

ARIC Manuscript Proposal # 3291

PC Reviewed: 12/11/18
SC Reviewed: _____

Status: _____
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Priority: 2
Priority: _____

1.a. Full Title: Early Risk Factor Exposure and Future Heart Failure (HF) Phenotype Development (Heart Failure with Preserved or Reduced Ejection Fraction)

b. Abbreviated Title (Length 26 characters): Risk factors for HF Phenotypes

2. Writing Group:

Laura Cohen, Elizabeth Oelsner, Mark Pletcher, Eric Vittinghoff, Norrina Allen, Mathew Maurer, Andrew Moran, Yiyi Zhang; Others welcome
I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal.
--LPC

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3. Timeline: December 1, 2018 – November 30, 2019

The analyses will be completed within six months, and the full manuscript within one year, following approval of this manuscript proposal.

4. Rationale:

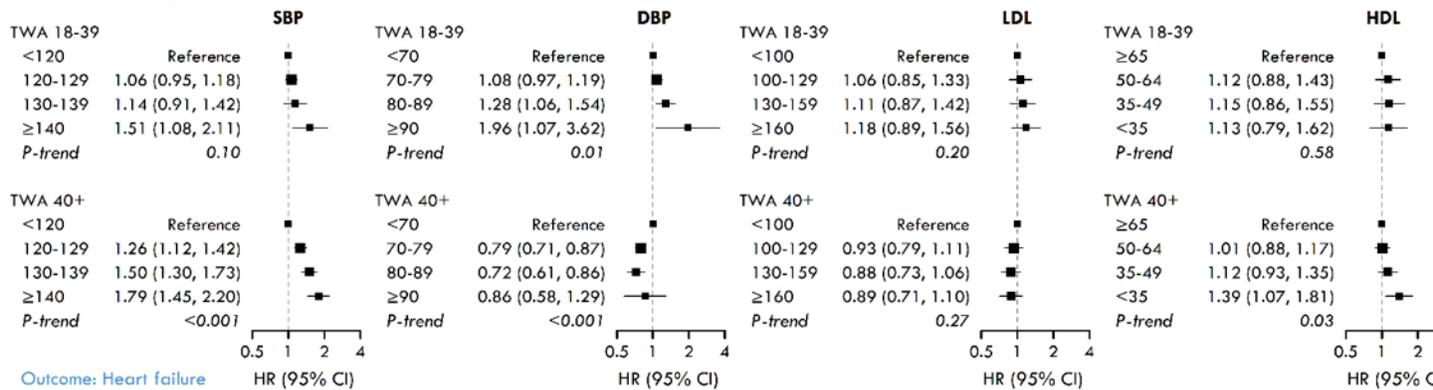
We propose to study the independent contribution of coronary heart disease (CHD) risk factor exposures during midlife (age 40 to 64 years) to the risk of incident heart failure (HF) and HF phenotype in later life, after accounting for later life risk factor exposures (age ≥ 65 years).

Current estimates indicate 6.5 million adults in the United States are living with heart failure and 50% of these adults are diagnosed with heart failure with preserved ejection fraction (HFpEF).^{1,2} In contrast to heart failure with reduced ejection fraction (HFrEF), large randomized clinical trials have failed to show a

single treatment that provides benefit in HFpEF, underscoring prevention of HFpEF as the basis of disease management.³

As such, primary prevention, or the recognition and control of risk factors believed to contribute to HFpEF development is of particular public health importance. Although the risk factor profiles overlap for HFrEF and HFpEF, the disease processes are distinct and the contribution of each risk factor is likely different.⁴ HFrEF can result directly from coronary artery disease and is generally believed to have similar risk factors as CHD, including hypercholesterolemia, diabetes, hypertension, obesity, and smoking. In order to implement primary prevention and prevent HF development, clinicians depend on national risk factor control guidelines which define standard of care and insurance reimbursements. Current HFpEF prevention guidelines focus on preventing hypertension, hyperglycemia and type 2 diabetes mellitus (DM), and obesity, but it remains unknown if there is a critical time window for preventive interventions during the life course.⁵

