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Cumulative Use of Proton Pump Inhibitors and Risk of Dementia: The Atherosclerosis Risk in Communities Study

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ABSTRACT

Background. 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 (1987-89) through 2017. PPI use was assessed via visual medication inventory at clinic Visits 1 (1987-89) to 5 (2011-13) and reported annually in study phone calls (2006-2011). The present study uses ARIC Visit 5 as baseline, since this was the first visit in which PPI use was common. PPI use was examined two ways: current use at Visit 5 and duration of use prior to Visit 5 (Visit 1 to 2011, exposure categories: 0 days, 1 day – 2.8yrs, 2.8-4.4yrs, >4.4yrs). The outcome was incident dementia after visit 5. Cox Proportional Hazard models were used, adjusted for demographics, co-morbid 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. Minimum cumulative PPI use was 112 days and maximum use was 20.3 years. There were 585 cases of incident dementia over median follow up time. 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 prior to 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 amounts 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 use of prescribed PPIs for > 4.4 years by individuals ages 45 years and older is associated with a higher incidence of newly diagnosed dementia.

Keywords: Dementia; Aging; Proton Pump Inhibitors

INTRODUCTION

Proton pump inhibitors (PPIs), available via prescription and over-the-counter, are currently the first-line therapy for the short-term treatment (4 to 8 weeks) of gastroesophageal reflux disease (GERD) and peptic ulcers [1-4]. In a study based on U.S. emergency department visits, PPI use increased from 4% to 9% from 2002 to 2009 [5]. PPIs were dispensed over 115 million times in 2016.[6] Additionally, 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 seven 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 sub-optimal generalizability. Study participants were predominantly white or Asian. Another limitation was that in about 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 intra-individual 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 herein are whether current and greater cumulative exposure to prescribed PPIs would be associated with 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 four US communities: Washington County, Maryland; Forsyth County, North Carolina; selected suburbs of Minneapolis, Minnesota; and Jackson, Mississippi. In 1987-89 (Visit 1), ARIC recruited and examined 15,792 men and women aged 45 to 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, then twice-yearly thereafter [18,19].

ARIC Visit 5 (2011-13), 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 the present study. All participants who were dementia-free at Visit 5 were included for analysis (n=347 prevalent dementia cases). Participants who attended Visit 5 prior to 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 PPIs analysis (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 two weeks. Medications were inventoried by trained staff. PPI use was also ascertained from annual phone calls (contact years 2006 through 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 exam to 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 and including 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 thirty participants from both analyses of PPI exposures.

Histamine$_2$ receptor antagonists (H2RAs) are an alternative class of medication used to treat GERD and other gastric-acid related disorders. In a secondary analysis we examined H2RAs use as an active comparator. Assessment of H2RAs was similar to that of PPIs, including

both via 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 three sources: i) for those who completed in-person examinations at Visits 6 (2016-2017) and 7 (2018-2019), dementia status was ascertained via neuropsychological examination, ii) twice-yearly participants were called by telephone and the Six Item Screener conducted, with follow-up proxy completion of the AD8 screening tool when appropriate, and iii) surveillance via hospital discharge codes and death records, which were gathered as part of the cohort's standard procedures. Suspected dementia cases were adjudicated by a panel of physicians and neuropsychologists who classified both dementia status (yes/no) and estimated date of 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 anti-hypertensives, H2RAs, anticholinergics, aspirin and Vitamin B12 use were assessed via in-person medication inventory at Visit 5. Body mass index (BMI; 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 three times using a random-zero sphygmomanometer after a 5-minute rest, and the average of the final two measurements was used. Hypertension was defined as current use of anti-hypertensive medication, systolic blood

pressure (BP)>140 mmHg, or diastolic BP>90 mmHg. Diabetes was defined as treatment for diabetes, a fasting glucose level of ≥126 mg/dL, non-fasting 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 done.

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 (12/31/2017), whichever came first. Models for current PPI use analysis adjusted for the following: Model 1: age, sex, race-center, education, and APOE4 genotype; Model 2: model 1 + body mass index; Model 3: model 2 + current H2RA use, current anticholinergic use, aspirin use, diabetes mellitus, stroke, and hypertension. The cumulative PPI use models were similar, except that 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 determine if these modified the association. We also examined if the addition of participant B12 medication use as an explanatory variable to model 3 changed our observed results.

