1. Full Title: The Association of Obesity with HF Phenotypes in the ARIC Study

b. Abbreviated Title (Length 26 characters): Obesity, HFpEF and HFrEF

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

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3. Timeline: We aim to submit this manuscript to the ARIC publications committee <6 months from the date of approval of this manuscript proposal.
4. Rationale:

It is estimated that there are at least 5.7 million patients with heart failure in the United States over the age of 18 years.\textsuperscript{1} In 2009, there were an estimated over 1 million hospital discharges for heart failure, making acute decompensated heart failure the most common cause of hospital admission in patients over the age of 65.\textsuperscript{2} The lifetime risk of developing heart failure in adults over the age of 40 is 1 in 5 and \textbf{approximately 50\%} of people who develop heart failure \textbf{die within 5 years} of diagnosis.\textsuperscript{3,4} From a healthcare cost perspective, in 2010 the estimated annual cost to the nation for heart failure was $32 billion.\textsuperscript{2}

Of those with heart failure, nearly half have a preserved ejection fraction, or heart failure with preserved ejection fraction (HFpEF).\textsuperscript{5,6} While hospitalizations for heart failure with reduced ejection fraction (HFrEF) have stabilized over the past decade, hospitalizations for HFpEF are steadily on the rise.\textsuperscript{5,7} Unfortunately, compared to the multitude of proven therapies for HFrEF, there are no proven therapies for HFpEF to date. We have a very limited understanding of the underlying mechanisms of HFpEF, the associated risk factors, the predictors of poor outcomes, and which treatments should be targeted at which patients.\textsuperscript{8} There is therefore increasing emphasis on characterizing the epidemiology and correlates of these two HF phenotypes in the general population.

Obesity is well established as a potent risk factor for the development of HF.\textsuperscript{9} Obesity predisposes to HF via several mechanisms, including augmented blood volume, increased metabolic demand and myocardial injury.\textsuperscript{10} These processes lead to cardiac remodeling that can result in both systolic and diastolic dysfunction.\textsuperscript{11} Indeed, obesity has been associated with both HFpEF and HFrEF in epidemiologic studies.\textsuperscript{10,12} However, the predominant HF phenotype among individuals with obesity, and how that compares to the distribution of HF phenotypes among individuals in lower weight categories, has not yet been defined. Given the strong relationship between obesity and HF, and clinical differences in the approach to HFpEF and HFrEF, characterizing the association of obesity with HF phenotypes among individuals in the general community is a matter of considerable clinical and public health importance.

Therefore, in this analysis of the Atherosclerosis Risk in Communities (ARIC) Study, we will assess and compare the cross-sectional and longitudinal association of obesity with HFpEF and HFrEF within the ARIC community surveillance and cohort populations. We will additionally aim to characterize the distribution of HF phenotypes across weight categories in the general community.

5. Main Hypothesis/Study Questions:

Aims:

1) To evaluate and compare the association of obesity with HFpEF and HFrEF prevalence in the ARIC community surveillance population, and to assess how the
distribution of HF phenotypes among individuals with obesity (BMI ≥ 30 kg/m²) differs from those observed for HFpEF and HFrEF in lower BMI categories.

2) To evaluate and compare the longitudinal association of obesity with HFpEF and HFrEF in the subgroup of adjudicated HF cases in the ARIC cohort, and to assess how the distribution of incident HF phenotypes among individuals with obesity differs from those observed for incident HFpEF and HFrEF in lower BMI categories.

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:** The analysis evaluating the association between obesity status and the prevalence of HF phenotypes (HFpEF and HFrEF) within the ARIC community surveillance population will primarily be a cross-sectional analysis. However, we will additionally evaluate and compare the associated 30 day and 1 year mortality for HFpEF and HFrEF within each BMI category in the community population. The analysis evaluating the association between obesity status and the incidence of HF phenotypes within the ARIC cohort population will be a prospective analysis assessing the relationship of BMI category at Visit 4 with incident HF occurring from 2005 onwards (the beginning of ARIC adjudication). We will assess whether there is congruence in the findings from these cross-sectional and prospective analyses.

**Exposures:** The primary exposure will be body mass-index (in kg/m²), categorized as normal weight (18.5-24.9), overweight (25.0-29.9) and obese (≥ 30). If there are sufficient numbers of obese individuals within the study populations, we will further subdivide those with obesity into grade I obesity (BMI 30.0-34.9) and grade II or higher obesity (BMI ≥ 35).

**Outcomes:** The primary outcome in the cross-sectional analysis of the community surveillance population will be prevalent HF, which will be subdivided into HFpEF (ejection fraction ≥ 50%) and HFrEF (ejection fraction < 50%). The primary outcome of the prospective analysis in the cohort analysis will be incident HF, defined as the first adjudicated hospitalization or death related to HF occurring after the beginning of adjudication until 12/31/12 (or the most recent follow-up available). Incident HF cases will be subdivided into incident HFpEF and HFrEF using the same definitions described above for the cross-sectional analysis.

