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Association of Proton Pump Inhibitor Use With Incident Dementia and Cognitive Decline in Older Adults: A Prospective Cohort Study

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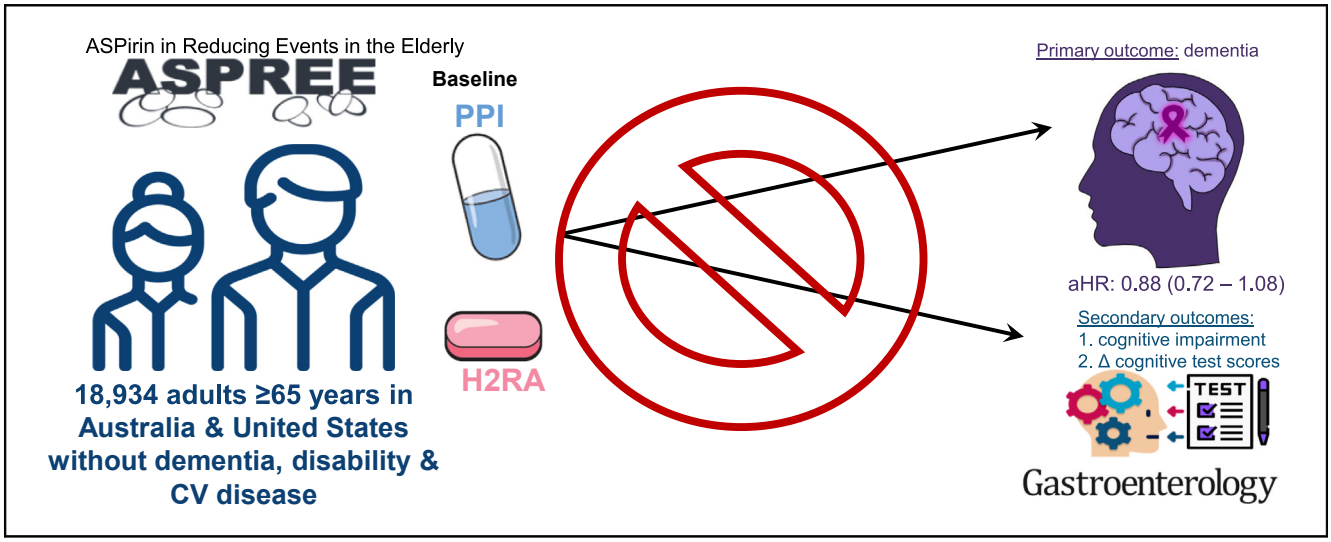

BACKGROUND & AIMS: Prior studies have suggested that proton pump inhibitor (PPI) use is associated with increased risk of dementia; however, these have been limited by incomplete assessment of medication use and failure to account for confounders. Furthermore, prior studies have relied on claims-based diagnoses for dementia, which can lead to misclassification. We investigated the associations of PPI and histamine-2 receptor antagonist (H2RA) use with dementia and cognitive decline. **METHODS:** We conducted a post hoc analysis of ASPirin in Reducing Events in the Elderly (ASPREE), a randomized trial of aspirin in the United States and Australia, including 18,934 community-based adults ≥65 years of all races/ethnicities. Baseline and recent PPI and H2RA use were determined according to review of medications during annual in-person study visits. Incident dementia was defined according to Diagnostic and Statistical Manual for Mental Disorders, Fourth Edition, criteria. Secondary endpoints include cognitive impairment, no dementia (CIND) and changes in cognition. Associations of medication use with dementia and CIND outcomes were examined using Cox proportional hazards models. Changes in cognitive test scores were examined using linear mixed-effects models. **RESULTS:** Baseline PPI use vs nonuse was not associated with incident dementia (multivariable hazard ratio, 0.88; 95% confidence interval, 0.72–1.08), CIND (multivariable hazard ratio, 1.00; 95% confidence interval, 0.92–1.09), or with changes in overall cognitive test scores over time (multivariable B, −0.002; standard error, 0.01; $P = .85$). Similarly, no associations were observed between H2RA use and all cognitive endpoints. **CONCLUSIONS:** In adults ≥65 years of age, PPI and H2RA use were not associated with incident dementia, CIND, or decline in cognition over time. These data provide reassurance about the safety of long-term use of PPIs among older adults.

Keywords: Proton Pump Inhibitors; Dementia; Pharmacoepidemiology; Cognition.

Proton pump inhibitors (PPIs) are among the most widely used medications worldwide.[1,2] They are used to treat acid-related upper gastrointestinal illnesses, including gastroesophageal reflux disease and peptic ulcer disease. Extremely effective in suppression of acid secretion, they are also generally well-tolerated, with few immediate side effects.

