Cumulative Use of Proton Pump Inhibitors and Risk of Dementia

The Atherosclerosis Risk in Communities Study

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Abstract

Background and Objectives
Studies on the association between proton pump inhibitor (PPI) use and dementia report mixed results and do not examine the impact of cumulative PPI use. We evaluated the associations between current and cumulative PPI use and risk of incident dementia in the Atherosclerosis Risk in Communities (ARIC) Study.

Methods
These analyses used participants from a community-based cohort (ARIC) from the time of enrollment (1987–1989) through 2017. PPI use was assessed through visual medication inventory at clinic visits 1 (1987–1989) to 5 (2011–2013) and reported annually in study phone calls (2006–2011). This study uses ARIC visit 5 as baseline because this was the first visit in which PPI use was common. PPI use was examined 2 ways: current use at visit 5 and duration of use before visit 5 (from visit 1 to 2011, exposure categories: 0 day, 1 day–2.8 years, 2.8–4.4 years, >4.4 years). The outcome was incident dementia after visit 5. Cox proportional hazard models were used, adjusted for demographics, comorbid conditions, and other medication use.

Results
A total of 5,712 dementia-free participants at visit 5 (mean age 75.4 ± 5.1 years; 22% Black race; 58% female) were included in our analysis. The median follow-up was 5.5 years. The minimum cumulative PPI use was 112 days, and the maximum use was 20.3 years. There were 585 cases of incident dementia identified during follow-up. Participants using PPIs at visit 5 were not at a significantly higher risk of developing dementia during subsequent follow-up than those not using PPIs (hazard ratio (HR): 1.1 [95% confidence interval (CI) 0.9–1.3]). Those who used PPIs for >4.4 cumulative years before visit 5 were at 33% higher risk of developing dementia during follow-up (HR: 1.3 [95% CI 1.0–1.8]) than those reporting no use. Associations were not significant for lesser durations of PPI use.

Discussion
Future studies are needed to understand possible pathways between cumulative PPI use and the development of dementia.

Classification of Evidence
This study provides Class III evidence that the use of prescribed PPIs for >4.4 years by individuals aged 45 years and older is associated with a higher incidence of newly diagnosed dementia.

Glossary

ARIC = Atherosclerosis Risk in Communities; **BMI** = body mass index; **CKD** = chronic kidney disease; **GERD** = gastroesophageal reflux disease; **H2RAs** = Histamine$_2$ receptor antagonists; **HR** = hazard ratio; **NHLBI** = National Heart, Lung, and Blood Institute; **PPIs** = proton pump inhibitors.

Introduction

Proton pump inhibitors (PPIs), available through prescription and over the counter, are currently the first-line therapy for the short-term treatment (4–8 weeks) of gastroesophageal reflux disease (GERD) and peptic ulcers.[1-4] In a study based on US emergency department visits, PPI use increased from 4% to 9% from 2002 to 2009.[5] PPIs were dispensed more than 115 million times in 2016.[6] In addition, up to 63% of PPI prescriptions did not have a documented gastrointestinal diagnosis and may have been inappropriately prescribed.[5,7] Long-term use of PPIs has not been approved; nevertheless, chronic PPI use is common.[8]

Chronic PPI use has been linked to numerous health conditions such as stroke, cardiovascular disease, chronic kidney disease, and dementia.[1,2] Previous studies on the relationship between PPI use and dementia report mixed results.[9-15] Two recent meta-analyses report no association among 7 case-control/cohort studies (pooled HR: 1.10 [95% CI 0.88–1.37])[16] and 8 cohort studies (pooled risk ratio (RR): 1.17 [95% CI 0.95–1.44]).[17] However, precision was somewhat poor, and the heterogeneity of the included studies was high (I^2 = 95%–96%).[16,17] Furthermore, there were numerous limitations including suboptimal generalizability. Study participants were predominantly White or Asian. Another limitation was that in approximately half the studies, dementia diagnosis was defined entirely by ICD codes, and these are known to have poor sensitivity. Finally, a majority of the studies did not account for intraindividual variation in PPI use over follow-up, but instead defined the exposure as short-term or any use of PPIs during follow-up. Examining long-term or cumulative exposure to PPIs may be necessary due to the long latency period of dementia. Our primary research hypotheses tested in this study are whether current and greater cumulative exposure to prescribed PPIs would be associated with a higher risk of incident dementia in the Atherosclerosis Risk in Communities (ARIC) study.

