ARIC Manuscript Proposal #1948

PC Reviewed: 5/29/12  Status: A  Priority: 2
SC Reviewed: _________  Status: _____  Priority: ____

1.a. Full Title:
All-Cause Mortality in Hypertensive Normal Weight Adults

b. Abbreviated Title (Length 26 characters):
Mortality and Normal weight hypertension

2. Writing Group:
Writing group members:
Lester M. Arguelles, Alain Bertoni, Mary L. Biggs, Peter de Chavez, Alan Dyer, Sherita Golden, C. Elizabeth Lewis, Kiang Liu, Kenneth J. Mukamal, Mercedes Carnethon

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

First author: Lester M. Arguelles
Address: Department of Preventive Medicine, 680 N Lake Shore Drive, Suite 1400, Chicago, IL 60611

Phone: (312) 503-2764  Fax: (312) 908-9588
E-mail: lm.arguelles@northwestern.edu

ARIC author to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator).

Name: Sherita H. Golden
Address: Welch Center for Prevention
2024 E. Monument St., Suite 2-600
Baltimore, MD 21205

Phone: (410) 502-0993  Fax: 410.955.0476
E-mail: sahill@jhmi.edu

3. Timeline:

Analyses are ongoing as the data were released under the approved ancillary study, “Epidemiologic Studies of Type 2 Diabetes in Normal Weight Adults”. We will prepare the manuscript for submission to a journal in July 2012.
4. **Rationale:**

Studies have shown that obese patients with known cardiovascular disease, such as heart failure or coronary artery disease, for example, were at decreased risk of morbidity and mortality relative to non-obese patients, substantiating an ‘obesity paradox’.\(^1\) This paradox has also been found among those with hypertension, considered a mediating risk factor in the link between obesity and cardiovascular disease and puts individuals at increased risk for cardiovascular diseases such as CHD and stroke, which are leading causes of death in the US. Stamler et al.\(^2\) reported that individuals who were lean and hypertensive had a higher risk for death due to cirrhosis, nonmalignant respiratory disease, violence, and malignant neoplasms compared to median weight or obese hypertensives. However, they concluded this increase risk was due more so to differences in alcohol consumption and smoking rather than obesity status. Uretsky et al.\(^3\), in a cohort of patients with coronary artery disease and well treated hypertension, found that non-obese patients were at increased risk of death, incident nonfatal myocardial infarction, or incident nonfatal stroke relative to their obese counterparts. Although large prospective studies have demonstrated that it was obese hypertensives at greatest risk for cardiovascular disease, not lean hypertensives,\(^4,5\) an issue with these studies was that hypertension was measured baseline. As such, the duration of hypertension was not accurately assessed, thereby confounding the results. In this investigation, we propose to examine the risk of cardiovascular and all-cause mortality between participants who were normal weight, overweight, or obese at the time of incident hypertension. By using an “inception cohort” approach, the effects of residual, unmeasured, confounding by duration of hypertension, which can be increasingly deleterious over time, can be addressed to a degree by truncating the duration to the interval between study examinations.

Restricting our study population to incident hypertension greatly reduces the sample size, making any single study too small to execute this study. As such, we propose to pool data from the Atherosclerosis Risk in Communities (ARIC), Cardiovascular Health Study (CHS), Coronary Artery Risk Development in Young Adults (CARDIA), Framingham Offspring Study (FOS) and the Multi-Ethnic Study of Atherosclerosis (MESA) to compare all-cause mortality rates in the sample of participants who had incident hypertension during their cohort follow-up. The resulting pooled dataset will include a large, diverse (e.g., race/ethnic, gender, and age) sample of participants with incident hypertension and the largest sample to date of participants who were normal weight when hypertension was identified. Given the substantial number of incident hypertension cases in these combined cohorts, it will also be possible to analyze these data according to normal weight, overweight, and obese status, where normal weight would be the reference.

5. **Main Hypothesis/Study Questions:**

Our objective is to compare the incidence of all-cause mortality in participants who were normal weight with overweight or obese persons at the time of incident hypertension.