There has been increasing concern in both the lay press and scientific literature about the potential adverse effects of PPIs,[3] including increased risk of dementia. A recent survey revealed that more than one-third of older adults are apprehensive about the risk of dementia with PPI use.[4] Much of this concern is based on a retrospective analysis in a large German administrative claims database concluding that patients prescribed PPIs had a nearly 1.5-fold increased risk of incident dementia diagnosis compared with those not prescribed PPIs.[5] However, subsequent observational studies and meta-analyses[6,7] found conflicting results. Most studies to date, including the previously mentioned German study, have been limited by incomplete assessment of PPI use and important confounders, including educational status, smoking status, and use of other medications, beyond PPIs. As shown previously, the number and type of concomitant medications not only may influence risk of dementia,[8] but also may reflect disease severity not otherwise captured by a list of comorbidities.[9] Furthermore, most of these studies have relied on International Classification of Diseases diagnosis codes for dementia, which can lead to differential misclassification and thus effect overestimates. Experimental and mechanistic evidence to support this conclusion is also limited. Although some have found data linking PPI exposure to acetylcholine production,[10] other studies have found contrasting results.[11] Prospective studies with detailed assessment of PPI use, validated measures of cognitive decline/dementia, and rigorously ascertained covariates are urgently needed.

Therefore, we conducted a post hoc observational study within the ASPirin in Reducing Events in the Elderly (ASPREE) trial[12] to investigate the associations of PPI and histamine-2 receptor antagonist (H2RA) use with cognitive decline and incident dementia. In this multinational cohort of older adults who underwent annual face-to-face visits to assess physical health and detailed cognitive testing, we were uniquely able to examine use of acid suppressive medications in the context of other clinical and lifestyle risk factors that may either confound or modify the association of these medications with dementia and cognitive decline.

WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

Prior studies have linked proton pump inhibitor use with an increased risk for dementia, alarming both patients and providers. Most of these studies used diagnosis codes to ascertain dementia and are limited by incomplete assessment of proton pump inhibitors, which are often available over the counter.

NEW FINDINGS

In this prospective cohort of older adults with annual visits confirming medication lists and detailed cognitive function testing, we were able to uniquely assess the relationship between acid suppression use and changes in cognitive function testing, incidence cognitive impairment, and dementia. We found no association between acid suppression and incident dementia, cognitive impairment, and even decline in cognitive function scores over time.

LIMITATIONS

We do not have data on duration of acid suppression use before enrollment in the cohort. All observational cohort studies are limited by residual confounding.

CLINICAL RESEARCH RELEVANCE

Providers can cite these data with patients, especially older adults, to reassure them that reports on the association between longer-term proton pump inhibitor use and dementia are unlikely to be true given the unique data, large sample size, and rigorous methodology used in this study.

Methods

Study Population

ASPREE is a randomized controlled trial comparing daily low-dose aspirin vs placebo in 19,114 Australian and US adults aged 70 years or older (or aged 65 years or older among US African American and Hispanic individuals) that began enrollment between 2010 and 2014. All participants were free of cardiovascular disease, dementia, or physical disability at trial entry and were expected to survive for at least 5 years.[12] Participants were enrolled in the trial if they scored greater than 78 on the baseline Modified Mini-Mental State Examination (3MS). After the trial ended, participants were invited to participate in the ASPREE-eXTension (ASPREE-XT) study, an ongoing observational study as described elsewhere,[13] with the latest data providing an additional 2 years of follow-up time.

Participants were excluded from this analysis if they withdrew/died before their first annual visit (n = 15), or had missing baseline covariate information (n = 165). After these exclusions, the study cohort comprised 18,934 participants who were followed for up to 7 years after enrollment.

The trial was conducted in accordance with the Declaration of Helsinki 1964 as revised in 2008, the National Health and Medical Research Council Guidelines on Human Experimentation, the federal patient privacy (Health Insurance Portability and Accountability Act) law, and the International Conference of Harmonization guidelines for Good Clinical Practice. This study was exempt from ethics review, as only existing

Abbreviations: **3MS, Modified Mini-Mental State Examination; ASPREE, ASPirin in Reducing Events in the Elderly; CI, confidence interval; CIND, Cognitive impairment, no dementia; H2RA, histamine-2 receptor antagonists; HR, hazard ratio; OTC, over-the-counter; PPI, proton pump inhibitor.**

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nonidentifiable data were used. Details of the ASPREE trial have been described elsewhere.[12]

Assessment of PPI and H2RA Use

At baseline and annual follow-up study visits, participants were asked to bring with them all current medications or a list of their currently prescribed medications, or to recall by self-report. In a minority of cases (16%), medical records from their primary care providers could be used in place of, or to supplement, this information. For the primary analysis, participants were grouped according to PPI use (omeprazole, esomeprazole, pantoprazole, lansoprazole, rabeprazole, or dexlansoprazole). In secondary analyses, PPIs were grouped by generation (first: omeprazole, pantoprazole, and lansoprazole, and second: esomeprazole, rabeprazole, and dexlansoprazole). As a control in our study given shared clinical indications with PPIs, participants were also grouped according to H2RA use (famotidine, cimetidine, nizatidine, or ranitidine).

