ARIC Manuscript Proposal # 3288

1.a. Full Title: Association between proton pump inhibitor use and the risk of dementia: The Atherosclerosis Risk in Communities (ARIC) Cohort Study

b. Abbreviated Title (Length 26 characters): PPI use and dementia risk

2. Writing Group:
  Writing group members:

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I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. [please confirm with your initials electronically or in writing]

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3. Timeline: Data analyses to begin immediately after proposal approval; A manuscript is expected to be prepared within 10 months.

4. Rationale:
   Proton pump inhibitor (PPI) use in the community is substantial and increasing. PPIs are effective in the treatment of GERD and peptic ulcers and hence are frequently prescribed for these conditions. (1) There are several aspects of PPI use and prescription that are of concern.
First, PPI use is common and older adults comprise a very high fraction of PPI users. In a study of U.S. emergency department visits, 9% of the population overall in 2009 used PPIs. Of these users, 46.7% were older than 65 years (2). Secondly, up to 63% of PPI prescriptions did not have a documented gastrointestinal diagnosis (2) and hence their use could be considered inappropriate. Thirdly, the prevalence of PPI use is increasing in the general population. In a study based on U.S. emergency department visits, PPI use increased from 4% to 9% in 2002-2009 (2). Finally, PPI use is expensive and costs an estimated $11 billion in annual medical expenditures (3).

There are concerns regarding the health consequences of PPI. The FDA has not approved long-term PPI use; nevertheless, chronic PPI use is common (4). In 2010 and 2012, the Food and Drug Administration (FDA) issued two safety warnings regarding PPIs (5-7). The first pertained to increased fracture risk and the second for increased infection with Clostridium difficile (5-6). In addition to the FDA warnings, associations with other negative health consequences including pneumonia, vitamin deficiencies (magnesium and vitamin B$_{12}$), renal disease, cardiovascular events, and small intestinal bacteria growth have been reported in the literature (1, 8,9). Concerns for cognitive impairment and dementia have also been reported (1, 10-11). In this manuscript, we focus on the association between PPI use and cognitive outcomes.

PPIs could play a role in cognitive impairment through two plausible pathways: vitamin B$_{12}$ deficiency and impaired amyloid metabolism (10-12). Lam et al. reported a significant association of PPI use and low levels of Vitamin B$_{12}$ (13). Low B$_{12}$ levels are reported to be associated with a decline in cognition (14). As a second plausible mechanism, PPI use may affect β-amyloid levels. In experimental mice models, PPI use has been associated with increased β-amyloid levels in brains (12, 15). PPIs may modify the γ-secretase enzyme which cleaves a precursor protein to β-amyloid, and hence contributes to the development of Alzheimer’s disease (12) by increasing β-amyloid plaques.

Epidemiological data supporting the association between PPIs and impaired cognition is mixed. While preclinical data found associations with plausible mechanisms, epidemiological studies have been inconsistent (16-20). These epidemiologic studies varied greatly in study design, dementia ascertainment, confounders modeled (such as obesity, functional status, physical activity, and NSAID use), and length of follow-up time (< 10 years) (10, 11, 21). The ARIC cohort is well suited to add to the literature on PPI use and cognitive outcomes. Strengths of the ARIC cohort include detailed ascertainment of PPI use and cognitive outcomes as follows: 1) PPIs were approved by the FDA in 1989 and this was coincident with the start of ARIC visits, thereby classifying PPI users as first-time users and reducing selection bias (22); 2) a series of cognitive, and functional assessments were used to assess cognition; 3) dementia and cognitive impairment cases were physician adjudicated; 4) follow-up time is over 15 years and dementia has a long natural history; and, 5) high quality measurement of the covariates of interest.

We propose to explore the association of PPI use with the incidence of both dementia and mild cognitive impairment (MCI) based on a longer follow-up time and precise event adjudication. Histamine-2 receptor antagonists (H$_{2}$RA) will be used as a ‘control’ exposure.

5. Main Hypothesis/Study Questions:

1. PPI use is associated with dementia and MCI, independent of known dementia risk factors.
2. There is no association between histamine-2 receptor antagonists (H2RA) and dementia or MCI. H2RA are another class of medications used for similar gastrointestinal diagnoses as PPIs. The lack of an association will demonstrate the specificity of an association between PPI use and dementia and MCI. It will also help address potential concerns about indication bias.

6. Design and analysis (study design, inclusion/exclusion, outcome and other variables of interest with specific reference to the time of their collection, summary of data analysis, and any anticipated methodologic limitations or challenges if present).

Study Design
Visit 2 will serve as baseline. We will exclude individuals with a history of dementia or MCI at baseline from analysis.

Exposure
Primary exposure of PPI and H2RA will be ascertained in two ways:
1. The ARIC study measure PPI and H2RA use by visual inspection of pill bottles at each ARIC visit.
2. Annual telephone follow-up calls starting in September 2006, where participants read all medications they were taking that were prescribed by a doctor.
Secondarily, we will also assess PPI use modeled by a cumulative use and b) by PPI type.
PPI use will be analyzed as a time dependent variable.