*We hypothesize that rates of all-cause mortality will be higher among those normal weight with hypertension, compared to those who are overweight or obese with hypertension, once accounting for the duration of hypertension. Moreover, we will determine if the increased risk of all-cause mortality persists in the normal weight hypertensives after adjustment for disease risk factors that tend to cluster with obesity and predispose toward mortality.*

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).**
Inclusions/exclusions

The sample will be restricted to those who were free of CVD at the time of incident hypertension. Preliminary analyses indicate that across 5 cohorts, there are 7106 cases of incident hypertension and the proportion of normal weight hypertension ranged from 18% (CARDIA) to 40% (CHS) across cohorts.

Variables

Cohort Definition: Participants will be categorized as normal weight (BMI<25 kg/m\(^2\)) or overweight/obese (BMI ≥25 kg/m\(^2\)) at the time hypertension is initially identified. Normal weight hypertension was defined according to the following criteria: SBP ≥140 or DBP ≥90 or antihypertensive medication use at a single examination and the diagnosis of hypertension by a physician. Body weight (kg) and height (m) was abstracted from each clinical examination. Standard procedures were used to determine incident hypertension and weight status across cohorts.

Cardiovascular and all-causes mortality. Cardiovascular mortality will be defined as death from any of the following causes: atherosclerotic CHD (fatal MI and definite and possible fatal CHD), cerebrovascular disease (fatal ischemic and hemorrhagic stroke) and other atherosclerotic and cardiovascular deaths.

Covariates: We will include the following sociodemographic characteristics that are measured across all cohorts: age, sex, race/ethnicity, and education. Cardiovascular disease risk factors including systolic and diastolic blood pressure, antihypertensive medication use, smoking status, triglycerides, HDL-cholesterol and physical activity that are also measured across cohorts will be included as covariates. With the exception of age, all continuous variables are converted to standardized scores (mean=0, SD=1) because of different assays and instrumentation across cohorts.

Weight status. Body weight (kg) and height (m) will be abstracted from each clinical examination. Participants will be categorized as normal weight (BMI<25 kg/m\(^2\)) or overweight/obese (BMI ≥25 kg/m\(^2\)) at the time T2DM is initially identified. We will carry out secondary analyses excluded participants who are underweight (BMI<18.5 kg/m\(^2\)).

Brief analysis plan and methods:

First, an overall description of the cohort of those who experienced incident hypertension will be described according to their and baseline characteristics, which will include covariates pre-specified in our multivariable models. We will generate crude and age-adjusted rates of all-cause mortality across cohorts using Poisson regression, where person-time begins at the time of incident hypertension to the mortality event or the end of follow-up, whichever comes first. Second, the study cohort will be stratified according to normal weight, overweight, and obese, and their baseline characteristics will be compared. To compare rates of all-cause mortality in normal weight persons with hypertension to overweight and obese persons with hypertension, Cox proportional hazards models will also be used to estimate multivariable adjusted hazard ratios and 95% CIs for mortality. To assess the effects of confounding on the weight status and all-cause mortality association, 3 models will be presented. Model 1 will not include any covariates (unadjusted); Model 2 will include demographic characteristics (age, sex, race and education); Model 3 will additionally include diabetes status, smoking status, waist circumference, triglycerides and HDL-cholesterol. Hazard ratios that are determined individually
in each cohort will then be pooled together using fixed or random effects to generate meta-
estimates. In addition to defined weight status, we will also examine the risk of all-cause mortality across BMI and waist circumference as a continuous variable. Cubic splines will be used to assess the linearity of the relationship to log hazard of all-cause mortality.

To examine the possible bias incurred by blood pressure medication indication, the analysis will be stratified according to HTN with and without medication, and if possible, stratified according to what the medications are indicated for, such as arrhythmia, which is cardiovascular related and probably associated with increased mortality, or other uses, such as migraines, which is likely not related to mortality. Further sensitivity analysis will also include exclusion of those who died within 2-years of their incident hypertension as these events would be less likely to be associated with hypertension. We will also examine the modifying effect of controlled and uncontrolled hypertension on weight status and all-cause mortality relationship. For example, those with blood pressure within the normal range, but are taking HTN medications, might be considered controlled, and those with HTN, with or without medications, might be considered uncontrolled.

Further, if it is possible to harmonize CVD mortality across the cohorts, the rates of CVD mortality in each weight group can be explored in this study.

References:


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)?

11. a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? 

_ X_ Yes _____ No

11.b. If yes, is the proposal

_ X_ A. primarily the result of an ancillary study (list number* 2008.13___)

___ 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.