Our group previously analyzed CHD risk factor exposures and outcomes from age 20 years until death or old age using data from several large observational studies.^{6,7} The results suggest that cumulative (time-weighted average; TWA) high systolic blood pressure (SBP) and diastolic blood pressure (DBP) during young adulthood and midlife, and LDL cholesterol exposure during young adulthood are strong predictors of later life heart failure risk, independent of later life blood pressures, implying that early BP control may help prevent later life HF (see figure below; manuscript currently under review; ARIC ancillary study 2016.18). The relation of early and midlife risk factor exposure to HF subtype has not been assessed yet in this cohort.



We propose to extend our analyses to examine the independent contribution of midlife risk factor exposures on future risk of specific HF phenotypes (HFrEF and HFpEF). The two HF phenotypes will be distinguished by basic ejection fraction criteria estimated from echocardiograms performed at the time of the event (i.e., gathered from the in-hospital echocardiogram). Additionally, we will examine the magnitude of the contribution of incident CHD events as a mediating factor along the causal pathway to either HF phenotype. Further, we will explore exposure to risk factors during the young adult period (age 18-39 years) compared to midlife exposure (age 40-64 years) in order to assess which lifetime period is more critical for future HF development.

5. Main Hypothesis/Study Questions:

Aim 1. Estimate the associations between CHD risk factors exposures in midlife (time-weighted average body mass index [BMI], SBP, DBP, LDL, HDL, fasting blood glucose, during age 40-64 years) and the development of specific HF phenotypes (HFrEF vs. HFpEF). We hypothesize that elevated BP (SBP ≥140 mmHg or DBP ≥90 mmHg), elevated fasting blood glucose levels, and obesity

will be associated with incident HFpEF development, independent of later life exposure; whereas LDL and elevated BP will be associated with incident HFrEF development, independent of later life exposure.

Aim 2. Examine to what degree incident CHD events may mediate the associations between midlife CHD risk factor exposures and HFpEF and HFrEF development. We hypothesize that intermediate incident CHD prior to HF development will be a stronger mediator between midlife risk factor exposure and HFrEF incidence compared to HFpEF incidence.

Aim 3. Examine whether CHD risk factor exposures during young adulthood (age 18 – 39 years) are also associated with and the development of HF, independent of midlife exposure (age 40-64 years). We hypothesize that exposures to elevated levels of SBP, DBP, blood glucose, and obesity during young adulthood will be associated with future development of HF, independent of midlife exposures. We hypothesize that young adult exposures to elevated SBP and DBP will be associated equally with HFrEF and HFpEF subtypes.

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).

Demographic variables: Age, sex, race/ethnicity, education, study sites

Anthropometric variables: Height, weight, BMI, waist circumference

Lipid variables: Total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, use of lipid-lowering medication

Blood pressure variables: Systolic BP, diastolic BP, use of antihypertensive medication, use of diuretics, self-reported history of hypertension

Diabetes variables: Fasting status, serum glucose, hemoglobin A1c, use of anti-diabetes medication, self-reported DM

Other clinical variables: Smoking status, age of smoking initiation, age of smoking cessation, cigarettes per day, alcohol drinks per day, serum creatinine, spot urine creatinine, spot urine albumin, history of HF, history of CHD, history of chronic kidney disease

Outcomes variables: HF, HFpEF, HFrEF, ejection fraction (as a continuous variable when available or as categories defined by ARIC, “LVEF_CUR_LOW” or “LVEF_PREV_LOW”), CHD, stroke, non-cardiovascular death, all-cause mortality, time to events.