Secondary analyses employed H2RA use as an active comparator. This design compared PPI use to 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 to 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 to 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 manuscript proposal process (https://sites.cscc.unc.edu/aric/pubs-policies-and-forms-pg).

RESULTS

A total of 6,538 participants attended Visit 5. Of these, 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 due to 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 of calculating cumulative exposure where 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 analysis.

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. (Median use was 3.8 years; IQR 2.2-5.1 years; mean use was 4.4 years.) Baseline characteristics of cumulative PPI users and nonusers are displayed in Table 1. Current PPI users had a mean age of 75.6 ± 5.1 years, similar to 75.3 ± 5.1 years among 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 to 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% Confidence Interval (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 to 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 non-significant 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 B12 use as an explanatory covariate to model 3 did not change the results presented 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: 0.78 (0.55, 1.11))

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

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 to nonuse. 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's 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 a majority of the studies was defined as users vs nonusers. In our analysis, the risk of dementia among current PPI users is in agreement of 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's disease after a 3-year lag window (Odds Ratio [OR]: 1.03 [95% CI: 1.00-1.05 [23]. Additionally, it found no association with ≥3 years of PPI use (OR: 0.99 [95% CI: 0.94-1.04]) [23]. A US cohort study by Grey et al. 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 prior to baseline among a dementia-free population.

The underlying mechanism between PPIs and dementia has been postulated through two plausible pathways: vitamin B_{12} deficiency and impaired amyloid metabolism [24]. Lam et al. reported a significant association between PPI use and low levels of Vitamin B_{12} [25]. Low B_{12}

levels are associated with a decline in cognition [26]. We are unable to comment on participant B12 levels in our dataset. However, adjusting for participant baseline B12 use did not alter the results on 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's disease by increasing β-amyloid plaques within the brain [24]. Another pathway is via 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 hypo-chlorhydria[38]. Specific gut microbiota changes reported with PPI use include an overall decrease in microbial diversity as well as dysbiosis or alterations in the composition of the microbiome. In turn, dysbiosis and decreased microbial diversity has been reported in patients with Alzheimer's disease and in animal models of dementia[39,40]. Specific pathways postulated to link gut dysbiosis and Alzheimer's disease include neuro-inflammation, 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 H. 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 is 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 suggests 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 one 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 like reduced unmeasured confounding and has increased potential for overlapping characteristics between groups. [44] As a secondary analysis, we examined the relationship between PPIs and dementia with H2RAs as an active comparator. Results from this analysis were similar to those of the main analyses; nominally >4.4 cumulative years of exposure to PPIs was associated with greater risk as compared to use of H2RAs, but there was no association with use for 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 via 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 (year 1989). Additionally, 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 to previous studies [10,12] conducted within the United States (~10-12% Black race). Finally, we adjusted for the APOE4 genotype.

We acknowledge the following limitations. While we were able to adjust for many of the 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 in the cumulative analysis due to small cell sizes. However, <2% of the total sample used anticholinergics at Visit 5. We could not continuously measure PPI use and utilized 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. Additionally, we cannot be certain that everyone in our control group did not take PPIs due its over-the-counter availability. ARIC participants were asked to not include over-the-counter medications in unless they were prescribed by a doctor. Our study sample included only individuals in the US 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 prior to 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.

CONCLUSION

In summary, we found a positive but non-significant 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 in developing dementia in late life. Future studies should explore possible pathways or mediators between PPI use and the development of dementia.