Assessment of Dementia and Other Cognitive Outcomes

Dementia. In ASPREE, cognitive testing was performed at baseline, and then at years 1, 3, and 5, and at a final visit, which occurred during 2017 (between years 3 to 7, depending on the year of enrollment). In ASPREE-XT, cognitive testing was performed annually. A battery of 4 cognitive tests was administered: (1) the 3MS, to measure global cognition; (2) the Hopkins Verbal Learning Test–Revised, to measure episodic memory; (3) the Symbol Digit Modalities Test, to measure psychomotor speed; and (4) the single letter (F) Controlled Oral Word Association Test to measure language and executive function.[14]

Individuals with suspected dementia were referred for further standardized cognitive and functional assessments (as described previously[14]), based on cognitive testing, review of medical records, and/or in-person visits. Specifically, triggers for further evaluation of dementia were (1) a 3MS score <78; (2) a drop of more than 10 points from the predicted score based on their own baseline 3MS, adjusted for age and education; (3) report of memory concerns or other cognitive problems to a specialist; or (4) a clinician diagnosis of dementia in the medical records or a prescription of antidementia drugs. Follow-up evaluations were administered 6 or more weeks after the initial dementia flag to reduce the possibility of delirium as the cause for reduced cognitive performance.

Using this information, a panel of neurologists, neuropsychologists, and geriatricians blinded to randomized study drug group or other participant details adjudicated cases of dementia according to the Diagnostic and Statistical Manual for Mental Disorders, Fourth Edition (DSM-4). This required evidence of memory impairment plus evidence of at least 1 of the following: aphasia, apraxia, agnosia, or executive dysfunction. The date of diagnosis of dementia was taken as the date the dementia trigger occurred that resulted in a confirmed dementia diagnosis by the adjudication committee.

In ASPREE, dementia was subclassified as follows: (1) probable Alzheimer disease (AD) (the most common cause of dementia)[15] or (2) mixed presentations, referring to other forms of dementia, which included possible AD (meeting core AD criteria but without evidence of gradual cognitive decline), etiologically mixed presentations including those with neuroimaging consistent with moderate or marked cerebrovascular pathology and small vessel ischemia, and those with non-AD causes. In ASPREE-XT, given recent data ascertainment, subclassification of dementia has not yet occurred.

Cognitive impairment, no dementia. Cognitive impairment, no dementia (CIND) was diagnosed when participants who met a dementia trigger did not meet adjudication criteria for dementia.

Cognitive decline and change. Raw scores from each cognitive test were standardized to a z score using the baseline mean and standard deviation, with higher scores indicating better cognition. A mean was then obtained over all 4 tests of the cognitive battery.

Assessment of Other Covariates

Potential confounders were assessed at baseline based on known risk factors for neurocognitive outcomes. These included age, sex, years of education (self-report), country, race/ethnicity, smoking status (never vs former/current), alcohol consumption (never vs former/current, self-reported), body mass index (determined at baseline visit), family history of dementia (self-report), chronic kidney disease (defined as estimated glomerular filtration rate <60 mL/min per 1.73 m^2 or urinary albumin-to-creatinine ratio >3 mg/mmol), diabetes (self-report of diabetes mellitus or fasting glucose ≥ 126 mg/dL [≥ 7 mmol/L] or on treatment for diabetes), hypertension (on treatment for high blood pressure or blood pressure $>140/90$ mm Hg at study entry), concomitant medications (see more details later in this article), and depression score (total score of 30) measured at study entry using the Center for Epidemiologic Studies Depression Scale. Covariate assessment was reported previously[16] and is described in greater detail in the original ASPREE protocol.[17]

Statistical Analysis

To determine which medications were most often used concomitantly by PPI users, as well as to minimize potential effects of multicollinearity, a network analysis was constructed using a co-occurrence matrix. Nodes represent classes of medications, and edges represent co-occurrence. Edges from the PPI node were weighted according to frequency of co-occurrence. Networks were visualized using the iGraph package.[18] We selected medication classes most commonly co-occurring with PPIs (>750 co-occurrences) to serve as covariates in our models.

Person years of follow-up accrued from the date of enrollment until the date of diagnosis of cognitive endpoints, death, or the end of follow-up, whichever came first. In the primary analysis, we computed hazard ratios (HRs) and 95% confidence intervals (CIs) using Cox proportional hazards models to examine associations between baseline PPI and H2RA use with incident dementia and CIND, adjusting for baseline covariates listed previously, baseline cognition (3MS), co-occurring medications, and the randomized trial intervention (aspirin or placebo). Given the small number of dual users of PPI and H2RA, these participants were classified as both PPI and H2RA users in the analyses. The proportional hazards assumption was satisfied using the Schoenfeld residual test.

To examine associations of baseline PPI or H2RA use with baseline cognition, we constructed multivariate linear

regression models. To study changes in the composite cognition (composite z score) and 4 individual cognitive domains, we used linear mixed-effects models with potential confounders as fixed effects and participant-specific intercepts and slopes included as random effects.

To address potential misclassification of exposure, we conducted a sensitivity analysis repeating the main analyses but excluding participants who initiated PPIs during follow-up. In a second sensitivity analysis, we simulated an active comparator study, in which we compared baseline PPI use with baseline H2RA use in relation to dementia risk, excluding the small number of participants (n = 79).

