ARIC Manuscript Proposal #4053

PC Reviewed: 5/17/22  
SC Reviewed: _________

Status: _____  
Status: _____

Priority: 2  
Priority: _____

1. **Full Title:** Medication non-adherence, socioeconomic status, and adverse outcomes in older adults: The Atherosclerosis Risk in Communities (ARIC) Study
   
   **Abbreviated Title (Length 26 characters):** Medication non-adherence, socioeconomic status, and adverse outcomes in older adults

2. **Writing Group:**
   
   Writing group members:
   
   Christina Yin, Morgan Grams, Josef Coresh, Anna M Kucharska-Newton, David Couper, Pamela Lutsey, and Jung-Im Shin

   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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   **ARIC author** to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator).

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3. **Timeline:**

   Manuscript submission for ARIC review will be completed within one year from the approval of the manuscript proposal.
4. **Rationale:**
Medication adherence refers to the degree to which patients follow medical instructions regarding their prescribed medication. Medication non-adherence is a major public health concern, and it significantly hinders the treatment of diseases and is associated with poor health outcomes. A previous study has shown that approximately 20% to 50% of patients with chronic diseases are not adhering to their medications. Older adults (aged ≥65 years), in particular, are more likely to have a greater burden of chronic diseases that require multiple prescribed medications. A study reported that medication non-adherence was 69.6% among older adults who have been recently discharged from hospitals.

Low socioeconomic status (SES), such as income, education, and neighborhood, may be related to medication adherence. People living in low SES are challenged by limited access to healthcare and a lack of care coordination that may contribute to low medication adherence. Moreover, health literacy, an important factor for medication adherence may be more frequently inadequate among people living in low SES. A systematic review and meta-analysis of SES and medication non-adherence in antihypertensive drugs reported that only 32 out of the 56 included studies reported any SES measures and only 7 out of the 32 studies looked at more than one SES component in their analysis. None of the studies used comprehensive measures of SES. In this study, the meta-analyzed adjusted risk estimate for nonadherence according to SES (high vs. low from 30 studies) was 0.89 (95% CI, 0.87-0.92). Moreover, while it is known that both medication non-adherence and SES affect health outcomes, it remains unknown whether the impact of medication non-adherence on health outcomes differs by SES.

This proposed study aims to examine 1) the association between SES and medication non-adherence and 2) whether the associations between medication non-adherence and adverse health outcomes differ by SES in older adults, using comprehensive measures of SES.

5. **Main Hypothesis/Study Questions:**

**Aim 1:** To evaluate the association of cumulative SES (i.e., based on area-level and individual-level SES components) with medication non-adherence in older adults.

**Hypothesis 1:** We hypothesize that the prevalence of medication non-adherence will be higher in participants with lower cumulative SES, adjusting for participants’ characteristics.

**Aim 2:** To determine if the associations between medication non-adherence and adverse health outcomes differ by cumulative SES status in older adults.

**Hypothesis 2:** We hypothesize that risk of mortality and hospitalization associated with medication non-adherence will be greater among participants in low cumulative SES, compared with those in high cumulative SES.
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:**
A cross-sectional study (Aim 1) and prospective cohort study (Aim 2) of the Atherosclerosis Risk in Communities (ARIC) study participants who attended the Visit 5 examination from 2011 to 2013 (mean age 76 years). We will analyze the visit 5 (baseline) and follow-up data.

**Inclusion/exclusion:**
Participants from ARIC Visit 5 who were taking at least one medication (prescribed or over-the-counter (OTC), but not vitamins or dietary supplements, non-injectable solutions, creams/lotions or devices) will be included. Participants with missing Gree-Levin Scale data, SES, or other key covariates will be excluded. We will exclude participants who were neither white or Black.

**Exposure variable for Aim 2 and outcome variable for Aim 1**
Medication non-adherence information is available from ARIC Visit 5. Medication non-adherence is assessed using the Gree-Levin Scale which consists of four questions. Each positive response corresponds to one point. Low medication adherence is represented by a high Gree-Levin score, with 3-4 being low adherence, 1-2 being intermediate adherence, and 0 being high adherence.