Methods

Study Population and Design

The ARIC study is a population-based cohort of adults recruited from 4 US communities: Washington County, MD; Forsyth County, NC; selected suburbs of Minneapolis, MN; and Jackson, MS. In 1987–1989 (visit 1), the ARIC study recruited and examined 15,792 men and women aged 45–64 years, who predominantly identified as Black or White. Participants attended multiple in-person clinic visits: visit 2 (1990–1992), visit 3 (1993–1995), visit 4 (1996–1998), visit 5 (2011–2013), visit 6 (2016–2017), and visit 7 (2018–2019).

Participants were also contacted annually by telephone from study baseline until 2011 and then twice-yearly thereafter.[18,19]

ARIC visit 5 (2011–2013), attended by 6,538 participants, was the first study visit in which PPI use was common. Therefore, ARIC visit 5 served as the baseline visit for this study. All participants who were dementia-free at visit 5 were included for analysis (n = 347 cases with prevalent dementia). Participants who attended visit 5 before the 2011 annual phone call were excluded from analysis (n = 30) due to complications of calculating cumulative exposure. Participants missing covariates of interest were excluded. A total of 5,712 participants were included for the current PPI use and cumulative exposure to PPI analyses (Figure).

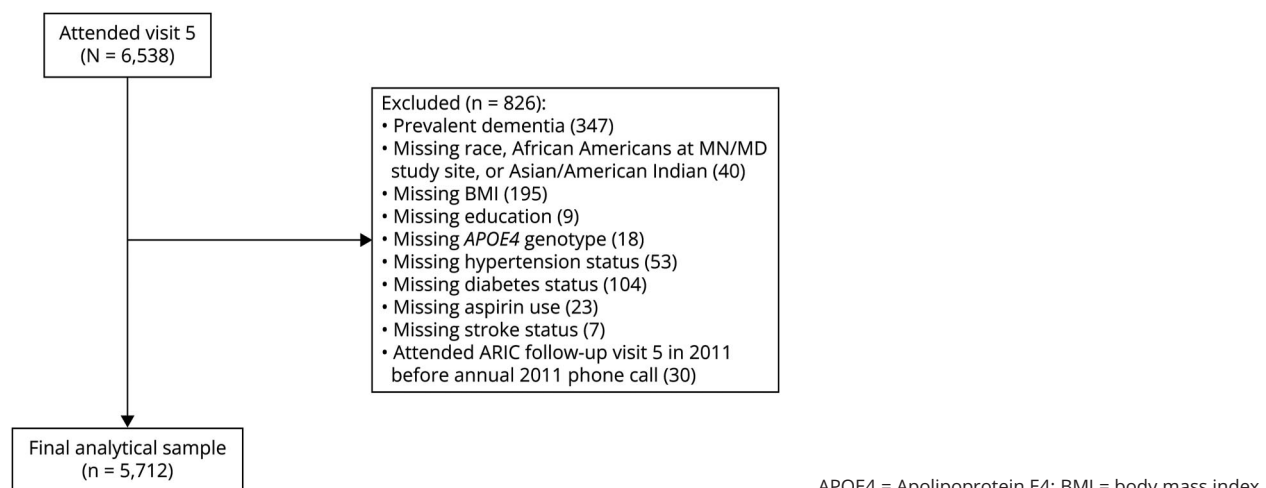### Standard Protocol Approvals, Registrations, and Patient Consents

The Institutional Review Boards of the collaborating institutions approved ARIC, and all participants gave written informed consent.

