1.a. Full Title: Genome-wide Association Study of Orthostatic Hypotension in individuals of European Ancestry and in African descent– The ARIC Study

b. Abbreviated Title (Length 26 characters): Genome-wide association of orthostatic hypotension

2. Writing Group: Nora Franceschini, Kari E North, Kathryn M Rose, Eric Boerwinkle, Gerardo Heiss, Jim Pankow, Wei Sun, Georg Ehret, others interested

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

First author: Nora Franceschini, MD, MPH
Address: Department of Epidemiology
University of North Carolina Chapel Hill
Bank Of America Center
137 E. Franklin St., Suite 306
CB #8050
Chapel Hill, NC 27514

Phone: 919-966-1305 Fax: 919-966-9800
E-mail: noraf@unc.edu

Corresponding/senior author (if different from first author correspondence will be sent to both the first author & the corresponding author):
Address: Gerardo Heiss, MD, PhD
University of North Carolina
School of Public Health- Department of Epidemiology
Bank of America Center, 137 E. Franklin Street, Suite 306, Chapel Hill, NC 27514
Phone: (919) 962-3253
Fax: (919) 966-9800
E-mail: gerardo_heiss@unc.edu

3. Timeline: All genotyping is complete. Analyses to begin immediately
4. **Rationale:** Orthostatic hypotension (OH), defined as decrease in systolic blood pressure of 20 mm Hg or more, or a decrease in diastolic blood pressure of 10 mm Hg or more on standing up from a supine position, is a manifestation of autonomic dysfunction. It has been found to be associated with incident hypertension (Rose, Holme et al. 2002), coronary heart disease (Rose, Tyroler et al. 2000), stroke (Eigenbrodt, Rose et al. 2000) and increased mortality (Rose, Eigenbrodt et al. 2006) among ARIC participants. For example, ARIC participants with OH at baseline had a 2-fold increase in risk of dying from cardiovascular disease (CVD) and a 2-fold increase in risk of dying of other causes, unrelated to cancer, including kidney diseases (Rose, Eigenbrodt et al. 2006). Most previous studies of OH are based on the elderly and other high risk populations that are often symptomatic. In contrast, ARIC participants were middle-aged and largely asymptomatic for OH. Further, the associations of OH with CVD-related outcomes often persisted in apparently healthy subgroups of the population (Rose, Tyroler et al. 2000; Rose, Eigenbrodt et al. 2006). Thus, the findings from ARIC, a middle-aged and ostensibly healthy population are of particular interest as they suggest that OH may be a marker of subclinical autonomic dysfunction.

Family studies have suggested a genetic component for blood pressure response to postural changes and OH (Streeten, Kerr et al. 1972; DeStefano, Baldwin et al. 1998; Pankow, Rose et al. 2000). For example, a relatively severe form of orthostatic hypotension with an autosomal dominant mode of transmission was described in 4 families (Streeten, Kerr et al. 1972). In addition, a genome-wide linkage scan in 498 white hypertensive sib-pairs in the HyperGEN Study revealed suggestive evidence for linkage for change in systolic blood pressure on chromosome 18q (maximum LOD 2.6 at 80 cM), in a region which overlaps to findings in familial orthostatic hypotension (DeStefano, Baldwin et al. 1998; Pankow, Rose et al. 2000).

In the ARIC population-based study, the blood pressure response to a change in posture is normally distributed and with a wide range, with a mean close to zero and with a substantial portion of individuals having either strong increases or decreases (Nardo, Chambless et al. 1999). The prevalence of OH in the ARIC cohort at baseline is 5% (Rose, Eigenbrodt et al. 2006). Approximately 70% of hypertension individuals with and without OH were using anti-hypertensive medications (Rose, Eigenbrodt et al. 2006). We propose to study the association of genome-wide variants with postural changes in blood pressure using both quantitative measures and the categorical outcome of OH.

5. **Main Hypothesis/Study Questions:** Investigate the association of genome-wide genetic variants and postural changes in blood pressure and OH in individuals of European Ancestry. We plan to expand our analyses to African Americans as the genotyping data is available. Use of GWAS data in African-Americans will follow CARE procedures.

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).**
**Subjects:** Individuals of European ancestry and African descent with available measures of sitting and upright blood pressures. Use of GWAS data in African-Americans will follow CARE procedures.

**Exclusions:** we will not exclude individuals using medications associated with hypotension (antihypertensive, tricyclic antidepressants, benzodiazepines, phenothiazines) since 70% of the sample is on at least one medication. Instead, we will adjust for medications in the analysis.

**Exposure:** 2.5 million HapMap genetic variants identified in CEPH trios for whites and 1.0 million genetic variants in African American. We will not pursue imputation in African descent samples at this point but would consider it if adequate accuracy of imputation using HapMap YRB samples is demonstrated.

**Outcome:** OH will be defined per established guidelines (1996) as a decrease in systolic blood pressure of 20 mm Hg or more, or a decrease in diastolic blood pressure of 10 mm Hg or more. We will also investigate the association of genetic variants with quantitative measures of orthostatic changes in blood pressure.

**Study design:** Cross-sectional analysis of prevalent OH and continuous postural changes in systolic and diastolic blood pressures, race-stratified.

**Statistical analyses:** We will use additive models (1 df) adjusted for sex, age, and center. Further analysis will be considered adjusting for sex, age, center, education, smoking status, HDL and LDL cholesterol, physical activity, BMI, resting heart rate, and history of diabetes. In addition, we will consider adjusting for medications associated with hypotension in (antihypertensive, tricyclic antidepressants, benzodiazepines, phenothiazines) and systolic blood pressure.

**Statistical significance:** Bonferroni correction adjustment (1/ number of tests performed) (~10^-7)

**Validation and Replication:** We will pursue validation/replication of findings by genotyping selected variants in existing databases with measures of postural changes in blood pressure (eg, HyperGEN, replication for whites and blacks). We will consider meta-analyses using data from ARIC and HyperGEN.

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**  **X**  **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?  **X**  **Yes**  **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”?  **X**  **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)?

ARIC manuscript #361A, Rose K. Orthostatic hypotension and the incidence of coronary heart disease: The Atherosclerosis Risk in Communities Study. ARIC manuscript # 1104. Rose, K. Orthostatic Hypotension Predicts Mortality in Middle-Aged Adults. The Atherosclerosis Risk in Communities (ARIC) Study

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*2006.03 (Stampede and Geneva genotype funding in Caucasians) and 2007.02 (CARe, genotyping in African Americans).

___ 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:


