of being censored due to only one assured dementia diagnosis record[11] or diagnosis during the lag window.[14,51] Also,

several studies excluded individuals with cancer records.[10,22,23] Despite the possible selection bias, only one study[9] used inverse probability weighting as the ROBINS-I tool[17] recommended strategy to adjust for the bias.

The presence of competing risk of death also could have induced bias in the context of survival, that is, an underestimation of dementia incidence.[58] In fact, the mean or median age of participants from six cohorts[11–14,57] in our primary analysis was 75 years or older, and four of them reported no evidence of increased dementia risk by PPI use.[12–14] In dementia cohort studies, truncation of follow-up by death could introduce interval censoring, which occurs because the diagnosis of dementia can only be made at follow-up visits, and it could weaken the effect of the exposure to PPIs on the dementia risk. In the literature, it has been pointed out that the increased age of participants apparently causes attenuation of the effect of risk factors, or the association even becomes protective.[58]

Another issue is a bias due to confounding by controlling for post-intervention variables that could have been affected by the intervention.[13,14] Moreover, lifestyle factors such as smoking status[13,14,51] or genetic factors such as APOE-ε4[57] were partially controlled, although these are accepted dementia risk factors. Due to the possible bias by unmeasured confounding, we examined the E-value, restricting the analysis to studies of better quality ($n = 2$). We obtained an E-value of 2.45, which indicates that an unmeasured confounder would have to be associated with a 2.45-fold increase in the risk of dementia and PPI intake, above and beyond the measured confounders to explain the mean RR of 1.54 (95% CI = 1.12; 2.13). To shift the lower CI limit (i.e., 1.12) to the null, the unobserved confounder would need to be related to an RR of 1.49 with PPI intake and dementia. In this case, the estimate seems moderately robust, but substantial confounder associations with PPI intake and dementia could potentially move the confidence interval to include 1.[32]

Although we found conflicting results in the primary analysis and sensitivity analyses, we tried to mitigate the risk of bias in our analysis by conducting a structured risk of bias assessment and excluding the studies with critical or high risk from the analysis. Unfortunately, there were only two studies with better quality (ROBINS-I: moderate), which makes it hard to restrict the analyses to studies with a higher quality only. This problem was also discussed in the recent umbrella review on the adverse health outcomes by PPI intake.[7] To our knowledge, nevertheless, this is the largest meta-analysis on the association between PPI use and the risk of dementia, and several rigorous statistical approaches were used for sensitivity analyses.

5 | CONCLUSION

In conclusion, this systematic review and meta-analysis provided no clear evidence that PPI use raises the risk of dementia. Yet, this does not mean that there is no clinical implication of PPI use on the risk of dementia. PPI therapy should always be provided with a planned treatment strategy according to appropriate indications and guideline recommendations. Due to the discrepancies between the primary and sensitivity analyses and the lack of well-performed research, better-designed subsequent studies are warranted for more reliable evidence.

ACKNOWLEDGEMENTS

Open Access funding enabled and organized by Projekt DEAL.

COMPETING INTERESTS

The authors declare no competing interests.

CONTRIBUTORS

E.K., I.R. and N.A. developed search strategies and searched the literature. I.R. and N.A. developed the protocol, were involved in the design and quality assessment, and selected studies, extracted data and developed the initial drafts of the manuscript. N.A., M.N. and S.B. conducted statistical analysis. F.G., A.G., M.T., R.G., C.M. and J.L. reviewed the subsequent draft in preparation of the final draft of the manuscript. All authors read and approved the final draft of the manuscript.

REGISTRATION AND PROTOCOL

The study protocol was registered at PROSPERO (Registration: CRD42020197968), and the study was conducted according to the protocol except for the use of the credibility ceiling method due to an ongoing debate on its fundamental statistical flaws.[59]

DATA AVAILABILITY STATEMENT

All data generated or analysed during this study are included in this published article and its supplementary information file.

ORCID

Nayeon Ahn https://orcid.org/0000-0003-4414-114X
Michael Nolde https://orcid.org/0000-0001-6893-7367