**Table 1. Gree-Levin Scale Questions**

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
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<tbody>
<tr>
<td>1. Do you ever forget to take your medicine?</td>
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<tr>
<td>2. Are you careless at times about taking your medicine?</td>
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<tr>
<td>3. When you feel better do you sometimes stop taking your medicine?</td>
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<td></td>
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<tr>
<td>4. Sometimes if you feel worse when you take your medicine, do you stop taking it?</td>
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</tbody>
</table>

**Outcome variables for Aim 2**
Mortality during follow-up after visit 5
First all-cause hospitalization as well as rate of all-cause hospitalizations during follow-up after visit 5

**Potential effect measure modifiers for Aim 2 and exposure variables for Aim 1**
Cumulative SES
We will use a area-level SES variable (i.e., area deprivation index [ADI]) and two individual-level SES variables (i.e., education and household income) to derive cumulative SES scores. Individual SES variables will be scored as 0–4 for highest to lowest ADI quintiles (i.e., lowest to highest SES), 0–2 for lowest to highest education, and 0–3 for lowest to highest income, then
will be summed to create a cumulative SES score of 0–9. We will categorize participants into three groups of low (score 0–2), middle (score 3–6), and high cumulative SES (score 7–9).

**Area-level SES**
We will use the existing ADI data at visit 5 that have been linked with ARIC participant address at the census tract level.
Area-level SES will be categorized into quintiles, with 0 being the highest ADI quintile and 4 being the lowest ADI quintile. A higher ADI quintile corresponds to a lower area-level SES.

**Individual-level SES**
In the ARIC study, education level is determined from Visit 1, which surveyed the highest education completed. Education is categorical into three groups of less than high school; high school or equivalent; and college or higher education.
Household income is ascertained from Visit 4. For analysis purposes, we will further categorize household income into three groups. The three groups are household income< $25,000 per year; $25,000 to < $50,000 per year; and ≥ $50,000 per year ($50,000 in 2013 corresponds to 60,535 in 2021).

**Other variables:**
Age, sex, race-center, hypertension, diabetes, coronary artery disease, heart failure, stroke, peripheral artery disease, chronic lung disease, liver disease, estimated glomerular filtration rate (eGFR), health literacy, smoking status, alcohol intake, body mass index, physical activity index, depression scale (CES-D), insurance type, SBP, HbA1c, total cholesterol, history of hospitalization at visit 5, and number of medications (prescribed or OTC).

**Statistical analysis:**
- We will summarize the baseline characteristics of the study population by medication adherence status (low adherence: yes/no) using t-test (for continuous variables) and Pearson chi-squared test (for categorical variables).
- **Aim 1**
  a. We will estimate the prevalence of medication non-adherence according to cumulative SES.
  b. We will quantify the association of cumulative SES with medication non-adherence using multivariable logistic regression model.
- **Aim 2**
  a. We will plot the Kaplan-Meier curve for mortality and first hospitalization by medication non-adherence and cumulative SES groups.
  b. We will examine if the association of low medication adherence with mortality and first hospitalization differs by cumulative SES using Cox proportional hazards regression models with interaction term between medication non-adherence and cumulative SES variables.
  c. We will also examine if the association of low medication adherence with all-cause hospitalization rate differs by cumulative SES using negative binomial regression model with interaction term between medication non-adherence and cumulative SES variables.
i. Model 1: Medication non-adherence and cumulative SES variables adjusted for sociodemographic variables (age, sex, race-center, and insurance type)
ii. Model 2: Model 1 + clinical characteristics
iii. Model 3: Model 2 + lifestyle characteristics

We will repeat the analysis using each component of cumulative SES (education, income, and ADI).

We will perform the sensitivity analysis only among participants who were taking at least 5 medications (polypharmacy).

Limitations:
Residual confounding is possible.

7.a. Will the data be used for non-ARIC analysis or by a for-profit organization in this manuscript? ____ Yes _√_ No

b. If Yes, is the author aware that the current derived consent file ICTDER05 must be used to exclude persons with a value RES_OTH and/or RES_DNA = “ARIC only” and/or “Not for Profit”? ____ Yes ____ No
(The 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 _√_ No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the current derived consent file ICTDER05 must be used to exclude those with value RES_DNA = “No use/storage DNA”? ____ 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.csc.unc.edu/aricproposals/dtSearch.html

____√____ 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 #2043
Predictors of Medication Adherence in Cardiovascular Disease: Understanding the Complex Relationships Between Disease Burden, Health Literacy, and Socioeconomic Status
11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? ____ Yes √ 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 https://sites.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.
Reference