Measurement of Exposure

Participants were asked to bring to in-person clinic visits all over the counter and prescription medications used during the preceding 2 weeks. Medications were inventoried by trained staff. PPI use was also ascertained from annual phone calls (contact years 2006–2011) during which participants were asked to assemble all current medications and "read the names of all the medications prescribed by a doctor." Over-the-counter medications not prescribed by a doctor were excluded. The first PPI drug became available over the counter in 2003.

Two exposures of PPIs were evaluated. Current exposure to PPIs was defined as use of PPIs at visit 5. Those who were not using PPIs at visit 5 served as the reference group. Cumulative exposure to PPIs was defined as years of use from date of visit 1 examination to date of the annual phone call in 2011. If a participant was taking a PPI at a visit or call, they were assumed to be taking it until the next visit. If information was missing for a given call or visit, the last observation carried forward method was used. Cumulative PPI use was the sum of all PPI use from visit 1 (pre-FDA approval of PPIs) to 2011 (before ascertainment at visit 5). Participants who had never used PPIs before visit 5, and did not use PPIs at the time of visit 5, served as the reference group. The remaining observations were categorized into tertiles of cumulative PPI use. Thirty participants were excluded from analyses because they had participated in visit 5 in 2011 and did not have their annual follow-up call before their visit. For ease of defining the population, we excluded these 30 participants from both analyses of PPI exposures.

Figure Flowchart of Participants in the Atherosclerosis Risk in Communities Study, 2011–2017

Attended visit 5
(N = 6,538)

Excluded (n = 826):
• Prevalent dementia (347)
• Missing race, African Americans at MN/MD
  study site, or Asian/American Indian (40)
• Missing BMI (195)
• Missing education (9)
• Missing *APOE4* genotype (18)
• Missing hypertension status (53)
• Missing diabetes status (104)
• Missing aspirin use (23)
• Missing stroke status (7)
• Attended ARIC follow-up visit 5 in 2011
  before annual 2011 phone call (30)

Final analytical sample
(n = 5,712)

APOE4 = Apolipoprotein E4; BMI = body mass index.

Histamine$_2$ receptor antagonists (H2RAs) are an alternative class of medication used to treat GERD and other gastric acid–related disorders. In a secondary analyses, we examined H2RA use as an active comparator. Assessment of H2RAs was similar to that of PPIs, including both through in-person medication inventory and regular phone calls. H2RAs were categorized into the same tertiles of cumulative exposure as PPIs for consistency.

Ascertainment of Outcome

Following a previous ARIC study,[20] incident dementia was ascertained using information from 3 sources: (1) for those who completed in-person examinations at visits 6 (2016–2017) and 7 (2018–2019), dementia status was ascertained through neuropsychological examination, (2) twice-yearly participants were called by telephone and the Six-Item Screener was conducted, with follow-up proxy completion of the AD8 screening tool when appropriate, and (3) surveillance through hospital discharge codes and death records, which were gathered as part of the cohort's standard procedures. Suspected cases with dementia were adjudicated by a panel of physicians and neuropsychologists who classified both dementia status (yes/no) and estimated date at onset.

Other Covariates

Covariates in this analysis were assessed at ARIC visit 5 (baseline) unless otherwise stated and included educational attainment (ARIC visit 1), sex, age, smoking status, race, and ARIC center. Use of antihypertensives, H2RAs, anticholinergics, aspirin, and vitamin B$_{12}$ use were assessed through in-person medication inventory at visit 5. Body mass index (BMI; in kg/m^2) was computed from weight and standing height. BMI was categorized into underweight/normal weight, overweight, and obese categories. Very few individuals were in the underweight BMI category. Sitting blood pressure was measured 3 times using a random-zero sphygmomanometer after a 5-minute rest, and the average of the

final 2 measurements was used. Hypertension was defined as current use of antihypertensive medication, systolic blood pressure (BP) > 140 mm Hg, or diastolic BP > 90 mm Hg. Diabetes was defined as treatment for diabetes, a fasting glucose level of ≥126 mg/dL, nonfasting glucose level ≥200 mg/dL, and/or a self-reported history of a physician diagnosis of diabetes. APOE4 genotyping has been previously described.[21] APOE4 was coded as either present, not present, or missing if the participant requested not to have genotyping performed.

