ARIC Manuscript Proposal Form

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Publication Committee Review Date: **_05/14/24**
ARIC Manuscript Proposal Number: **#4447**

1.a. Full Title: Association of Obesity with Aortic Valve Disease: The Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters): Obesity and AVD

2. Writing Group [please provide a middle initial if available; EX: Adam L Williams]:
Writing group members: Chunxiao Zhang, Ethan Moser, Anne Eaton, Jeremy Van't Hof, Weihong Tang, Amil Shah, Aaron Folsom, Lin Yee Chen

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. __CXZ __ **[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 (The ARIC author should be involved enough in ARIC to be able to point the lead author to appropriate ancillary study PIs and to be able to search ARIC manuscript proposals if the lead author doesn't have the access needed to do such a search).

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3. Timeline: Data collection has been completed. Data analysis and manuscript preparation will be done in the next 6 months.

4. Rationale:

Aortic valve disease (AVD) is common among older adults. AVD is associated with a greater risk of various adverse events, including all-cause mortality, incident heart failure (HF), and incident atrial fibrillation (AF).[1,2] AVD can be primarily classified as aortic valve stenosis (AS) and aortic valve insufficiency (AI) based on the pathological abnormality and sequential hemodynamic change. Recent guidelines categorize AVD into four stages (A, B, C, and D),[3,4] and even early stages (A and B) are associated with adverse cardiovascular outcomes.[1] The underlying causes and risk factors for AVD are not fully understood. Current evidence suggests potential associations with atherosclerotic risk factors, such as hypertension, dyslipidemia, and diabetes.[5,6]

Obesity, particularly the accumulation of visceral adiposity, contributes to metabolic disorders that result in hypertension, dyslipidemia, and atherosclerosis.[7] While these adverse effects are widely acknowledged, the role of obesity in the development of AVD has not been extensively investigated. The association between obesity and AS has received the most attention. Although some study limitations exist, [8,9] a few studies have indicated a positive association of obesity with AS.[9,10] A Mendelian randomization study suggested this association is causal.[10] The few cohort studies examining whether obesity contributes to AI suggest a weak association, at best.[11] Furthermore, no study evaluated "pure" AI. In ARIC, we have the ability to evaluate AI without AS. Previous studies have mostly studied Whites, so there is little information on whether obesity is associated with AVD in Black individuals. The prevalence of obesity is substantially higher in Blacks than Whites[12], so even if the relative risk is no different in Blacks vs. Whites, the population-attributable risk may be greater.

Therefore, we propose to explore the association between obesity and AVD in ARIC. Body mass index (BMI) and waist-hip ratio will be measures for obesity. Incident AVD diagnosis between visits 5 and 7 is available from echocardiograms of both visits and hospital discharge ICD codes. AS was quantified with trans valvular aortic valve peak jet velocity and aortic valve area at Doppler. AI was qualitatively assessed by overreading echocardiographers based on color Doppler signal.

5. Main Hypothesis/Study Aims:

Aim 1: Evaluate the associations of BMI and waist-hip ratio with incident AVD from visit 5 through visit 7.

- **Hypothesis 1A:** a higher BMI at visit 5 will be prospectively associated with a higher incidence of AVD (AS and AI, stages A to D) through visit 7.
- **Hypothesis 1B:** a higher waist-hip ratio at visit 5 will be prospectively associated with a higher incidence of AVD (AS and AI, stages A to D) through visit 7.

Aim 2: Conduct a stratified analysis in Blacks and Whites (and interaction test) to explore whether there are race-based differences in the association between obesity and AVD.

6. Design and analysis - please address the following aspects:

Study design

Prospective cohort study design (visit 5 to visit 7).

Inclusion:

- Participants who had echocardiographic measures at visit 5. The main analysis will focus on AVD that is based on repeat echo data at visit 7. We will perform a secondary analysis that will consider hospitalization for AVD between visits 5 and 7.

Exclusion:

- Prevalent AVD at visit 5.
- History of heart valve replacement or repair at visit 5.
- History of AF at visit 5.
- History of HF at visit 5.
- Participants who reported race other than Black or White.
- Non-White participants at the Minneapolis and Washington County field centers due to low numbers.
- Missing data on covariates.

Preliminary analysis suggests there are 1,931 ARIC participants who meet inclusion and exclusion criteria.

Variables

Exposures:

BMI will be described as continuous and categorical at visit 5. Continuous BMI will be standardized as per 1-SD increment. Categorical BMI will be defined according to the CDC guidelines:

- Healthy weight and Underweight (BMI < 25)
- Overweight (25 <= BMI < 30)
- Obesity (BMI >= 30)

Waist-hip ratio will be described as continuous and categorical at visit 5. The continuous waist-hip ratio will be standardized as per 1-SD increment. Categorical waist-hip ratio will be defined according to the WHO guidelines:

- Waist-hip ratio is classified as Women: >= 0.85. Men: >= 0.9.

