ARIC Manuscript Proposal # 1569

PC Reviewed: 11/10/09	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: The heart failure population burden due to acquired risk factors: The Atherosclerosis Risk in Communities study

b. Abbreviated Title (Length 26 characters): Heart failure burden

2. Writing Group:
Patricia Chang
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Others are welcome

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

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3. Timeline:

Analyses will begin once the manuscript proposal is approved.

4. Rationale:

Heart failure (HF) is a common, costly, disabling, and often fatal disorder that affects approximately 5.7 million Americans. Despite improvements in medical care and advances in therapy, hospital discharges for HF have increased 155% over the past two decades[1] and HF has become the most common condition for hospital admission[2] and readmission.[3] Although the considerable morbidity and mortality attributed to HF can be reduced by treatment,[4, 5] approximately half of those with HF die within five-years of diagnosis.[1] Thus, the aging U.S. population, combined with HF treatment costs that are the most expensive of all Medicare diagnoses,[6] make HF a major - and growing - public health burden.

Numerous studies have evaluated associations between HF and acquired risk factors, including previous coronary heart disease (CHD), diabetes, elevated blood pressure, atrial fibrillation, hypercholesterolemia, overweight/obesity, cigarette smoking, and arrhythmias[7-9] and how such associations vary by race and sex.[10, 11] Yet, few have explicitly measured the population impact of these acquired risk factors.[12, 13] Population burden measures, such as the attributable fraction (AF) and potential impact fraction (PIF) are of direct relevance to public health professionals given the policy implications of measures that estimate the proportion of cases that could be prevented if a risk factor was eliminated. Similarly, disability adjusted life years (DALYs) and years of life lost (YLL) are disease burden measures that inform on the years lived with disability and premature mortality, respectively, associated with a specific exposure.[14-16] Traditional measures of incidence, prevalence, or mortality do not combine morbidity and mortality effects into metrics comparable across different diseases.

5. Main Hypothesis/Study Questions:

a. First, we propose to estimate the following using ARIC cohort data:

> The risk of developing HF by race and sex conditional on survival without disease at index ages of 45, 55, 65, and 75 years
>
> The proportion of HF cases attributed to hypertension, overweight/obesity, diabetes, hypercholesterolemia, and cigarette smoking (estimated individually).
>
> The estimated potential impact on the population HF burden of interventions that reduce the prevalence of hypertension, diabetes, hypercholesterolemia, and cigarette smoking (estimated individually).

b. ARIC community surveillance data from 2005 will then be used to estimate age-, race- and sex-specific one-year HF incidence and mortality rates. Based on these rates we will calculate:

> YLLs and DALYs for HF by race and sex

c. Results from parts (a) and (b) would then be combined to estimate:

HF DALYs attributable to hypertension, overweight/obesity, diabetes, hypercholesterolemia, and cigarette smoking (estimated individually).

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).

ARIC COHORT:

Exclusions: Participants with prevalent HF at baseline will be excluded (i.e. those who reported taking medications for HF (n=83) or those with stage 3 HF defined by the Gothenburg criteria (n=699)). Other exclusions are participants that self-report race other than black or white or blacks from the Minneapolis and Washington County study centers (n=89).

Outcome definition: Incident hospitalized HF is identified by the first occurrence of hospital discharge diagnosis codes 428.X or I50.x.

Main exposures:

1) BMI at baseline: BMI < 25 kg/m^2 = normal weight, BMI 25-30 kg/m^2 = overweight, and BMI > 30 kg/m^2 = obese.

2) Hypertension at baseline: either a diastolic blood pressure ≥ 90 mm Hg or a systolic blood pressure ≥ 140 mm Hg, or anti-hypertensive medication use during the previous 2 weeks.

3) Diabetes at baseline: either fasting plasma glucose ≥ 126, self-report of physician diagnosis of diabetes, or use of diabetes medication in the prior 2 weeks

4) Hypercholesterolemia at baseline: either total cholesterol ≥240 mg/dl or use of cholesterol lowering drugs in the prior 2 weeks.

ARIC SURVEILLANCE:

Outcome definition: Year 2005 adjudicated HF events and associated mortality data as well as death certificates listing HF as an underlying or contributing cause of death.

Covariates: Age, sex, and race.

STATISTICAL METHODS

Lifetime risk calculation: Lifetime risks of HF, adjusted for the competing risk of death, are given by:

$$\hat{F}_A^* = \sum_{j=A_{\min}}^{A} h_A \hat{U}_{A-1}$$

where A represents age, j indexes ordered failure times among N participants, *h* is the hazard or conditional probability estimate of developing HF at time t_j given survival beyond time t_{j-1}, and $\hat{U}$ is the estimated survival probability.[17] The variance of the cumulative incidence adjusted for competing risk of death is estimated using a Taylor series linear expansion.[18]

AF Calculation: AF estimates will be calculated as follows:

$$AF_{\exp} = (RR - 1)/RR$$

As the above formula is biased in the presence of confounding,[19] we will estimate AFs in each confounder stratum separately. The resulting AFs will be combined with weights determined by the proportion of cases in each stratum.[20]

Calculation of DALYs: The burden of disease for any cause, expressed in DALYs, years of life lost (YLL), and years of life with disability (YLD) is:

$$\text{DALYs} = \text{YLLs} + \text{YLDs},$$

where

$$\text{YLLs} = \sum \text{number of deaths x life expectancy at age of death}$$

and

$$\text{YLDs} = \sum \text{number of years with a disability x disability weight}$$

For YLD estimation, we will adopt an incidence-based approach that measures years with disability as *incidence x duration*, defined as the one-year incidence of disease multiplied by the mean duration of disability.[21] Here, the mean duration of disability is estimated by the median survival, as HF is considered an irrecoverable condition.

The burden of disease due to mortality (YLLs) will be calculated as the age-specific one-year mortality rate (e.g. any mention on death certificate) multiplied by the age-specific life expectancy based on standard life-table analysis. Year 2004 U.S. life tables will be used as the reference.[22]

For calculation of DALYs attributable to hypertension, diabetes, hypercholesterolemia, or overweight/obesity, the DALYs estimated above are multiplied by the AF for the specific risk factor, assuming that disease progression is the same for any given risk factor.[23]

The expected proportional change in average HF incidence after a reduction in the prevalence of a categorical outcome with n discrete levels is given by the potential impact fraction (PIF):

$$\frac{\sum_{i=1}^{n} P_i RR_i - \sum_{i=1}^{n} P_i' RR_i}{\sum_{i=1}^{n} P_i' RR_i},$$

where *RR(i)* represents the relative risk at exposure level *i, P(i)* is the population prevalence, and *P'(x)* is the counterfactual population prevalence.[24] Community surveillance sampling weights will be applied when appropriate and confidence intervals will be estimated using bootstrapping techniques.

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 ____ 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)?

This manuscript is related to #1342 (Loehr, The preventable burden of HF due to obesity and hypertension: the Atherosclerosis Risk in Communities (ARIC) study). Drs. Loehr, Rosamond, Poole, Chang, and Heiss are members of the writing group and have approved of this proposal.

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.

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