Analytic Plan

We have harmonized and pooled individual-level basic cardiovascular disease risk factor and outcomes data from ARIC study with similar data from several other NIH-funded prospective cohort studies (related ancillary study proposals approved for ARIC, CARDIA, CHS, MESA, Framingham Offspring, and Health ABC).⁸ The pooled data permits us to model risk across the adult years and provides a sufficient number of HF events to support robust inferences that may be generalizable to the broader adult U.S. population. Inclusion of ARIC will be an essential component of this work given its racial/ethnic diversity, meticulous follow-up, and gold-standard measures of CHD risk factors.

HF will be defined in accordance to the ARIC adjudication process. HF phenotype determination will be in line with the definitions provided by the American College of Cardiology / American Heart Association (ACC/AHA) 2013 guidelines, which were reiterated in the European Society of Cardiology (ESC) 2016 guidelines.^{9, 10} HFrEF is defined by an ejection fraction $\leq 40\%$ and HFpEF by an ejection fraction $\geq 50\%$. Those with clinic HF and an EF between 41-49% are labeled “borderline” or “intermediate” by ACC/AHA guidelines and mid-range by ESC guidelines; this population is likely more similar to HFpEF than HFrEF in phenotype. Participants with quantitative EF measurements will be

defined according to these guideline definitions. HF participants who have categorical EF assessments and who are unclassified by EF will be analyzed as part of sensitivity analyses.

Statistical analyses. As in our prior analyses of the association between young adult risk factor exposures and CHD outcomes,^{6,7} we will impute lifetime risk factor trajectories for BMI, SBP, DBP, LDL, HDL, and blood glucose, starting from age 18 for every participant. To accomplish this, we will use linear mixed models to estimate latent trajectories underlying the observed values for each participant, and imputed risk factor levels annually from age 18 years until the end of follow-up for each participant. Individual trajectories will then be used to estimate time-weighted average (TWA) exposures (similar to “pack years” of tobacco exposure) to each risk factor during young adulthood (age 18-39 years), midlife (age 40-64 years) and older adults (age ≥ 65 years).

Cause-specific Cox proportional hazards model will be used to estimate the associations between midlife risk factor exposures and later life HF_{rEF} and HF_{pEF} risks, accounting for competing risks of death, alternate HF subtype, and unclassified HF subtype. We will use age as the time scale, with the origin for time to event set at 65 years. All models will be adjusted for race/ethnicity, sex, birth year, body mass index (BMI), smoking status, cigarettes smoked per day, diabetes, years with diabetes, use of lipid-lowering and anti-hypertensive medications, and the later adult TWAs of other CHD risk factors. To examine the mediation effect of incident CHD events on the association between midlife risk factor exposures and the development of HF subtypes, we will assess the change in the β -coefficient of each risk factor comparing the base model (without adjustment for time-varying CHD status) and the model further adjusted for incident CHD events. The 95% CIs for the difference in the race β coefficient between the 2 models will be calculated using bootstrap methods with 1000 replications. To compare the contribution of young adult exposures to midlife exposures, we will further include young adult and midlife risk factor exposures simultaneously in the same model. Additionally, to examine the robustness and consistency of our findings, we will perform several sensitivity analyses, including additionally adjusting for the most recent directly observed value carried forward; excluding individuals who ever used anti-hypertensive or lipid lowering medications; repeating analyses by cohort, as well as leaving out one cohort at a time to confirm that our findings were not driven by any single study. All analyses will be performed using STATA version 14 (StataCorp LP, College Station, Texas).

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? _ n/a ___ Yes _ n/a ___ 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”? _ n/a ___ Yes _ n/a ___ 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/aric/mantrack/maintain/search/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)?

No prior ARIC manuscript proposals have looked at the independent contribution of midlife risk factor exposures on future risk of specific HF phenotypes (HF_rEF and HF_pEF). The other proposals related to HF_pEF:

#2281 - Race and Gender Differences in Heart Failure with Preserved Ejection Fraction: Morbidity, Case Fatality, and their Determinants

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 at <https://www2.csc.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.csc.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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