Outcome:

- **Incidence of AVD** (i.e., Stage A to D) classified on the AHA stage classification from visit 5 through visit 7. In addition, for a secondary analysis we will identify incident AVD from hospital discharge ICD codes.
- Category of AVD based on stages.

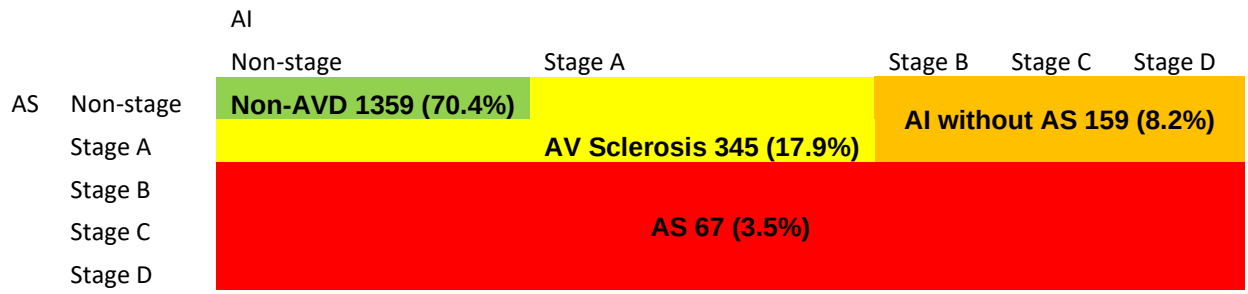
Stage A is at risk for aortic valve dysfunction, including aortic valve sclerosis.

Stage B progressive aortic valve dysfunction, including mild AS or AI.

Stage C severe asymptomatic aortic valve dysfunction.

Stage D severe symptomatic aortic valve dysfunction.

Stages C and D define severe AS and AI.



Covariates

Age, sex, race, education, smoking status, drinking, diabetes, systolic blood pressure, antihypertensive medications, coronary heart disease, HDL-C LDL-C, and eGFR at visit 5.

Data analysis

Baseline characteristics at visit 5 will be described as mean ± SD for continuous variables and proportions for categorical variables.

- Multinomial regression models will be used to estimate the odds ratios of AVD (aortic sclerosis, AI, and AS) associated with increased BMI and waist-hip ratio from visit 5 through visit 7.

For Aim 1 analyses pooling both races, the following models will be used:

- Model 1: (demographic factors) age, sex, race, education.
- Model 2: (comorbidities) Model 1 plus smoking status, drinking, diabetes, systolic blood pressure, antihypertensive medications, coronary heart disease, HDL-C LDL-C, and eGFR.
- Model 3: (Interaction between BMI or Waist-Hip ratio with Race) Model 2 plus interaction.
- Due to the limited sample size in the AS group, only model 1 and the interaction between BMI or Waist-Hip ratio with Race based on model 1 will be reported.

To obtain race-specific ORs (our Aim 2), we will stratify by race and repeat Models 1 and 2.

Sensitivity analysis 1: We will repeat the analysis above. An inverse probability weighting will be incorporated into the sensitivity analysis to handle the missing data.

Sensitivity analysis 2: If there is substantial hospitalized AVD between visits 5 and 7, we will assess selection bias by repeating the main analysis incorporating hospitalized AVD.

7.a. Will the data be used for non-ARIC analysis or by a for-profit organization in this manuscript? (Non-ARIC analysis means that the authors are not regarded as ARIC investigators and the "ARIC author" is essentially just a facilitator rather than an integral part of the writing group.) ☐ **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 is distributed to ARIC PIs annually, 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 or the "sponsoring" ARIC 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 website at: https://aric.cscc.unc.edu/aric9/proposalsearch [ARIC Website□Publications□Proposal Search]

☒ 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)?
#3632. The Association Between Lipid Profiles and the Incidence of Aortic Stenosis in Older Adults: Atherosclerosis Risk in Communities Study
#4226. Association of Left Atrial Function with Valvular Heart Disease: The Atherosclerosis Risk in Communities (ARIC) Study

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or does it use current [or ongoing] ancillary study data (this includes ACHIEVE)? ☒ Yes ☐ No → Skip to question 12

11.b. If yes to 11.a., is the proposal

☒ **A. primarily the result of an ancillary study**

☐ **B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables)**

11.c. If yes to 11.a., list number* _2015.29, 2015.34_

*ancillary studies are listed by number
https://aric.cscc.unc.edu/aric9/researchers/ancillary_studies/approved_ancillary_studies [ARIC Website□Ancillary Studies□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 https://aric.cscc.unc.edu/aric9/publications/policies_forms_and_guidelines [ARIC Website□Publications□Publication Policies, Forms, and Guidelines]. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to PubMed central.

References: ____

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