Outcome
The following outcomes will be considered:
1. Incident dementia from Visit 2 (1987-89) to 2017 will be defined by combining all available information:
   • Visit 5 (2011-2013) and 6 (2016-2017) cognitive assessments and battery tests
   • Telephone Interview for Cognitive Status (TICSm)
   • Hospitalization Discharge Codes
   • Phone-based dementia surveillance via the Six Item Screener (SIS; administered to all participants during twice-annual phone calls) and when scores are low follow up AD8 interviews with proxies.
2. Visit 5 and 6 syndromic adjudicated events: dementia or MCI, dementia, MCI
3. 25-year cognitive change from Visit 2 through Visit 6

Covariates
All covariate information will be obtained from Visit 2 The following are covariates of interest: age, sex, education, BMI, race, polypharmacy/number of drugs, functional movement, physical activity, anticholinergic drug usage, H2RA use, NSAIDs use (aspirin), comorbid conditions (hypertension, diabetes, stroke/TIA, depression, hyperlipidemia, and heart disease), and ApoE4 allele status.

Statistical Analyses:
Baseline characteristics will be between exposed and unexposed users and summarized as mean (SD) if continuous variables or medians (IQR) if categorical variables.

Multivariable Cox regression will be used to assess the hazard of incident dementia by PPI use during follow-up. Follow-up time will begin at the visit 1 exam until an adjudicated dementia case from visits 5/6 and TICS, a dementia hospitalization ICD code, loss-to-follow-up, death, or the visit 6 exam date. A secondary analysis will be conducted to account for duration of PPI use and incident dementia/MCI. Durations of PPI use include 1 year, ≥1 year, ≥3 years, and ≥5 years in total PPI use.

For adjudicated outcomes, relative risk regression with a Poisson distribution and a log link will be used to assess the association between PPI use and risk of incident dementia and MCI. Inverse probability weighting will be used to account for selection bias related to death and differential participation from visit 2.

Additional analyses will assess interactions by sex, race, SES and APOE4 status, by including cross-product terms in the models. Results will also be reported stratified by these key covariates, given inherent interest, include evaluation of interaction by stratification by various covariates to assess if there is a difference in the association by sub-group (i.e. H2RA use, PPI type, sex, race, APOE4 status). A race-specific analysis may be conducted to assess if there is an issue of convergent validity with cognitive tests and race groups. H2RA will serve as an active comparator in the analyses (23).

**Limitation:**
The main limitations of the analyses are the medication ascertainment gap from 1998 to 2006, and potential indication bias and selection bias related to the dementia outcome.

**References**
5. Food and Drug Administration. FDA drug safety communication: Possible increased risk of fractures of hip, wrist, and spine with the use of proton-pump inhibitor. 2010.
6. Food and Drug Administration. FDA drug safety communication: Clostridium difficile-associated diarrhea can be associated with stomach acid drugs known as proton-pump inhibitors (PPIs). 2012.


7.a. Will the data be used for non-CVD analysis in this manuscript? _X_ Yes  ____ No

b. If Yes, is the author aware that the file ICTDER03 must be used to exclude persons with a value RES_OTH = “CVD Research” for non-DNA analysis, and for DNA analysis RES_DNA = “CVD Research” would be used? _X_ Yes  ____ No
(This file ICTDER has been distributed to ARIC PIs, and contains
the responses to consent updates related to stored sample use for research.)

8.a. Will the DNA data be used in this manuscript? __X__ Yes    ___ No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating
   Center must be used, or the file ICTDER03 must be used to exclude those with value
   RES_DNA = “No use/storage DNA”? __X_ Yes    ____ No

9. The lead author of this manuscript proposal has reviewed the list of existing ARIC
   Study manuscript proposals and has found no overlap between this proposal and
   previously approved manuscript proposals either published or still in active status.
   ARIC Investigators have access to the publications lists under the Study Members Area of
   the web site at:  http://www.cscc.unc.edu/ARIC/search.php

   _X____ Yes       _______ No

10. What are the most related manuscript proposals in ARIC (authors are encouraged to
    contact lead authors of these proposals for comments on the new proposal or
    collaboration)?

ARIC Manuscript Proposal #XXXX: Association between the use of proton pump inhibitors and
   cardiovascular disease in the Atherosclerosis Risk in Communities (ARIC) Cohort Study (Bell)

ARIC Manuscript Proposal #2509: Association between the use of proton pump inhibitors and
   chronic kidney disease in the Atherosclerosis Risk in Communities (ARIC) Cohort Study

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any
   ancillary study data? _____ Yes    _X__ No

11.b. If yes, is the proposal
   __   A. primarily the result of an ancillary study (list number* __________)
   __   B. primarily based on ARIC data with ancillary data playing a minor role
         (usually control variables; list number(s)* __________  __________ __________)

*ancillary studies are listed by number at http://www.cscc.unc.edu/aric/forms/

12a. Manuscript preparation is expected to be completed in one to three years. If a
    manuscript is not submitted for ARIC review at the end of the 3-years from the date of the
    approval, the manuscript proposal will expire.

12b. The NIH instituted a Public Access Policy in April, 2008 which ensures that the public
    has access to the published results of NIH funded research. It is your responsibility to upload
    manuscripts to PubMed Central whenever the journal does not and be in compliance with this
    policy. Four files about the public access policy from http://publicaccess.nih.gov/ are posted in
http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to PubMed central.