Statistical Analysis

Baseline covariates were examined by cumulative PPI exposure categories. Cox proportional hazard models estimated the association of PPI use and risk of incident dementia. We examined PPI exposure as current PPI use and by categories of cumulative PPI use. Follow-up time began at visit 5 and continued until incident dementia, death, loss to follow-up, or end of the follow-up period (December 31, 2017), whichever came first. Models for current PPI use adjusted for the following: model 1: age, sex, race center, education, and APOE4 genotype; model 2: model 1 + body mass index; and model 3: model 2 + current H2RA use, current aspirin use, diabetes mellitus, stroke, and hypertension. Model 3 was not adjusted for anticholinergic use due to small cell sizes. Interaction terms for age, sex, and BMI with PPI use were added to the fully adjusted models to evaluate whether these characteristics modified the association. We also examined whether the addition of participant B$_{12}$ medication use to model 3 changed our observed results.

Secondary analyses used H2RA use as an active comparator. This design compared PPI use with H2RA use, another drug commonly used for the same indication. The analysis included only individuals who were using either PPIs or H2RAs. The same general methods were used as in the primary analyses. For the current use analysis, the exposure was defined as PPI use at visit 5 compared with use of H2RAs at visit

5. For the cumulative use analysis, due to less frequent use of H2RAs, the exposure was defined as any use of PPIs before visit 5 compared with any use of H2RAs before visit 5. Sensitivity analyses assessed the individual time lengths (i.e., >4.4 cumulative years of PPI use vs > 4.4 cumulative years of H2RA use). Analyses were conducted in RStudio version 3.6.1.[22]

Data Availability

Qualified researchers may obtain access to ARIC study data through the NIH National Heart, Lung, and Blood Institute (NHLBI) BioLINCC repository (https://biolincc.nhlbi.nih.gov/home/).

Results

A total of 6,538 participants attended visit 5. Of them, 796 participants were excluded from the current PPI use analysis for the following reasons: prevalent dementia at visit 5 [n = 347], were of Black race at MN or MD study site or were Asian or Native American [n = 40; excluded because of small numbers], missing data at visit 5, including BMI [n = 195], education [n = 9], APOE4 genotype [n = 18], hypertension status [n = 53], diabetes status [n = 104], aspirin use [n = 23], and stroke status [n = 7]. An additional 30 participants were excluded from the cumulative PPI use analysis for having visit 5 before the 2011 annual phone call, due to complications in calculating cumulative exposure when this happened. These participants would have had their exposure calculated after the baseline visit (visit 5). For consistency, 5,712 participants were used for the cumulative PPI use and current PPI use analyses.

The median follow-up was 5.5 years. A total of 585 (10.2%) participants developed dementia over follow-up. There were 1,490 cumulative PPI users (26.1%) from visit 1 to 2011 and 1,450 current PPI users (25.4%) at visit 5. Cumulative PPI use ranged from 112 days to 20.3 years by 2011. (the median use was 3.8 years; interquartile range 2.2–5.1 years; mean use was 4.4 years) Baseline characteristics of cumulative PPI users and nonusers are summarized in Table 1. Current PPI users had a mean age of 75.6 ± 5.1 years, similar to 75.3 ± 5.1 years among

Table 1 Baseline Characteristics by Proton Pump Inhibitor Use, Atherosclerosis Risk in Communities Study, 2011–2013