**Exclusions:** For all analyses, we will exclude individuals with a BMI less than 18.5 kg/m² (underweight) and those missing data on BMI or the outcomes of interest. For the prospective analysis, we will include ARIC Visit 4 participants and exclude individuals with known HF prior to the beginning of HF adjudication, those individuals with an adjudicated HF diagnosis but missing data on HF phenotype and the small number of participants who are not black or white.
**Covariates:** Age, sex, race, smoking status, alcohol use, systolic blood pressure, use of anti-hypertensive medications, diabetes, LDL-, and HDL-cholesterol, triglycerides and estimated GFR. These covariates will be assessed simultaneously with BMI and prevalent HF in the cross-sectional community surveillance analysis, and assessed at Visit 4 in the prospective cohort analysis.

**Main Analyses:** We will compare the distribution of HF phenotypes among individuals in each BMI category in both cross-sectional (community surveillance) and longitudinal (cohort) analysis.

1) All analyses in the community surveillance population will be weighted to account for the stratified random sample in the ARIC community surveillance data.

2) We will perform univariate comparisons of characteristics across BMI categories, using the Chi-squared test for categorical variables and ANOVA for continuous variables.

3) In the cross sectional analyses, we will evaluate the proportion of individuals with HFpEF and HFrEF within each BMI category, using the chi-squared test to assess differences in the distribution of HF phenotypes across BMI categories

4) We will subsequently perform multinomial logistic regression analyses estimating the OR and 95% CIs for prevalent HF associated with higher BMI categories for HFpEF and HFrEF. We will use the technique of seemingly unrelated regression to compare the magnitude of the associations of higher BMI with both phenotypes of prevalent HF. Regression models will be adjusted for the confounding variables of age, sex, race, smoking status and alcohol use in Model 1 (confounder model), and for those variables as well as systolic blood pressure, use of anti-hypertensive medications, diabetes, LDL-, and HDL-cholesterol, triglycerides and estimated GFR in Model 2 (mediator model).

5) We will use Poisson models to assess the 30-day and 1-year mortality associated with prevalent HFpEF and HFrEF in the overall community surveillance population and within each BMI category. Regression models will include the covariates above as well as therapies at the time of discharge (ACE inhibitors or angiotensin II receptor blockers, beta blockers, calcium channel blocker, diuretics, aldosterone antagonists, and implantable cardioverter-defibrillator).

6) For prospective analyses using the cohort population, we will construct Poisson regression models to calculate the crude and adjusted incidence rates for HFpEF and HFrEF (occurring from 2005 onwards) associated with BMI category at Visit 4.

7) We will construct Cox regression models to estimate the HRs and 95% CIs for incident HFpEF and HFrEF associated with higher BMI categories, using the covariates and modeling approach described above. We will again use seemingly unrelated regression to compare the magnitude of the associations for higher BMI with incident HFpEF and HFrEF.

8) We will subsequently perform competing risk regression to assess the association of higher BMI category at Visit 4 with each phenotype of HF (HFpEF vs HFrEF),
using the other HF phenotype as the competing outcome in regression models. Models will again be constructed with the covariates described above.

9) We will repeat the above analyses in subgroups stratified by age (> or <= 60 years), race and gender, and we will test for any significant interactions in the association of obesity with HF phenotypes across these demographic subgroups.

**Sensitivity Analyses:**
- In the prospective analyses, we will perform additional sensitivity analyses adjusting for incident CHD as a time-varying covariate to understand the contribution of interval ischemic events to the observed associations.
- Given the interval between Visit 4 and the beginning of HF adjudication in 2005, we will consider performing sensitivity analyses using the results from adjudicated HF data to impute HF phenotype data for the HF events occurring between Visit 4 and 2005, in order to estimate whether there are any trends in the relationship between obesity status and HF phenotypes over time.
- In the prospective analysis, we will consider additional adjustment for ECG evidence of LVH and levels of hs-cTnT and NT-proBNP at Visit 4.

**Limitations:**
- One limitation is the lack of adjudication for heart failure cases occurring before 2005 in the ARIC cohort, and consequently, the time gap between ARIC Visit 4 and the incident HFpEF and HFrEF cases included in this analysis.
- There is a possibility that BMI measurements in the cross-sectional analysis will not reflect the weight prior to the initial diagnosis of HF, given the cachexia associated with HF. Given this possibility, we are interested in assessing whether there is congruence between the results from the cross-sectional and prospective analyses.
- There is also the likelihood of residual confounding in this observational study.

7.a. Will the data be used for non-CVD analysis in this manuscript?  
_____ Yes  ____X__ 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?  
_____ Yes  ____X__ No  
(This file ICTDER03 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  ____ 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 # 1342: The preventable burden of heart failure due to obesity and hypertension: the Atherosclerosis Risk in Communities (ARIC) study

ARIC Manuscript Proposal # 1125: Diabetes, obesity and insulin resistance as risk factors for incident hospitalized heart failure: The Atherosclerosis Risk in Communities (ARIC) Study

ARIC Manuscript Proposal # 1570: The heart failure population burden due to acquired risk factors: The Atherosclerosis Risk in Communities study

ARIC Manuscript Proposal #1891: Phenotypic profile of heart failure with preserved ejection fraction in African Americans: risk factors, cardiac structure and function, and prognosis.


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/

12. 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.
References