REFERENCES

1. GBD 2016 Dementia Collaborators. Global, regional, and national burden of Alzheimer's disease and other dementias, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol*. 2019;18(1):88-106. doi:10.1016/S1474-4422(18)30403-4
2. Luengo-Fernandez R, Leal J, Gray A. UK research spend in 2008 and 2012: comparing stroke, cancer, coronary heart disease and dementia. *BMJ Open*. 2015;5(4):e006648. doi:10.1136/bmjopen-2014-006648
3. Freedberg DE, Kim LS, Yang YX. The risks and benefits of long-term use of proton pump inhibitors: expert review and best practice advice from the American Gastroenterological Association. *Gastroenterology*. 2017;152(4):706-715. doi:10.1053/j.gastro.2017.01.031
4. Rückert-Eheberg IM, Nolde M, Ahn N, et al. Who gets prescriptions for proton pump inhibitors and why? A drug-utilization study with claims data in Bavaria, Germany, 2010–2018. *Eur J Clin Pharmacol*. 2022;78(4):657-667. doi:10.1007/s00228-021-03257-z
5. Ahrens D, Behrens G, Himmel W, Kochen MM, Chenot JF. Appropriateness of proton pump inhibitor recommendations at hospital discharge and continuation in primary care. *Int J Clin Pract*. 2012;66(8):767-773. doi:10.1111/j.1742-1241.2012.02973.x
6. Jaynes M, Kumar AB. The risks of long-term use of proton pump inhibitors: a critical review. *Ther Adv Drug Saf*. 2018;10:2042098618809927.