	Exposure to proton pump inhibitors before baseline			
	0 d (N = 4,222)	1 d–2.8 y[a] (N = 497)	2.8–4.4 y[a] (N = 496)	>4.4 y[a] (N = 497)
Age	75.3 (5.1)	75.5 (5.2)	75.4 (5.0)	75.9 (5.1)
Male	1837 (43.5)	164 (33.0)	184 (37.1)	187 (37.6)
Black	954 (22.6)	150 (30.2)	96 (19.4)	65 (13.1)
Education				
Basic	541 (12.8)	77 (15.6)	64 (12.9)	70 (14.1)
Intermediate	1717 (40.7)	208 (41.9)	269 (54.2)	221 (44.5)
Advanced	1964 (46.5)	212 (42.7)	163 (32.9)	206 (41.4)
Body mass index	28.6 (5.7)	29.3 (5.9)	29.4 (5.7)	29.4 (5.5)
Hypertension (%)	3,088 (73.1)	389 (78.3)	374 (75.4)	395 (79.5)
H$_2$ receptor antagonist use (%)	271 (6.4)	37 (7.4)	37 (7.5)	37 (7.4)
Diabetes (%)	1,308 (31.0)	169 (34.0)	176 (35.5)	189 (38.0)
APOE (e4 carrier) (%)	1,192 (28.2)	109 (21.9)	135 (27.2)	104 (20.9)
Smoking (%)				
Never	1,601 (37.9)	202 (40.6)	184 (37.1)	182 (36.6)
Former	1969 (46.6)	217 (43.7)	253 (51.0)	247 (49.7)
Current	259 (6.1)	31 (6.2)	20 (4.0)	20 (4.0)
Aspirin use (%)	2,816 (66.7)	372 (74.8)	375 (75.6)	390 (78.5)
Anticholinergic use (%)	18 (0.4)	4 (0.8)	11 (2.2)	6 (1.2)
Vitamin B$_{12}$ use (%)	176 (4.2%)	23 (4.6)	28 (5.6)	32 (6.4)

All values are mean (SD) or frequency (%) as indicated. Some percentages will not add to 100% due to missing information.
Hypertension defined as systolic blood pressure >140 mm Hg, diastolic blood pressure >90 mm Hg, and/or on antihypertensive medication.
Diabetes was defined as treatment for diabetes, a fasting glucose level of ≥126 mg/dL, nonfasting glucose level ≥200 mg/dL, and/or a self-reported history of a physician diagnosis of diabetes. Education defined as basic (less than completed high school), intermediate (high school or equivalent), or advanced (at least some college). Vitamin B$_{12}$ use was defined as a participant who reported taking a medication with vitamin B$_{12}$ or B complex.
[a] Minimum PPI use was 112 d (0.31 y), maximum use was 20.3 y. The median use was 3.8 y; the mean use was 4.4 y.

nonusers ($p > 0.05$). Users were more likely to be female, of White race, have HTN and diabetes, and not have the APOE4 genotype compared with nonusers.

Current use of PPIs at visit 5 was not associated with an increased risk of incident dementia in the minimally adjusted (hazard ratio (HR): 1.05 [95% CI 0.87–1.26]) or fully adjusted models (HR: 1.09 [95% CI 0.90–1.31]) (Table 2). H2RAs were not significantly associated with an increased risk in dementia in the fully adjusted model (HR: 1.30 [95% CI 0.97–1.75]).

After minimal adjustment, participants who used PPIs for more than 4.4 cumulative years were at a 38% higher risk of developing dementia later in life (HR: 1.38 [95% CI 1.04–1.82]) compared with those who had never used PPIs (Table 3). The association persisted after full adjustment (HR: 1.33 [95% CI 1.00–1.77]). Short-term (1 day–2.8 cumulative years) and intermediate (>2.8–4.4 cumulative years) PPI users had a nonsignificant higher risk of developing dementia (Table 3). There were no significant interactions of cumulative PPI use by age, sex, or BMI category. The addition of participant B_{12} use as an explanatory covariate to model 3 did not change the results summarized in Tables 2 and 3.