As another sensitivity analysis, we conducted a Bayesian survival analysis. Specifically, using Markov chain Monte Carlo Gibbs Sampling with 10,000 iterations, we generated parameter estimates using an uninformative prior and an informative prior. For the informative prior, we generated a plausible range for PPI coefficient β_1 based on previously published β values from a recent meta-analysis.[19] Then, assuming this interval is captured by $\mu \pm 2\sigma$, where μ and σ are the mean and standard deviation of the normal prior, respectively, the hyperparameters used were $\mu = 0.11$ and $\sigma = 0.15$.

Last, in an analysis designed to explore the association between new use of PPIs after age 65 with incident dementia, we examined the association between PPI and H2RA use (using "time-varying" repeated exposures) by excluding baseline PPI users and then examining the association of updated PPI use as assessed in the visit during each follow-up interval with incident cognitive outcomes. This "time-varying" approach also enabled us to evaluate the relationship between sustained use (increasing duration) of PPIs beyond age 65 with incident dementia.

All P values were 2-sided. For time-to-event analyses and interaction tests, $P < .05$ was considered to indicate statistical significance to reduce type II error. A Bonferroni correction was made for the 5 cognitive function tests, such that $P < .01$ was considered to indicate statistical significance. Analyses were performed using the "survival"[20] and "nlme"[21] packages in R v.3.6.1.

Results

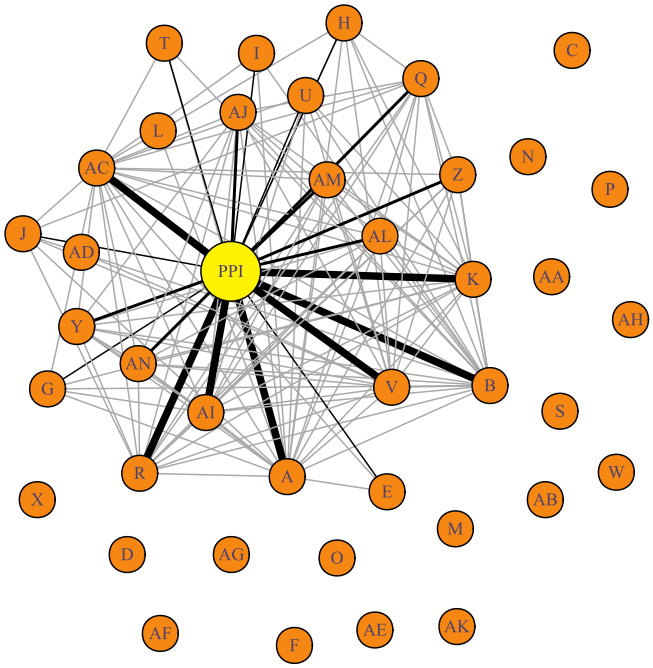
Among the 18,934 older adults who met the inclusion criteria of our current analysis, there were 4667 (24.6%) users of PPI and 368 (1.9%) users of H2RA at enrollment. Characteristics of the cohort categorized according to baseline PPI use are shown in Table 1. Compared with nonusers, PPI users were more likely to be White, have a lower education level, higher depression score, and higher prevalence of chronic kidney disease. In addition, PPI users took more medications at baseline, including renin-angiotensin system agents (eg, angiotensin-converting enzyme inhibitors, lipid-modifying agents (eg, statins), anti-inflammatory and antirheumatic drugs (eg, nonsteroidal anti-inflammatory drugs), psycholeptics (eg, antidepressants), and psychoanaleptics (eg, benzodiazepines). When specifically looking at types of medications co-occurrent with PPI use, the most common drug classes were antihypertensives, analgesics, and lipid-modifying agents (Figure 1).

Table 1. Participant Characteristics According to Baseline PPI Use

Characteristics	PPI nonuser (n = 14,267)	PPI user (n = 4667)
Age at randomization, *y* (SD)	75.0 (4.6)	75.4 (4.5)
Female, %	55.4	59.4
Race/ethnicity, %		
White AUS	83.5	92.0
White US	6.7	2.7
Non-White	9.8	5.3
Education, %		
<12 y of schooling	42.8	52.3
12 to 15 y	30.2	26.2
16+ y	27.0	21.6
Smoking, %		
Never	56.0	53.7
Former/Current	44.0	46.4
Alcohol (%)		
Never	17.1	18.3
Former/Current	82.8	81.7
BMI,[a] mean (SD)	27.9 (4.7)	28.8 (4.6)
H2RA use, %	2.0	1.7
History of cancer, %	18.9	20.4
History of hypertension, %	73.0	78.3
History of type 2 diabetes, %	10.4	11.7
History of chronic kidney disease, %	25.8	29.2
Family history of dementia, %	24.9	25.5
CES-D score, mean (SD)	3.1 (3.2)	3.6 (3.5)
Concomitant medications, %[b]		
0	20.2	9.0
1–4	66.2	65.4
5–9	13.2	24.6
10+	0.4	1.0
RAAS agents (eg, ACEi), %	37.6	44.5
Lipid-lowering agents (eg, statins), %	29.7	39.0
Anti-inflammatory drugs (eg, NSAIDs), %	12.4	20.1
Calcium channel blockers (eg, amlodipine), %	16.0	18.5
Psycholeptics (eg, antidepressants), %	8.6	16.1
Psychoanaleptics (eg, benzodiazepines), %	6.4	11.1