7. Veettil SK, Sadoyu S, Bald EM, et al. Association of proton-pump inhibitor use with adverse health outcomes: a systematic umbrella review of meta-analyses of cohort studies and randomised controlled trials. *Br J Clin Pharmacol*. 2022;88(4):1551-1566. doi:10.1111/bcp.15103
8. Kumar R, Kumar A, Nordberg A, Långström B, Darreh-Shori T. Proton pump inhibitors act with unprecedented potencies as inhibitors of the acetylcholine biosynthesizing enzyme—a plausible missing link for their association with incidence of dementia. *Alzheimers Dement*. 2020;16(7):1031-1042. doi:10.1002/alz.12113
9. Ahn N, Nolde M, Günter A, et al. Emulating a target trial of proton pump inhibitors and dementia risk using claims data. *Eur J Neurol*. 2022;29(5):1335-1343. doi:10.1111/ene.15284
10. Chen LY, Lin HJ, Wu WT, et al. Clinical use of acid suppressants and risk of dementia in the elderly: a pharmaco-epidemiological cohort study. *Int J Environ Res Public Health*. 2020;17(21):8271. doi:10.3390/ijerph17218271
11. Gomm W, von Holt K, Thomé F, et al. Association of proton pump inhibitors with risk of dementia: a pharmacoepidemiological claims data analysis. *JAMA Neurol*. 2016;73(4):410-416. doi:10.1001/jamaneurol.2015.4791
12. Gray SL, Walker RL, Dublin S, et al. Proton pump inhibitor use and dementia risk: prospective population-based study. *J Am Geriatr Soc*. 2018;66(2):247-253. doi:10.1111/jgs.15073
13. Imfeld P, Bodmer M, Jick SS, Meier CR. Proton pump inhibitor use and risk of developing Alzheimer's disease or vascular dementia: a case–control analysis. *Drug Saf*. 2018;41(12):1387-1396. doi:10.1007/s40264-018-0704-9
14. Taipale H, Tolppanen AM, Tiihonen M, Tanskanen A, Tiihonen J, Hartikainen S. No association between proton pump inhibitor use and risk of Alzheimer's disease. *Am J Gastroenterol*. 2017;112(12):1802-1808. doi:10.1038/ajg.2017.196
15. Wang H, Tian L, Yan X. No association between acid suppressant use and risk of dementia: an updated meta-analysis. *Eur J Clin Pharmacol*. 2022;78(3):375-382. doi:10.1007/s00228-021-03248-0
16. Zhang Y, Liang M, Sun C, et al. Proton pump inhibitors use and dementia risk: a meta-analysis of cohort studies. *Eur J Clin Pharmacol*. 2020;76(2):139-147. doi:10.1007/s00228-019-02753-7
17. Sterne JA, Hernán MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ*. 2016;355:i4919. doi:10.1136/bmj.i4919
18. Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ*. 2019;366:l4898.
19. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71.
20. Torres-Bondia F, Dakterzada F, Galván L, et al. Proton pump inhibitors and the risk of Alzheimer's disease and non-Alzheimer's dementias. *Sci Rep*. 2020;10(1):21046. doi:10.1038/s41598-020-78199-0
21. Lin H-C, Huang K-T, Lin H-L, et al. Use of gastric acid-suppressive agents increases the risk of dementia in patients with upper gastrointestinal disease: a population-based retrospective cohort study. *PLoS ONE*. 2021;16(3):e0249050. doi:10.1371/journal.pone.0249050
22. Tai SY, Chien CY, Wu DC, et al. Risk of dementia from proton pump inhibitor use in Asian population: a nationwide cohort study in Taiwan. *PLoS ONE*. 2017;12(2):e0171006. doi:10.1371/journal.pone.0171006
23. Wu CL, Lei WY, Wang JS, Lin CE, Chen CL, Wen SH. Acid suppressants use and the risk of dementia: a population-based propensity score-matched cohort study. *PLoS ONE*. 2020;15(11):e0242975. doi:10.1371/journal.pone.0242975
24. Moayyedi P, Eikelboom JW, Bosch J, et al. Safety of proton pump inhibitors based on a large, multi-year, randomized trial of patients receiving rivaroxaban or aspirin. *Gastroenterology*. 2019;157(3):682-691.e2. doi:10.1053/j.gastro.2019.05.056
25. Lash TL, VanderWelle TJ, Haneuse S, Rothman KL. *Modern epidemiology*. 4thed. Philadelphia, PA: Wolters Kluwer; 2021.
26. VanderWeele TJ. Optimal approximate conversions of odds ratios and hazard ratios to risk ratios. *Biometrics*. 2020;76(3):746-752. doi:10.1111/biom.13197
27. Langan D, Higgins JPT, Jackson D, et al. A comparison of heterogeneity variance estimators in simulated random-effects meta-analyses. *Res Synth Methods*. 2019;10(1):83-98. doi:10.1002/jrsm.1316
28. IntHout J, Ioannidis JP, Rovers MM, Goeman JJ. Plea for routinely presenting prediction intervals in meta-analysis. *BMJ Open*. 2016;6(7):e010247. doi:10.1136/bmjopen-2015-010247
29. Rücker G, Schwarzer G, Carpenter JR, Schumacher M. Undue reliance on I(2) in assessing heterogeneity may mislead. *BMC Med Res Methodol*. 2008;8(1):79. doi:10.1186/1471-2288-8-79
30. Mathur MB, VanderWeele TJ. Meta-regression methods to characterize evidence strength using meaningful-effect percentages conditional on study characteristics. *Res Synth Methods*. 2021;12(6):731-749. doi:10.1002/jrsm.1504
31. Schmid CH, Stijnen T, White IR. *Handbook of meta-analysis*. Boca Raton, FL: CRC Press; 2021.
32. Mathur MB, VanderWeele TJ. Methods to address confounding and other biases in meta-analyses: review and recommendations. *Annu Rev Public Health*. 2022;43(1):19-35. doi:10.1146/annurev-publhealth-051920-114020
33. Schwarzer G, Carpenter JR, Rücker G. *Meta-analysis with R*. Cham, Switzerland: Springer International Publishing; 2015.
34. Rücker G, Schwarzer G, Carpenter JR, Binder H, Schumacher M. Treatment-effect estimates adjusted for small-study effects via a limit meta-analysis. *Biostatistics*. 2011;12(1):122-142. doi:10.1093/biostatistics/kxq046
35. Baujat B, Mahé C, Pignon JP, Hill C. A graphical method for exploring heterogeneity in meta-analyses: application to a meta-analysis of 65 trials. *Stat Med*. 2002;21(18):2641-2652. doi:10.1002/sim.1221
36. Smith LH, VanderWeele TJ. Bounding bias due to selection. *Epidemiology*. 2019;30(4):509-516. doi:10.1097/EDE.0000000000001032
37. Ahn N, Frenzel S, Wittfeld K, et al. Lack of association between proton pump inhibitor use and brain aging: a cross-sectional study. *Eur J Clin Pharmacol*. 2021;77(7):1039-1048. doi:10.1007/s00228-020-03068-8
38. Booker A, Jacob LE, Rapp M, Bohlken J, Kostev K. Risk factors for dementia diagnosis in German primary care practices. *Int Psychogeriatr*. 2016;28(7):1059-1065. doi:10.1017/S1041610215002082
39. de Souto Barreto P, Lapeyre-Mestre M, Mathieu C, et al. Prevalence and associations of the use of proton-pump inhibitors in nursing homes: a cross-sectional study. *J Am Med Dir Assoc*. 2013;14(4):265-269. doi:10.1016/j.jamda.2012.10.018
40. Huang ST, Tseng LY, Chen LK, Peng LN, Hsiao FY. Does long-term proton pump inhibitor use increase risk of dementia? Not really! Results of the group-based trajectory analysis. *Clin Pharmacol Ther*. 2019;106(3):616-622. doi:10.1002/cpt.1430
41. Clouston SAP, Shapira O, Kotov R, et al. Proton pump inhibitors and the risk of severe cognitive impairment: the role of posttraumatic stress disorder. *Alzheimers Dement (N Y)*. 2017;3(4):579-583. doi:10.1016/j.trci.2017.08.007
42. Cooksey R, Kennedy J, Dennis MS, et al. Proton pump inhibitors and dementia risk: evidence from a cohort study using linked routinely collected national health data in Wales, UK. *PLoS ONE*. 2020;15(9):e0237676. doi:10.1371/journal.pone.0237676
43. Goldstein FC, Steenland K, Zhao L, Wharton W, Levey AI, Hajjar I. Proton pump inhibitors and risk of mild cognitive impairment and dementia. *J Am Geriatr Soc*. 2017;65(9):1969-1974. doi:10.1111/jgs.14956
44. Herghelegiu AM, Prada GI, Nacu R. Prolonged use of proton pump inhibitors and cognitive function in older adults. *Farmacia*. 2016;64:262-267.