There was no significant difference between risk of dementia and PPIs when H2RAs were used as an active comparator for both cumulative (Table 4) and current exposure (HR: 0.83 [0.58–1.18])

Discussion

In this community-based cohort, participants with long-term cumulative (>4.4 years) use of PPIs from mid-to-late life had a modestly higher risk of dementia in late life compared with nonusers. Shorter-term use in midlife and current use in late life were not associated with increased risk of dementia in late life.

Previous cohort studies found mixed results when assessing the relationship between time-varying PPI use and risk of dementia or Alzheimer disease. Two heterogeneous meta-analyses report no significant association.[16,17] The follow-up time of the included cohort studies was similar to the follow-up of our study (1.5–8.4 years). Time-varying PPI use in most of the studies was defined as users vs nonusers. In our analysis, the risk of dementia among current PPI users is in agreement with the results of these meta-analyses.

Few previous studies have taken into account the long latency of dementia. A Finnish nationwide nested case-control study found no association for risk of Alzheimer disease after a 3-year lag window (odds ratio [OR]: 1.03 [95% CI 1.00–1.05]).[23] In addition, it found no association with ≥3 years of PPI use (OR: 0.99 [95% CI 0.94–1.04]).[23] A US cohort study also found a null association between daily PPI dose dispensed in the previous 10 years and risk of dementia during follow-up (HR 1.13, 95% CI 0.82–1.56).[10] Our study reports that long-term previous cumulative use (>4.4 years) was significantly associated with developing dementia. While we did not incorporate a long lag window, or define PPI dosage, we aimed to capture total use before baseline among a dementia-free population.

The underlying mechanism between PPIs and dementia has been postulated through 2 plausible pathways: vitamin B_{12} deficiency and impaired amyloid metabolism.[24] A previous study[25] reported a significant association between PPI use and low levels of vitamin B_{12}. Low vitamin B_{12} levels are associated with a decline in cognition.[26] We are unable to comment on participant B_{12} levels in our dataset. However, adjusting for participant baseline B_{12} use did not alter the relation between PPI use and dementia in our data. In experimental mice models, PPI use has been associated with an increase in β-amyloid levels in the brain.[24,27] PPIs may modify the γ-secretase enzyme, which cleaves a precursor protein to β-amyloid. This contributes to the development of Alzheimer disease by increasing β-amyloid plaques within the brain.[24] Another pathway is through vascular causes. PPIs have been implicated in the development of other health outcomes including stroke[28,29] and chronic kidney disease (CKD).[30,31] Studies report that CKD and stroke patients are at higher risk of developing dementia.[32-37] The microbiota-gut-brain axis is another postulated mediating pathway between cumulative PPI use and cognitive outcomes. PPI use has been associated with significant changes to the gut microbiome possibly driven by hypochlorhydria.[38] Specific gut microbiota changes reported with PPI use include an overall decrease in microbial diversity and dysbiosis or alterations in the composition of the microbiome. In turn, dysbiosis and decreased microbial diversity have been reported in patients with Alzheimer disease and in animal models of dementia.[39,40] Specific pathways

Table 2 Hazard Ratios of Incident Dementia by Current Proton Pump Inhibitor Use: The Atherosclerosis Risk in Communities Study, 2011–2017

	No PPI use	PPI use
# of dementia events	434	151
# of PY[a]	22,236.7	7,445.6
Crude IR/1000 PY (95% CI)	19.5 (17.7–21.4)	20.3 (17.2–23.8)
HR (95% CI)	No PPI use	PPI use
Model 1	1 (reference)	1.05 (0.87–1.26)
Model 2	1 (reference)	1.08 (0.89–1.30)
Model 3	1 (reference)	1.09 (0.90–1.31)

Abbreviations: APOE = Apolipoprotein E4; H2RA = H_2 receptor antagonist; HR = hazard ratio; PPI = proton pump inhibitor; PY = person-years.
Model 1: adjusted for demographics (age, sex, race, center, education) + APOE4.
Model 2: adjusted for model 1 covariates + BMI.
Model 3: adjusted for model 2 covariates + hypertension, diabetes, stroke, aspirin use, and current H2RA use.
[a] We calculated person-years of follow-up as time elapsed from the baseline date (visit 5) to whichever came first: dementia event, loss to follow-up, death, or administratively censored at December 2017.

