ARIC Manuscript Proposal # 1342

PC Reviewed: _2_/_12_/07   **Status:** _A___   **Priority:** _2__
SC Reviewed: _____   **Status:** _____   **Priority:** ____

1.a. Full Title: The preventable burden of heart failure due to obesity and hypertension: the Atherosclerosis Risk in Communities (ARIC) study

  b. Abbreviated Title (Length 26 characters): Preventable burden of HF

2.   Writing Group:

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

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3.   Timeline: Analysis to begin immediately, first draft by April 2008

4. Rationale:

   Heart failure (HF) is the most common reason for hospitalization for people over age 65(Rosamond, Flegal et al. 2007). Population-level interventions to decrease the burden of heart failure should be considered a high priority. Kannel has stated that symptomatic HF is a mainly a failure to prevent disease(Kannel 2004). Hypertension and obesity are modifiable HF risk factors that are highly prevalent in mid-life(Lee, Massaro et al. 2007). Studies have found that interventions to reduce these risk factors lead to only modest reductions in their prevalence(Katz 2004). Complete elimination of either of these risk factors is highly unlikely. We will estimate the predicted impact of a hypothetical and modest reduction in the prevalence of hypertension and obesity (both independently) on the population burden of heart failure using the generalized impact fraction.
   The generalized impact fraction is a useful measure of preventable burden of disease for situations in which the complete elimination of the exposure is unlikely. It was originally described by Walter in 1980 (Walter 1980), then further elucidated and coined by Morgenstern and Bursic in 1982(Morgenstern and Bursic 1982). It is defined as "the proportional reduction in the total number of new (incident) cases of a certain disease, resulting from a specific change in the distribution of a risk factor in the population at risk."(Morgenstern and Bursic 1982). It is based on the assumption of a hypothetical change in the distribution of an exposure given an intervention. The magnitude of change in the exposure distribution should be based on findings from previous studies of effective population-level interventions. Despite its introduction over 25 years ago, it hasn't caught on as either a replacement for or as an additional measure to report with the population attributable fraction. We propose to use the generalized impact fraction to predict the preventable burden of incident heart failure that is due to obesity/overweight and hypertension. This estimate will be based the association of these risk factors with incident heart failure observed in the ARIC cohort. Several hypothetical and feasible scenarios of reduced prevalence of obesity/overweight and hypertension will be specified to obtain a range of values for the generalized impact fraction.

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5. Main Hypothesis/Study Questions:

1) What would the predicted impact on the population burden of heart failure of a hypothetical, but feasible intervention that is effective in reducing the prevalence of obesity and/or overweight?
The generalized impact fraction will be calculated, overall and stratified by race, gender, and age for the potential impact of feasible weight reduction on the incidence of heart failure. The following data will be used:

> a) Several scenarios, based on findings from the literature, will be hypothesized for the feasible reduction in the prevalence of BMI by category (obese, and overweight). One will be a high risk targeted intervention, secondly an intervention that would attain the distribution proposed in healthy people 2010 and lastly a population-based intervention targeted uniformly at obese and overweight categories.

b) The prevalence of obesity and overweight as defined by BMI categories at baseline in ARIC.

c) The magnitude of association (hazard ratio) between overweight and obesity at baseline and incident heart failure.

2) What would be the predicted impact on the population burden of heart failure of a hypothetical intervention effective at reducing the prevalence of hypertension?
The generalized impact fraction will be calculated, overall and stratified by race, gender, and age for the potential impact of a feasible reduction in the proportion of people with hypertension on the incidence of heart failure. The following data will be used:

a) Several scenarios, based on findings from the literature, will be hypothesized for the feasible reduction in the prevalence of hypertension.

b) The prevalence of hypertension at baseline in the ARIC cohort.

c) The magnitude of association (hazard ratio) between hypertension and incident heart failure.

3) Determine the population attributable fraction for obesity and hypertension on the risk of incident heart failure.

4) The results from aims 1, 2, and 3 will be compared descriptively and graphically.

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
Prospective cohort study

Exclusion
Participants with prevalent heart failure at baseline will be excluded. Criteria to define prevalent HF at baseline are as follows: 1) those answering "yes" to the following question: "Were any of the medications you took during the last two weeks for heart failure?" (N=83), or those with stage 3 or 'manifest HF' by applying Gothenburg criteria (N = 699). Other exclusions include subjects not black or white, blacks form Minneapolis and Washington County (N = 89)

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 as defined by 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.

Outcome

Variables used to define the outcome -incident heart failure through the most recent year available:

> Hospital discharge diagnosis codes ('428.X') and dates for heart failure from cohort eligibility forms (CEL), and death from HF as indicated by codes from death certificates ('428.X or I50) and date of death.

Covariates

Covariates are race, gender, age, educational level at baseline, smoking history at baseline, alcohol use at baseline, diabetes mellitus and center.