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

	Exposure to Proton Pump Inhibitors before Baseline			
	0 days (N= 4,222)	**1 day - 2.8 years* (N= 497)**	**2.8 - 4.4 years* (N= 496)**	**>4.4 years* (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 (%)	3088 (73.1)	389 (78.3)	374 (75.4)	395 (79.5)
H2-Receptor Antagonist Use (%)	271 (6.4)	37 (7.4)	37 (7.5)	37 (7.4)
Diabetes (%)	1308 (31.0)	169 (34.0)	176 (35.5)	189 (38.0)
APOE (e4 carrier) (%)	1192 (28.2)	109 (21.9)	135 (27.2)	104 (20.9)
Smoking (%)				
Never	1601 (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 (%)	2816 (66.7)	372 (74.8)	375 (75.6)	390 (78.5)
Anti-cholinergic Use (%)	18 (0.4)	4 (0.8)	11 (2.2)	6 (1.2)
Vitamin B12 use (%)	176 (4.2%)	23 (4.6)	28(5.6)	32 (6.4)

All values are mean (standard deviation) or frequency (%) as indicated. Some percentages will not add to 100% due to missingness. Hypertension defined as systolic blood pressure >140, diastolic blood pressure >90 mmHg, and/or on anti-hypertensive medication Diabetes was defined as treatment for diabetes, a fasting glucose level of ≥126 mg/dL, non-fasting 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 B12 use was defined as a participant who reported taking a medication with vitamin B12 or B-complex.

*Minimum PPI use was 112 days (0.31 years), Maximum use was 20.3 years. Median use was 3.8 years; mean use was 4.4 years.

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]	22236.7	7445.6
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)

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 + current anti-cholinergic use, hypertension, diabetes, stroke, aspirin use, and current H2RA use

Abbreviations: PY = person-years; HR = hazard ratio; CI: Confidence Interval; PPI: Proton Pump Inhibitor; H2RA = H2 Receptor Antagonist; APOE = Apolipoprotein E4

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 days (n = 4,222)	**1 day - 2.8 years (n = 497)**	**>2.8 - 4.4 years (n = 496)**	**>4.4 years (n = 497)**
Outcome: Incident Dementia				
# of dementia events	415	56	56	58
# of person-years[a]	21,941.5	2,591.3	2,631.9	2,437.8
Crude IR/1000 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: HR = hazard ratio; CI: Confidence Interval; IR: incidence rate; H2RA = H2 Receptor Antagonist; APOE = Apolipoprotein E4

[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 12/31/2017.

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

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 (n = 1,481)	**1 day - 2.8 years (n = 451)**	**>2.8 - 4.4 years (n = 459)**	**>4.4 years (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 day - 2.8 years		0.82 (0.39, 1.70)		
	>2.8 - 4.4 years			1.01 (0.53, 1.93)	
	>4.4 years				1.02 (0.61, 1.70)

Abbreviations: H2RA = H2 Receptor Antagonist; APOE = Apolipoprotein E4

All results are Hazard Ratios (95% Confidence Intervals)

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 12/31/2017.

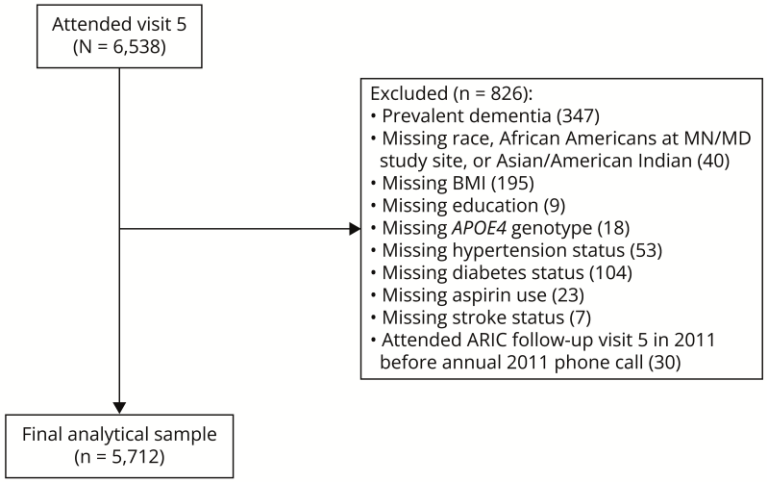
Adjusted for age, sex, race, center, education, BMI, APOE4, hypertension, diabetes, stroke, aspirin use

H2RAs are the reference group for each analysis

FIGURE TITLE AND LEGEND

Figure. Flow chart of participants in the Atherosclerosis Risk in Communities Study, 2011-2017

Figure Legend: BMI = Body Mass Index; APOE4 = Apolipoprotein E4



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