Table 3 Hazard Ratios for Incident Dementia by Cumulative Proton Pump Inhibitor Use, Atherosclerosis Risk in Communities Study, 2011–2017

| | Exposure to proton pump inhibitors before baseline | | | |
| | 0 d | 1 d–2.8 y | >2.8–4.4 y | >4.4 y |
	(n = 4,222)	(n = 497)	(n = 496)	(n = 497)
Outcome: incident dementia				
No. of dementia events	415	56	56	58
No. of person-years[a]	21,941.5	2,591.3	2,631.9	2,437.8
Crude IR/1,000 person-years (95% CI)	18.9 (17.1–20.8)	21.6 (16.3–28.1)	21.3 (16.1–27.6)	23.8 (18.1–30.8)
Model 1 HR (95% CI)	1 (reference)	1.12 (0.85–1.49)	1.09 (0.82–1.44)	1.38 (1.04–1.82)
Model 2 HR (95% CI)	1 (reference)	1.14 (0.86–1.51)	1.12 (0.85–1.49)	1.42 (1.07–1.87)
Model 3 HR (95% CI)	1 (reference)	1.10 (0.83–1.46)	1.09 (0.82–1.45)	1.33 (1.00–1.77)

Abbreviations: APOE = Apolipoprotein E4; H2RA = H_2 receptor antagonist; HR = hazard ratio; IR = incidence rate.
Model 1: adjusted for demographics (age, sex, race, center, education) + APOE4.
Model 2: adjusted for model 1 covariates + BMI.
Model 3: adjusted for model 2 covariates + hypertension, diabetes, stroke, aspirin use, and cumulative H2RA use.
[a] We calculated person-years of follow-up as time elapsed from the baseline date (visit 5) to whichever came first: dementia event, loss to follow-up, death, or administratively censored at December 2017.

postulated to link gut dysbiosis and Alzheimer disease include neuroinflammation, oxidative stress, and triggering of amyloid-beta aggregation.[39,40] A different consideration is the use of PPI as part of quadruple therapy for eradicating *Helicobacter pylori* infection. *H pylori*, a gastric pathogen, has been shown to be associated with dementia in both cohort and case-control studies, though all data are still observational.[41-43] The diagnosis of *H pylori* in these studies is based on seropositivity, and the timing of *H pylori* infection and dementia onset is not well characterized. The duration of quadruple therapy is typically 14 days. Hence, PPI use in this context is short-term. Our data suggest an association with cumulative long-term use (>4.4 years). Furthermore, we lack

information on the indications for PPI use in our dataset. It is possible that the relationship between PPI use and dementia is mediated by 1 or more of these pathways. Future studies assessing potential mediators in long-term cumulative PPI use and risk of dementia is warranted.

Active comparator designs reduce the risk of unmeasured confounding.[44] In active comparator studies, the comparison group is another drug of interest instead of a "no-use" comparison group.[44] This form of study design offers advantages such as reduced unmeasured confounding and has increased potential for overlapping characteristics between groups.[44] As a secondary analysis, we examined the relationship between

