ARIC Manuscript Proposal #2006

PC Reviewed: 10/9/12 **Status: A** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title:

Age and the Population Attributable Risk for Cardiovascular Disease in the Community

b. Abbreviated Title (Length 26 characters):

Age and Population Attributable Cardiovascular Risk

2. Writing Group:
Writing group members:

Susan Cheng, Amil Shah, Deepak Gupta, Brian Claggett, Hicham Skali, Hanyu Ni, Scott Solomon, and OTHERS WELCOME

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. __SC__

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3. Timeline: Analyses to begin Fall 2012.
A manuscript draft is expected during Winter 2012 / Spring 2013.

4. Rationale:

Advancing age remains the most powerful and, yet, potentially also the least understood risk factor for cardiovascular disease (CVD).[1-3] The conventional paradigm of age-related cardiovascular risk proposes that progressive accumulation of traditional modifiable factors over the life course contributes, in aggregate, to steadily increasing risk for all the major adverse events. However, prior epidemiologic studies have demonstrated that the prevalence of modifiable risk factors changes with age and that, in turn, the effect of certain risk factors on outcomes is modified by age.[4-6] To better understand relative changes in the importance of traditional risk factors on cardiovascular outcomes with aging, we propose to conduct an analysis of age- and time-stratified 'population attributable risk' estimates for cardiovascular disease endpoints in the Atherosclerosis Risk in Communities (ARIC) study. We will study age- and time-stratified estimates together in a comprehensive analysis, due to the challenges associated with studying each separately (i.e. identifying age-related associations that may or may not be related to birth cohort effects). Use of the 'population attributable risk' method allows estimations of the *proportion of disease risk* in a population that can be attributed to the assumed effects of one or more risk factors.[7-10] Thus, this method offers the ability to assess the relative importance of conventional risk factors (with respect to select cardiovascular endpoints) with increasing age and over time. Applying this type of an analysis in the ARIC cohort may shed light on which risk factors contribute the greatest 'proportion' of risk for specific cardiovascular events of interest in older versus younger individuals – and the degree to which any age-based findings in our study may or may not be related to secular time trends.

5. Main Hypothesis/Study Questions:

Our main hypothesis is that the 'population attributable risk' of traditional risk factors varies by age group (defined below) with respect to incidence of all cardiovascular endpoints, as well as incidence of specific types of cardiovascular disease. Our specific hypotheses are:

1) *The proportion of risk attributable to hypertension increases with age, as well as over time, for all cardiovascular events and particularly for incidence of heart failure (HF) and stroke.* We hypothesize that because the prevalence of hypertension increases with age, and because the population at large continues to age, then the population attributable risk of hypertension for all major cardiovascular outcomes will increase with both age and over time – particularly for those outcomes that tend to present in older age (such as HF and stroke).

2) *The proportion of risk attributable to hypercholesterolemia decreases with age, as well as over time, for all cardiovascular events including coronary heart disease (CHD).* Because cholesterol levels are known to decrease with age, and because cholesterol levels in the population at large are known to have decreased over time (with improved dietary patterns and increased use of cholesterol lower treatments), we hypothesize that the population attributable

risk of hypercholesterolemia for all major cardiovascular events will decreased with older age and over time.

3) *The proportion of risk attributable to smoking is decreases with advancing age, as well as over time, for all cardiovascular events.* We hypothesize that the proportion of risk for all major cardiovascular events that are attributable to smoking will decrease with older age (given lower rates of smoking in elderly compared to middle-aged adults) as well as over time (given time trends indicating the decreasing prevalence of smoking in the population at large).

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).

The study sample will include individuals who attended ARIC examination Visit 1 and were free of cardiovascular disease (CHD, HF, or prior stroke) at the time of this 'baseline' examination. For time trends analyses, the study sample will include individuals who attended the Visit 1 examination and remained free of cardiovascular disease when also attending the Visit 4 examination, which occurred approximately 10 years later. (In secondary time trend analyses, we may consider similarly selected 'baseline' samples of individuals attending the Visits 2 and 3 examinations.)

Descriptive Analyses

We will categorize the Visit 1 study sample by age into 3 groups, approximating tertiles (<50, 50-59, >=60 years), and also do the same for individuals who remained free of cardiovascular disease when attending Visit 4 (<60, 60-69, >=70 years). We will determine the means and frequencies of conventionally defined traditional cardiovascular risk factors, by age group, at each of the Visit 1 and Visit 4 examinations. (In secondary time trend analyses, the same will be done for 'baseline' samples comprising individuals who attended Visits 2 and 3.)

Population Attributable Risk

Independent variables. For calculating population attributable risk estimates, it will be necessary to define presence versus absence of the main risk factors as binary variables. Therefore, for risk factors that are based on continuous measures, the following definitions will be used: hypertension will be defined as SBP ≥140 mmHg or DBP ≥90 mmHg or taking anti-hypertensive medication; obesity will be defined as BMI ≥30 kg/m2; hypercholesterolemia will be defined as a total cholesterol ≥200 mg/dL or taking cholesterol lowering medication; and, diabetes will be defined as a fasting glucose ≥126 mg/dL or taking glucose lowering medication.