45. Lochhead P, Hagan K, Joshi AD, et al. Association between proton pump inhibitor use and cognitive function in women. *Gastroenterology*. 2017;153(4):971-979.e4. doi:10.1053/j.gastro.2017.06.061
46. Weiss A, Gingold-Belfer R, Boltin D, et al. Chronic omeprazole use in the elderly is associated with decreased risk of dementia and cognitive decline. *Dig Liver Dis*. 2021;54(5):622-628. doi:10.1016/j.dld.2021.11.018
47. Wod M, Hallas J, Andersen K, García Rodríguez LA, Christensen K, Gaist D. Lack of association between proton pump inhibitor use and cognitive decline. *Clin Gastroenterol Hepatol*. 2018;16(5):681-689. doi:10.1016/j.cgh.2018.01.034
48. Wu B, Hu Q, Tian F, Wu F, Li Y, Xu T. A pharmacovigilance study of association between proton pump inhibitor and dementia event based on FDA adverse event reporting system data. *Sci Rep*. 2021;11(1):10709. doi:10.1038/s41598-021-90108-7
49. Welu J, Metzger J, Bebensee S, Ahrendt A, Vasek M. Proton pump inhibitor use and risk of dementia in the veteran population. *Fed Pract*. 2019;36(Suppl 4):S27-S31.
50. Wu CY, Xiong LY, Ouk M, et al. Gastric acid suppressants and cognitive decline in people with or without cognitive impairment. *Alzheimers Dement (N Y)*. 2022;8(1):e12243. doi:10.1002/trc2.12243
51. Hwang IC, Chang J, Park SM. A nationwide population-based cohort study of dementia risk among acid suppressant users. *Am J Geriatr Psychiatry*. 2018;26(11):1175-1183. doi:10.1016/j.jagp.2018.06.002
52. Desai M, Nutalapati V, Srinivasan S, et al. Proton pump inhibitors do not increase the risk of dementia: a systematic review and meta-analysis of prospective studies. *Dis Esophagus*. 2020;33(10):doaa041. doi:10.1093/dote/doaa041
53. Khan MA, Yuan Y, Iqbal U, et al. No association linking short-term proton pump inhibitor use to dementia: systematic review and meta-analysis of observational studies. *Am J Gastroenterol*. 2020;115(5):671-678. doi:10.14309/ajg.0000000000000500
54. Yoon KB, Bang CS, Kim JS. Proton-pump inhibitors and the risk of dementia: a systematic review and meta-analysis. *Korean J Helicobacter Up Gastrointest Res*. 2021;21(2):135-143. doi:10.7704/kjhugr.2020.0057
55. Kim SY, Park JE, Lee YJ, et al. Testing a tool for assessing the risk of bias for nonrandomized studies showed moderate reliability and promising validity. *J Clin Epidemiol*. 2013;66(4):408-414. doi:10.1016/j.jclinepi.2012.09.016
56. Canevelli M, Grande G, Lacorte E, et al. Spontaneous reversion of mild cognitive impairment to normal cognition: a systematic review of literature and meta-analysis. *J Am Med Dir Assoc*. 2016;17(10):943-948. doi:10.1016/j.jamda.2016.06.020
57. 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. doi:10.1007/s00406-014-0554-0
58. Weuve J, Proust-Lima C, Power MC, et al. Guidelines for reporting methodological challenges and evaluating potential bias in dementia research. *Alzheimers Dement*. 2015;11(9):1098-1109. doi:10.1016/j.jalz.2015.06.1885
59. Mathur MB, VanderWeele TJ. Controversy and debate on credibility ceilings. Paper 1: fundamental problems with the "credibility ceiling" method for meta-analyses. *J Clin Epidemiol*. 2020;127:208-210. doi:10.1016/j.jclinepi.2020.05.006
60. Park SK, Nam JH, Lee H, Chung H, Lee EK, Shin JY. Beyond uncertainty: negative findings for the association between the use of proton pump inhibitors and risk of dementia. *J Gastroenterol Hepatol*. 2019;34(12):2135-2143. doi:10.1111/jgh.14745

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Ahn N, Nolde M, Krause E, et al. Do proton pump inhibitors increase the risk of dementia? A systematic review, meta-analysis and bias analysis. *Br J Clin Pharmacol*. 2023;89(2):602-616. doi:10.1111/bcp.15583