Table 4 Hazard Ratios for Incident Dementia by Cumulative Proton Pump Inhibitor Use With H2RAs as an Active Comparator, Atherosclerosis Risk in Communities Study, 2011–2017

| | | Exposure to proton pump inhibitors before baseline | | | |
| | | Any exposure | 1 d - 2.8 y | >2.8–4.4 y | >4.4 y |
		(n = 1,481)	(n = 451)	(n = 459)	(n = 571)
Outcome: incident dementia					
	# of dementia events	165	53	48	64
Exposure to H2RAs (ref) before baseline	Any exposure	0.97 (0.70–1.35)			
	1 d–2.8 y		0.80 (0.39–1.64)		
	>2.8–4.4 y			1.01 (0.53–1.93)	
	>4.4 y				1.02 (0.61–1.70)

Abbreviations: APOE = Apolipoprotein E4; H2RA = H_2 receptor antagonist.
All results are hazard ratios (95% CIs).
We calculated person-years of follow-up as time elapsed from the baseline date (visit 5) to whichever came first: dementia event, loss to follow-up, death, or administratively censored at December 2017.
Adjusted for age, sex, race, education, BMI, APOE4, hypertension, diabetes, stroke, and aspirin use.
H2RAs are the reference group for each analysis.

PPIs and dementia with H2RAs as an active comparator. Greater than 4.4 cumulative years of exposure to PPIs was not associated with greater risk when compared with use of H2RAs. Additionally, there was no association with shorter durations or current use. Few prior studies on the association of PPIs and risk of dementia have considered H2RAs.[12] However, a previous study found that H2RAs but not PPIs increased the risk of cognitive impairment among Black participants.[45] This study is in contrast with our findings and the hypothesized association.

Our study has several strengths. We have physician-adjudicated cases of dementia identified through ICD codes, screening, and cognitive functioning tests. We were able to capture PPI use since the beginning of the FDA approval for various PPI drugs. In addition, we assessed the association of PPI use and dementia among a community-based cohort of Black and White participants. Our study was more heterogeneous in race (22% Black race) compared with previous studies[10,12] conducted within the United States. Finally, we adjusted for the APOE4 genotype.

We acknowledge the following limitations. While we were able to adjust for many potential confounders, residual confounding may still be an issue, and therefore causal inference is limited. We attempted to adjust for anticholinergic medication use due to the reported associations between anticholinergic medication use and cognitive impairment.[46-48] We were, nevertheless, unable to adjust for anticholinergic use because <2% of the total sample used anticholinergics at visit 5. We could not continuously measure PPI use and used the last observation carried forward method to capture all use over a given year. Participants were called annually and may have ended and reinitiated use more than once throughout the contact year. Therefore, we may have misestimated our days of exposure. In addition, we cannot be certain that everyone in our control group did not take PPIs due their over-the-counter availability. ARIC participants were asked to not include over-the-counter medications unless they were prescribed by a doctor. Our study sample included only individuals in the United States who self-identified as Black or White and therefore may not be generalizable to other populations. We also excluded participants with missing covariate information on variables known to be associated with dementia risk including diabetes mellitus, hypertension, and BMI.[49] We believe that these data are missing at random—hence, we do not expect that the results were biased by their absence. Nevertheless, these covariates are associated with the outcome of interest, and this is a limitation. Many ARIC participants died before visit 5, and this could be considered as a source of selection bias. We argue that our sample would be expected to be representative of living older adults.

In summary, we found a nonsignificant association between current use of PPIs and risk of dementia over a median 5.5 years of follow-up. However, long-term cumulative users of PPIs had a 33% increased risk of developing dementia in late life. Future studies should explore possible pathways or mediators between PPI use and the development of dementia.

Appendix Authors

Name	Location	Contribution
Carin A. Northuis, MPH, PhD	University of Minnesota	Drafting/revision of the article for content, including medical writing for content; study concept or design; analysis or interpretation of data
Elizabeth J. Bell, MPH, PhD	Optum	Drafting/revision of the article for content, including medical writing for content; study concept or design
Pamela L. Lutsey, MPH, PhD	University of Minnesota	Drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data
Kristen M. George, MPH, PhD	University of California, Davis	Drafting/revision of the article for content, including medical writing for content; analysis or interpretation of data

Continued

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