ARIC Manuscript Proposal #3492

PC Reviewed: 10/8/19	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Polypharmacy, hyperpolypharmacy and dementia status among the elderly: The Atherosclerosis Risk in Communities Study

b. Abbreviated Title (Length 26 characters): Polypharmacy and dementia

2. Writing Group: Pam Lutsey, Joel Farley, Jeff Misialek, Kevin Sullivan, Eric Whitsel, Kamakshi Lakshminarayan, Anna Kucharska-Newton, Morgan Grams

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

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3. Timeline: Analyses will begin immediately; pen draft expected in ~6 mos.

4. Rationale:

Polypharmacy and hyperpolypharmacy are often defined as a patient's use of ≥5 or ≥10 concomitant medications, respectively.[1,2] Polypharmacy has been associated with an increased risk of drug-drug interactions as well as adverse outcomes such as mortality, falls, thrombotic events and major bleeding.[1,3-5] Based on data from NHANES,[6] over the time-frame of 1999-2000 to 2011-2012 the prevalence of polypharmacy has increased from 8.2% to 15.0% among all US

adults, and from 24% to 39% among individuals aged 65 and older. The prevalence of hyperpolypharmacy was not reported. However, using ARIC visit 5 data, the prevalence of hyperpolypharmacy was 16%.[7] In addition to having a higher prevalence of polypharmacy, aging-related changes in pharmacokinetics and pharmacodynamics put older adults at greater risk for adverse drug events. An increased prevalence of polypharmacy and hyperpolypharmacy among older individuals is not unexpected since multimorbidity (defined as the coexistence of two or more chronic conditions)[8] is highly prevalent among the older adults. The prevalence of multimorbidity is 60-70% in individuals older than 65, whereas it is >80% in those aged ≥85 years.[9] Dementia and mild cognitive impairment (MCI) are also more common in advanced age. It is plausible that cognitive decline may interfere with a patient's ability to follow prescribed regimens.

Potentially inappropriate medication (PIM) use is a related and important issue.[10,11] In a prior ARIC manuscript conducted using visit 5 data, 31% of participants had a PIM based on their age.[7] In 2019 the American Geriatrics Society (AGS) updated the Beers Criteria® for Potentially Inappropriate Medication Use in Older Adults,[12] which is "an explicit list of PIMs that are typically best avoided by older adults in most circumstances or under specific situations, such as in certain diseases or conditions." They are intended for use in adults aged 65 and older in ambulatory, acute and institutionalized settings of care (except hospice and palliative settings).

Using data from the 6th ARIC (2016-2017) visit we propose to report the prevalence of polypharmacy and hyperpolypharmacy among a community-based sample of >4,000 individuals aged 75-94 years, as well as interrelations between polypharmacy according to cognitive status (dementia, mild cognitive impairment). Secondary analyses will (separately) consider frailty as an outcome, and will estimate the prevalence of PIMs by dementia and frailty status. Findings from this analysis will provide perspective on the pervasiveness of polypharmacy among elderly individuals with and without cognitive impairment. We recognize that this topic is potentially provocative, and will carefully craft the discussion to balance a) the recognition that medications are prescribed and needed to manage often numerous medical conditions versus b) awareness that unnecessary drug use does take place[13] and a periodic review of medications may be appropriate in some instances. We will be careful not to infer causality; this paper will be largely descriptive.

5. Main Hypothesis/Study Questions:

Main hypotheses:

a) Polypharmacy and hyperpolypharmacy will be common among older adults. The prevalence will be highest among participants with dementia, followed by those with MCI, and then those with no cognitive deficits.

Secondary hypotheses:

b) Polypharmacy and hyperpolypharmacy will be highest among participants who are frail, followed by those who are pre-frail, then those classified as robust.
c) PIM usage will also be common overall, and will have the highest prevalence among participants with dementia, followed by those with MCI, and then those with no cognitive deficits.

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: Cross-sectional among participants who attended clinic visit 6.

Inclusion/exclusion: Blacks from MN and MD, not black or white, missing information on dementia status or prescription medications.

Key exposures:

- Medication use will be ascertained on the basis of medications reported at the time of the visit.
- Polypharmacy: A count of the number of medications used; polypharmacy will be defined as ≥5 medications and hyperpolpharmacy as ≥10 medications. Supplement use will not be considered.
- PIM usage: Defined by Beers Criteria.[14] Similar to a prior ARIC manuscript[7] we will focus on age-based PIM use in older adults (Beers Criteria Table 2), but will not include contradictions based on two or more combined criteria such as based on one's age plus an existing condition or the use of another medication concomitantly (Beers Criteria Table 3). Other criteria such as STOPP may be explored.

Outcomes:

- Dementia, MCI or normal, per visit 6 "level 1" classifications.
- Frail and pre-frail status as previously defined in ARIC.[15]

Other variables: Age, sex, race/ethnicity, education, possibly comorbid conditions (CVD in its various forms, cancer, COPD, etc.)

Data analysis: This manuscript will be largely descriptive. Means and prevalences will be reported. Interrelations between polypharmacy, hyperpolpharmacy and dementia status will be evaluated using relative risk regression (for dichotomous outcomes) or polytomous regression (for the 3-level dementia/MCI/normal outcome). Model 1 will be adjusted for age, race and sex. Model 2 will additionally adjust for educational attainment. We may also include a model (3) adjusted for comorbid conditions. In addition we may stratify according to specific conditions. Analyses of secondary hypotheses will follow a similar pattern.

Anticipated methodological limitations or challenges:

- We did consider using the Medicare Part D data, however it is our strong preference to use the clinic-based medication data since the Medicare data are only available on a subset, and inclusion of the Medicare data would complicate the analysis.
- Though not directly relevant to this descriptive manuscript, it is worth noting that it is difficult to disentangle the negative consequences of polypharmacy from the underlying health conditions for which the drugs are prescribed ('confounding by multimorbidity').

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? ____ Yes __X__ 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"? ____ Yes __X__ 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/mantrack/maintain/search/dtSearch.html

___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)?

2741**:** Medication Utilization Patterns 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? __X__ Yes ____ No

11.b. If yes, is the proposal
_X__ A. primarily the result of an ancillary study (list number* _2008.06 (NCS) _)
___ 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 https://www2.cscc.unc.edu/aric/approved-ancillary-studies

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://www.cscc.unc.edu/aric/index.php, under Publications, Policies & Forms. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to PubMed central.

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