Dependent variables. The primary dependent variables of interest will include the incidence (through year 2008) of CHD, HF, stroke, and cardiovascular death (separate models for each endpoint, in addition to a model using the combined endpoint). Analyses of HF will be performed using 2 approaches: 1) excluding individuals who developed CHD prior to the onset of incident HF, and 2) including individuals who developed CHD prior to HF onset and adjusting

for this event, as a 'prior CHD diagnosis' variable, in the model.

Analytical approach. There are multiple methods used for calculating PAR % (population attributable risk %).[7] Therefore, we will use a method that is considered internally valid when adjusted relative risks must be used to account for possible confounding: PAR % = pd_i *[(HR_i-1)/HR_i], where pd_i is the proportion of total cases in the population arising from the *i*th exposure category and HR_i is the adjusted hazards ratio for the *i*th exposure category. Within each age group in the Visit 1 sample, we will calculate the PAR for each of the following risk factors: obesity, hypertension, diabetes, hypercholesterolemia, and smoking. The PAR will be estimated using the HR estimate derived from multivariable models adjusting for all risk factors in addition to age, sex, race, and site. PAR estimates will be calculated for each age group and for each of the outcomes listed above.

For time trends analyses, we will create a subcohort of Visit 1 participants and a subcohort of Visit 4 participants, where subcohorts from each Visit are matched by age (within 5 years) and sex (to account for survival bias in women). We will perform analyses in the Visit 1 subcohort with the follow-up duration limited to 10 years. We will then perform the same analyses for individuals in the Visit 4 subcohort, also with the follow-up duration again limited to 10 years. PAR% estimates will be compared between the Visit 1 and Visit 4 'time windows'.

Secondary analyses. We will repeat the main analyses in the Visit 1 sample, using all available follow-up data, stratified by sex and race. For time trends analyses, if there are large differences observed between Visit 1 and Visit 4 samples, we will consider using similar sampling and methods for the Visit 2 and Visit 3 samples to aid in verifying results and potentially provide additional information with respect to time-dependent patterns of risk.

Limitations and challenges. It is well known that highly prevalent exposures will result in a loss of precision in the estimate of the PAR;[7] thus, PAR estimates for exposures that may be particularly relevant for any given sample (or subgroup) will be interpreted with caution. The number of individuals in each age group category will differ over time (with cohort aging), and so the main analyses of time trends will focus on age groups that are comparable in size from Visit to Visit. With respect to both age-based and time trend analyses, there are no known conventional statistics for comparing estimates between age groups or time windows. Therefore, comparisons will be reported qualitatively and interpreted as such.

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)?

MS # 196 (Howard) Does the association of risk factors and atherosclerosis change with age? An analysis of the combined ARIC and CHS cohorts. The Atherosclerosis Risk in Communities (ARIC) and Cardiovascular Health Study (CHS) investigators. Stroke 1997;28:1693-1701.

MS #460B (Howard) The effect of age on the correlational structure between risk factors and implications on the interpretation of analyses in the elderly

MS# 592 (Kim) Disease progression and mortality in older Americans.

MS #1050 (Paynter) Effect of Correcting for Long-Term Variation in Major Coronary Heart Disease Risk Factors: Relative Hazard Estimation and Risk Prediction in the Atherosclerosis Risk in Communities Study. Ann Epidemiol; 2012;22:191-197.

MS #1060 (Paynter) Paired comparison of observed and expected coronary heart disease rates over 12 years from the Atherosclerosis Risk in Communities Study. Ann Epidemiol; 2010;20:683-690.

MS# 1517 (Roy) Inflammation clarifies age related changes in the relationship of serum cholesterol to risk of coronary heart disease: The Atherosclerosis Risk in Communities Study.

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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5. Jousilahti P, Vartiainen E, Tuomilehto J, Puska P. Sex, age, cardiovascular risk factors, and coronary heart disease: A prospective follow-up study of 14 786 middle-aged men and women in finland. *Circulation*. 1999;99:1165-1172.
6. Curb JD, Abbott RD, MacLean CJ, Rodriguez BL, Burchfiel CM, Sharp DS, Ross GW, Yano K. Age-related changes in stroke risk in men with hypertension and normal blood pressure. *Stroke*. 1996;27:819-824.
7. Rockhill B, Newman B, Weinberg C. Use and misuse of population attributable fractions. *Am J Public Health*. 1998;88:15-19.
8. Levy D, Larson MG, Vasan RS, Kannel WB, Ho KK. The progression from hypertension to congestive heart failure. *JAMA*. 1996;275:1557-1562.
9. Wang WS, Wahlqvist ML, Hsu CC, Chang HY, Chang WC, Chen CC. Age- and gender-specific population attributable risks of metabolic disorders on all-cause and cardiovascular mortality in taiwan. *BMC Public Health*. 2012;12:111.
10. Schnohr P, Jensen JS, Scharling H, Nordestgaard BG. Coronary heart disease risk factors ranked by importance for the individual and community. A 21 year follow-up of 12 000 men and women from the copenhagen city heart study. *Eur Heart J*. 2002;23:620-626.