ACEi, angiotensin-converting enzyme inhibitor; AUS, Australia; BMI, body mass index; CES-D, Center for Epidemiologic Studies Depression Scale; NSAIDs, nonsteroidal anti-inflammatory drug; RAAS, renin-angiotensin system; SD, standard deviation; US, United States.
[a] kg/m^2
[b] Not including PPI use.

In ASPREE, we identified 572 incident cases of dementia (probable AD, n = 238; mixed presentations, n = 334) during 84,995 person years (median 4.5 years per person)



Line weight	Node	ATC Drug Class	Co-occurrence with PPI (n)
	A	Renin angiotensin system agents	2,101
	AC	Lipid modifying agents	1,843
	B	Analgesics	1,320
	K	Anti-inflammatory and antirheumatic products	947
	V	Diuretics	917
	R	Calcium channel blockers	874
	AI	Psychoanaleptics	763
	AJ	Psycholeptics	525
	AL	Thyroid therapy	422
	Q	Beta blocking agents	417
	AN	Vitamins	395
	Y	Drugs for treatment of bone diseases	323
	Z	Drugs used in diabetes	270
	AM	Urologicals	241
	H	Antigout medications	209
	U	Cough and cold medications	183
	T	Systemic corticosteroids	182
	G	Antiepileptics	168
	J	Other antihypertensives	158
	E	Antibiotics	128
	I	Antihistamines	108

Figure 1. Co-occurrence network analysis reveals patterns of medications concomitantly prescribed with PPIs in ASPREE. Shown graphically are pairwise co-occurrences between all medications taken by ASPREE participants. Apart from PPIs (*central yellow node*), drugs were binned into groups (*orange nodes*), defined according to the World Health Organization Anatomical Therapeutic Chemical Classification System. Edges between nodes are shown given a minimum of 100 co-occurrences; as a result, singletons represent drug classes with fewer than 100 co-occurrences with other drugs. Connections to PPIs are emphasized in *black* and weighted according to the number of co-occurrences (strong, >750; moderate, >250; weak, >100).

of follow-up. There was no association between baseline PPI use with risk for dementia (HR, 0.88; 95% CI, 0.72–1.08), probable AD (HR, 0.82; 95% CI, 0.59–1.14), or mixed presentations of dementia (HR, 0.93; 95% CI, 0.71–1.21) (Table 2) adjusting for age, sex, years of education, country, race/ethnicity, smoking status, alcohol consumption, body mass index, family history of dementia, chronic kidney disease, type 2 diabetes, hypertension, depression score, baseline cognition, the randomized trial intervention (aspirin or placebo), and the most concomitant medications identified previously. Similarly, no associations were observed between H2RA use and dementia (Table 2). A sensitivity analysis excluding 2751 baseline nonusers who initiated PPIs during follow-up yielded similar results. In a

Table 2. Association Between Baseline PPI and H2RA Use With Incident Dementia and Its Subtypes

	Dementia		Dementia, probable AD		Dementia, mixed	
	Nonuser	User	Nonuser	User	Nonuser	User
PPI						
No. of cases (n = 572)	449	123	191	47	258	76
Age-adjusted HR (95% CI)[a]	1 (referent)	0.81 (0.67–1.00)	1 (referent)	0.77 (0.56–1.07)	1 (referent)	0.91 (0.70–1.17)
Multivariable HR (95% CI)[b]	1 (referent)	0.88 (0.72–1.08)	1 (referent)	0.82 (0.59–1.14)	1 (referent)	0.93 (0.71–1.21)
H2RA						
No. of cases (n = 572)	559	13	231	4	322	9
Age-adjusted HR (95% CI)[a]	1 (referent)	1.05 (0.60–1.73)	1 (referent)	0.77 (0.29–2.08)	1 (referent)	1.20 (0.62–2.33)
Multivariable HR (95% CI)[b]	1 (referent)	1.00 (0.59–1.74)	1 (referent)	0.73 (0.27–1.99)	1 (referent)	1.15 (0.59–2.24)

[a]Adjusted by age, sex, and race/ethnicity.
[b]As in footnote "a" and additionally adjusted for years of education, body mass index, smoking history (never, past, current), alcohol history (never, past, current), family history of dementia, baseline depression score (Center for Epidemiologic Studies Depression Scale), hypertension, type 2 diabetes, history of cancer, chronic kidney disease, baseline mental status (3MS), and concomitant medications (agents acting on the renin-angiotensin system [eg, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers], lipid-modifying agents [eg, statins], diuretics [eg, thiazides], anti-inflammatory and antirheumatic drugs [eg, nonsteroidal anti-inflammatory drugs], calcium channel blockers, psycholeptics [eg, antidepressants], and psychoanaleptics [eg, benzodiazepines]).