Data Analysis

The generalized impact fractions (GIF) will be estimated using the following equation:

$$GIF = \frac{\sum P_i(RR_i) - \sum P_i'(RR_i)}{\sum P_i(RR_i)}$$

Where,

GIF = generalized impact fraction,

P_i = proportion of the population in exposure category, i,

P_i' = proportion of the population in exposure category i after an intervention or other change,

RR_i = Relative risk at exposure category i compared to the reference level

Since calculation of the GIF will be based on a single study population (the ARIC cohort), we will use methods proposed by Sander Greenland (Greenland 2004) for the attributable fraction using bootstrapping to have a distribution of values for the GIF. We will calculate the GIF and report the median, 2.5 % and 97.5 % uncertainty intervals (similar to 95 % confidence intervals). Rather than assume that our study population (a population-based sample from the target population) is fully representative of the target population (U.S. populations of black and white men and women from 1987-1989), we will bootstrap samples (with replacement) to determine a distribution of values for P_i, and HR_i.

The following data will be needed to calculate the GIF for the impact of reduction in prevalence of obesity and overweight on the incidence of heart failure: 1) P_i will be the prevalence of the exposure (obesity, overweight and normal weight) in the population at baseline (1987-1989); 2) P_i' will be the reduced prevalence of obesity, overweight and normal weight (reduced as compared to P_i) after a change in the distribution of BMI; and 3) RR_i will be the hazard ratio of heart failure for those overweight or obese as compared to those normal weight in the ARIC cohort. We will start with 1,000 bootstrap samples with replacement where each sample is the same size as the dataset. From these bootsrapped samples, we will have a distribution of prevalence values for obesity and overweight and the HR_i. For each bootstrapped sample, the GIF will be calculated given P'_i. From this we will have a distribution of GIF and can plot a histogram and note the 2.5 % and 97.5 % uncertainty intervals. The referent category will be normal weight. Complete case analysis will be performed. This same formula and methodology will be used to calculate the GIF for the reduction in prevalence of hypertension on the incidence of HF. All analyses will be performed stratified by race, gender and age-group.

Table 1. Example of bootstrapped samples that will be used in the calculation of the GIF for obesity and overweight

Bootstrap sample number	P_{normal}	P_{overwt}	P_{obese}	HR_{overwt}	HR_{obese}
1	$P_{normal,1}$	$P_{overwt,1}$	$P_{obese,1}$	$HR_{overwt,1}$	$HR_{obese,1}$
x	$P_{normal,x}$	$P_{overwt,x}$	$P_{obese,x}$	$HR_{overwt,x}$	$HR_{obese,x}$
100000	$P_{normal,10,000}$	$P_{overwt,10,000}$	$P_{obese,100000}$	$HR_{overwt,10,000}$	$HR_{obese,10,000}$

$$GIF_x = \frac{[P_{overwt,x}(RR_{overwt,x}) + P_{obese,x}(RR_{obese,x})] - [P'_{overwt}(RR_{overwt,x}) + P'_{obese}(RR_{obese,x})]}{P_{overwt,x}(RR_{overwt,x}) + P_{obese,x}(RR_{obese,x})}$$

Where, P_{normal} = proportion that are normal weight
P_{overwt} = proportion that are overweight
P_{obese} = proportion that are obese
HR_{overwt} is the hazard of HF in overweight as compared to normal weight
HR_{obese} is the hazard of HF in the obese as compared to normal weight

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 ICTDER02 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 ICTDER02 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 ICTDER02 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

There is some overlap with manuscript #1125 from the same lead author and writing group. See discussion below.

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)?

#1125 Loehr LR, Rosamond WD, McNeill A, Chang PP, Folsom AR, Chambless LE, Heiss G. Diabetes, obesity and insulin resistance as risk factors for incident hospitalized heart failure: the Atherosclerosis Risk in Communities (ARIC) study.

   The proposed paper will differ from manuscript #1125 in that we will be estimating the preventable burden of HF due to obesity. Estimates from manuscript #1125, including 1) hazard ratio for the association of obesity and overweight with incident HF and 2) estimates for the prevalence of obesity and overweight, will be used to calculate the generalized impact fraction in the proposed manuscript. However, the proposed analysis differs in that bootstrapping will be used to obtain a distribution of hazard ratios for this association and a distribution of prevalence values of obesity/overweight; and these values will then be used to estimate a distribution for the generalized impact fraction. The attributable fraction estimates originally proposed in manuscript #1125 instead be a part of the current proposal rather than manuscript #1125.

#927 Loehr LR, Rosamond WD, Chang PP, Folsom AR, Chambless LE. Heart failure incidence and survival (From the Atherosclerosis Risk in Communities [ARIC] study) Manuscript #927 has the same lead author and similar writing group as the proposed paper. Heart failure incidence is discussed in this paper. It was not the goal of this paper to explore the multivariable association of overweight/obesity or hypertension with HF, therefore only the univariate associations are mentioned in this paper.

#1133r Deswal A, Bozkurt B, Rosamond W, Heiss G, Chambless L, Chang P, Loehr L, Ballantyne C, Shahar E, Coresh J. The Obesity Paradox in Heart Failure. This paper investigates the effect of obesity on survival in those with heart failure. The lead author along with 5 co-authors from proposal #1133r have agreed to be co-authors in the proposed paper.

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

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Rosamond, W., K. Flegal, et al. (2007). Heart Disease and Stroke Statistics--2007 Update: A Report From the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. **115:** e69-171.

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