second sensitivity analysis, baseline PPI use compared with baseline H2RA use was similarly not associated with risk of dementia. In a third sensitivity analysis, there was no meaningful difference between baseline use of second-generation PPI use (HR, 0.94; 95% CI, 0.73–1.22) in relation to incident dementia compared with first-generation PPI use (HR, 0.91; 95% CI, 0.68–1.21). In the Bayesian survival sensitivity analysis, as expected, the HR for the uninformative prior model was similar to the classical models: HR, 0.88 (95% CI, 0.76–1.03). The informative estimates were also similar: HR, 0.87 (95% CI, 0.72–1.06).

To provide longer follow-up for the association between PPI use and risk for dementia, we leveraged data collected through additional follow-up of the cohort. During a total of 120,194 person years (median 6.3 years per person), we documented 861 incident cases of dementia since baseline. As in ASPREE, there remained no association between baseline PPI use with risk for dementia (HR, 0.91; 95% CI, 0.78–1.07).

In time-varying analyses, designed to assess the relationship between new use of PPIs and risk for dementia, neither new use nor new and sustained use (increasing duration) of PPIs beyond age 65 was associated with incident dementia (Supplementary Table 1).

We also evaluated the association between PPI and H2RA use with CIND. We identified 2825 incident cases of CIND. PPI use was also not associated with risk for CIND (HR, 1.00; 95% CI, 0.92–1.09) (Table 3). Similarly, no associations with CIND were observed with H2RA use.

Next, we studied the association between baseline PPI use and baseline cognitive scores as well as cognitive change over time. There was no association between PPI use and overall cognitive test scores at baseline (*B,* −0.0002; standard error [SE], 0.01; $P = .85$) or over time (*B,* −0.006; SE, 0.02; $P = 0.53$) (Table 4). Similarly, no associations were observed between H2RA use and cognitive scores. In assessing specific components of cognitive scores, at baseline and over time, PPI users had clinically unremarkable, but statistically significant, lower scores on controlled oral word association testing, as a marker of verbal fluency and executive function (baseline analysis: *B,* −0.05; SE, 0.02; $P = .002$; over time: *B,* −0.05; SE, 0.01; $P = .0002$).

Finally, we tested if there was evidence of any effect modification by preselected dementia risk factors on the association between PPI use and risk for dementia. Subgroup analyses according to these variables were further performed. We did not observe interactions by these covariates on our association of interest ($P > .31$). The null association pattern was in general consistent across different subgroups stratified by a list of dementia risk factors (Table 5).

Table 3. Association Between Baseline PPI and H2RA Use With Incident CIND

	Nonuser	User
PPI		
No. of cases (n = 2825)	2129	696
Age-adjusted HR (95% CI)[a]	1 (referent)	1.02 (0.93–1.11)
Multivariable HR (95% CI)[b]	1 (referent)	1.00 (0.92–1.09)
H2RA		
No. of cases (n = 2729)	2666	63
Age-adjusted HR (95% CI)[a]	1 (referent)	1.06 (0.82–1.36)
Multivariable HR (95% CI)[b]	1 (referent)	1.02 (0.79–1.31)

[a]Adjusted by age and sex.
[b]As in footnote "a," and additionally adjusted for body mass index, race/ethnicity, smoking history (never, past, current), years of education, alcohol history (never, past, current), family history of dementia, baseline depression score (Center for Epidemiologic Studies Depression Scale), hypertension, type 2 diabetes, history of cancer, chronic kidney disease, and agents acting on the renin-angiotensin system (eg, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers), lipid-modifying agents (eg, statins), diuretics (eg, thiazides), anti-inflammatory and antirheumatic drugs (eg, nonsteroidal anti-inflammatory drugs), calcium channel blockers, psycholeptics (eg, antidepressants), and psychoanaleptics (eg, benzodiazepines).

Discussion

In this analysis of a large, multicenter international trial of community-dwelling adults ≥ 65 years, free of independence-limiting physical disability and dementia, we found that baseline, new, and ongoing PPI and H2RA use were not associated with risk of dementia, cognitive impairment, or overall cognitive decline over more than 6 years of follow-up. As this is the first study to combine rigorous ascertainment of dementia status with prospective in-person collection of medication data and face-to-face cognitive assessments, these findings should be reassuring to older adults using PPIs and prescribers needing to prescribe PPIs to older adults.

Our study is supported by 2 prior prospective analyses. The first, using adjudicated dementia endpoints, found a similarly null association with PPI prescription database information in 3484 individuals of ages 65+.[6] The second, an analysis of prospectively collected data from the Nurse's Health Study 213,864 women of ages 55+ also found a null association between PPI use and cognitive scores.[22] In contrast, several studies, including recent ones, have found positive associations between PPI use and dementia risk. A 2015 analysis of data from the German Study on Aging, Cognition and Dementia (AgeCoDe), conducted among 3076 older adults age 75+ revealed a significantly greater hazard of dementia outcomes in those self-reporting ever-use of PPIs.[23] In another German study from 2016, a health insurance analysis found that regular PPI users had a 1.5-fold greater risk of incident dementia.[5] Corroborating these findings, a 2020 cohort study using Taiwanese administrative data found a 20% increased risk of dementia.[24] Further still, in a 2022 analysis of Korean insurance claims data, PPI use was again associated with up to a 27% increased risk of AD.[25] These previous results may differ from ours because of bias introduced from retrospective design,[23] limited covariate ascertainment, and/or less rigorous cognitive outcome ascertainment inherent from claims data[5,24,25] or alternative exposure assessments.[5,23–25] Our study significantly extends these prior findings through the combination of prospective in-person medication data; consideration of

Table 4. Association Between Baseline PPI Use and Baseline Cognitive Scores and Change Over The Study Period

	Baseline			Cognitive change over time		
	B	SE	*P* value	B	SE	*P* value
PPI users vs nonusers						
3MS (global function)	0.01	0.03	.39	0.003	0.03	.79
SDMT (psychomotor speed)	−0.009	0.02	.56	0.001	0.03	.94
COWAT (language, executive function)	−0.05	0.02	.002	−0.05	0.01	.0002
HVLT-R delayed recall (episodic memory)	0.04	0.02	.02	0.04	0.01	.02
Composite z score	−0.002	0.01	.85	−0.006	0.02	.53
H2RA users vs nonusers						
3MS (global function)	−0.10	0.03	.04	−0.04	0.04	.33
SDMT (psychomotor speed)	−0.02	0.05	.60	−0.04	0.06	.53
COWAT (language, executive function)	−0.04	0.05	.48	−0.05	0.05	.31
HVLT-R delayed recall (episodic memory)	0.09	0.05	.07	0.03	0.05	.49
Composite z score	−0.02	0.02	.62	−0.03	0.02	.38

NOTE. Adjusted for age, gender, body mass index, race/ethnicity, smoking history (never, past, current), years of education, alcohol history (never, past, current), family history of dementia, baseline depression score (Center for Epidemiologic Studies Depression Scale), hypertension, type 2 diabetes, history of cancer, chronic kidney disease, and agents acting on the renin-angiotensin system (eg, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers), lipid-modifying agents (eg, statins), diuretics (eg, thiazides), anti-inflammatory and antirheumatic drugs (eg, nonsteroidal anti-inflammatory drugs), calcium channel blockers, psycholeptics (eg, antidepressants), and psychoanaleptics (eg, benzodiazepines).
B, beta estimates; COWAT, controlled oral word association testing; HVLT-R, Hopkins Verbal Learning Test–Revised; SDMT, Symbol Digit Modalities Test; SE, standard error.

new use of PPIs among older adults; and in-depth cognitive testing and case adjudication by an expert panel using validated criteria. In addition, our study adjusts for several key confounding variables that were absent from most, if not all, of the positive studies, including race/ethnicity, body mass index, smoking status, alcohol intake, specific concomitant medications, and educational attainment.

In light of our null findings from a robust and prospective study, we propose that prior links between PPIs and dementia have been limited by confounding and may reflect PPI use as a marker of polypharmacy and comorbidity. Given the high co-occurrence of combined use of PPIs with antihypertensive agents and lipid-lowering agents in our cohort, PPI use could be a surrogate for cardiovascular disease, which is well-known to be linked with adverse cognitive outcomes.[26]

In support of this, there are limited data supporting biological plausibility between PPI use and adverse cognitive events. Previous studies finding positive associations between PPI use and dementia postulate that PPIs decrease gastric vitamin B12 absorption, which contributes to an elevated risk for cognitive decline. However, the association between vitamin B12 levels and dementia is still not firmly established,[27] and risk for B12 malabsorption from long-term PPI use is largely unfounded.[28] Moreover, we similarly found no signal between another acid suppression medication class, H2RA, and risk for dementia.

In a larger context, we note findings from other pharmacoepidemiologic studies of dementia are not consistently reproduced when using higher quality data derived from trials and/or in subsequent meta-analyses. Although early observational studies yielded positive, provocative associations between long-term medication use and risk for dementia—not limited to PDE5 inhibitors,[29] aspirin,[30] nonsteroidal anti-inflammatory drugs,[31] and anti-hypertensives[32]—they were later challenged by null results from clinical trials and meta-analyses.[14,33–35] Similarly, long-term PPI use has been associated with an increased risk of several adverse outcomes, but over time, most of these have been refuted by other larger studies. Thus, the frequent failure to reproduce observational pharmacoepidemiologic data underscores the importance of including rich metadata, inclusion of negative controls, robust sensitivity analyses, and ecological analyses, particularly when dedicated clinical trials are often infeasible for endpoints like dementia.

Strengths of this study include its use of data from a prospective clinical trial, conducted among participants who provided detailed medication, clinical, and cognitive data at repeated in-person follow-up visits. In addition, unlike other studies examining dementia among PPI users, we assessed cognitive decline through face-to-face cognitive assessments, which allowed for formal adjudication of major neurocognitive disorder outcomes. These in-person data also minimized concerns related to unmeasured confounding by polypharmacy or underlying comorbidities. Finally, our study is among the largest and most diverse to date; includes participants from 2 continents; and was limited to older adults, who are most susceptible to neurotoxicity and/or cognitive decline.

We acknowledge several limitations. First, all observational studies have a risk of residual confounding, which means there may be unmeasured variables related to both PPI use and dementia in the analysis. However, randomized clinical trials specifically relating the impact of PPI use on dementia are likely to be ethically and logistically infeasible. Second, we may have underestimated PPI and H2RA use in the cohort, given our limited ability to collect over-the-counter (OTC) use of these medications. However, OTC

Table 5. Association Between Baseline PPI Use and Incident Dementia According to Specific Subgroups

Characteristics	PPI use		P_{int}
	Nonuse	Use	
Age, *y*			
<75 (n = 11,059)			
Multivariate HR (95% CI)[a]	1 (referent)	0.73 (0.49–1.08)	
≥75 (n = 7875)			.31
Multivariate HR (95% CI)[a]	1 (referent)	0.82 (0.63–1.05)	
BMI, *kg/m*^{2}			
≥27.5 (n = 9,464)			
Multivariate HR (95% CI)[a]	1 (referent)	0.79 (0.58–1.06)	
>27.5 (n = 9470)			.37
Multivariate HR (95% CI)[a]	1 (referent)	0.78 (0.57–1.07)	
Sex			
Male (n = 8255)			
Multivariate HR (95% CI)[a]	1 (referent)	0.82 (0.60–1.12)	
Female (n = 10,679)			.95
Multivariate HR (95% CI)[a]	1 (referent)	0.79 (0.59–1.06)	
Baseline cognition			
3MS <94 (n = 8023)			
Multivariate HR (95% CI)[a]	1 (referent)	0.75 (0.59–0.96)	
3MS ≥94 (n = 10,911)			.82
Multivariate HR (95% CI)[a]	1 (referent)	1.06 (0.67–1.68)	
Country of origin			
United States (n = 2384)			
Multivariate HR (95% CI)[a]	1 (referent)	0.87 (0.43–1.75)	
Australia (n = 16,550)			.95
Multivariate HR (95% CI)[a]	1 (referent)	0.86 (0.69–1.06)	

[a]Adjusted for age, gender, body mass index, race/ethnicity, smoking history (never, past, current), years of education, alcohol history (never, past, current), family history of dementia, baseline depression score (Center for Epidemiologic Studies Depression Scale), hypertension, type 2 diabetes, history of cancer, chronic kidney disease, and agents acting on the renin-angiotensin system (eg, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers); lipid-modifying agents (eg, statins), diuretics (eg, thiazides), anti-inflammatory and antirheumatic drugs (eg, nonsteroidal anti-inflammatory drugs), calcium channel blocks, psycholeptics (eg, antidepressants), and psychoanaleptics (eg, benzodiazepines).

PPIs were only approved in Australia in 2015, toward the end of data collection. Furthermore, prescription users of PPI and/or H2RA are more likely to be consistent users of the medications. Arguing against confounding related to OTC availability, we did not see any difference upon stratification by participants' country of origin. Third, we did not have data on duration of medication use before enrollment or dose of medications taken. Finally, we did not account for apolipoprotein E4 allele status, although in one analysis of PPI use and dementia,[23] apolipoprotein E4 status did not differ significantly across patients with and without AD.

In a well-characterized, international prospective cohort, we demonstrate that among adults ≥65 years of age, use of PPI or H2RA was not associated with incident dementia, CIND, or declines in cognitive test scores over time. Although medications without a clear indication should always be discontinued,[36] and our study did not specifically assess other potential risks of long-term PPI use, our findings provide reassurance that long-term use of PPIs in older adults is unlikely to have negative effects on cognition.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2023.05.052.

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Data Availability
Data and study materials may be available upon request from Andrew T. Chan at achan@mgh.harvard.edu.

Supplementary Table 1. Association Between Recent and New Use of PPI With Incident Dementia (Time Varying, DSR Methodology)

	Dementia (all)	
PPI	Nonuser	User
No. of cases (n = 572)	444	123
New PPI use		
Multivariable HR (95% CI)[a]	1 (referent)	0.93 (0.78–1.12)
New PPI use, 1 year preceding (lag)		
Multivariable HR (95% CI)[a]	1 (referent)	0.93 (0.77–1.13)
Duration of use, cumulative years from baseline		
Multivariable HR (95% CI)[a]	1 (referent)	0.96 (0.91–1.00)

[a]Adjusted by age, sex, body mass index, race/ethnicity, smoking history (never, past, current), years of education, alcohol history (never, past, current), family history of dementia, baseline depression score (Center for Epidemiologic Studies Depression Scale), hypertension, type 2 diabetes, history of cancer, chronic kidney disease, select medications (see Table 3), and baseline cognition.