1.a. Full Title: Genome-wide association study of blood pressure using genotype-by-smoking and genotype-by-alcohol intake interactions: the ARIC Study

b. Abbreviated Title (Length 26 characters): Gene-environment interaction on blood pressure phenotypes

2. Writing Group: Nora Franceschini, Sharon Kardia, Aravinda Chakravarti, Alanna Morrison, DC Rao, Eric Boerwinkle, Gerardo Heiss, Kari E North

Others welcome

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):

Eric Boerwinkle, PhD
Kozmetsky Family Chair in Human Genetics
Professor and Director, Human Genetics Center and Div. of Epidemiology
1200 Herman Pressler, Suite E-447
Houston, Texas 77030
Phone: 713.500.9816
Fax: 713.500.0900
Email: Eric.Boerwinkle@uth.tmc.edu

3. Timeline: Analyses will begin when all genotyping and QC is completed.
4. **Rationale:**
To conduct a genome-wide genotype-by-behavioral interaction on blood pressure phenotypes: systolic (SBP) and diastolic (DBP) blood pressures and hypertension status among ARIC participants. Replication will be performed on the Framingham study (PI DC Rao). We will also consider cooperation with the CHARGE hypertension/BP working group.

5. **Main Hypothesis/Study Questions:**
Conduct a genome-wide genotype-by-smoking and genotype-by-alcohol intake interaction analyses on blood pressure phenotypes using the set of genotyped and imputed SNPs.
Primary analysis: SBP, DBP and hypertension status.

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 blood pressure.

**Variables** (phenotype): Visits 1-4 measurements of the blood pressure (quantitative) and categorical hypertension (defined by SBP, DBP and treatment status). For quantitative analysis, we will take in account medication treated measures of blood pressure (individuals taking anti-hypertensive medications) using standard statistical methods (by adding 10/5 to SBP/DBP).

**Exclusions:** Individuals without BP measures and who did not consent to use DNA.

**Exposure:** 2.5 million HapMap genetic variants identified in CEPH trios for whites.

**Model:** Linear regression for analysis of quantitative variables adjusted for age, sex and center, with and without BMI correction and using an additive genetic model (2 df test). For analysis of hypertension status, we will use logistic regression analysis adjusted for covariates described above. We will test for genotype-by-behavioral interaction using interaction terms and likelihood ratio test. We will perform analysis without pre-screening of SNPs based on significant main effect association. For SNPs with significant interactions, we will perform stratified analysis by the interaction variable in order to estimate the genetic effects in the subgroups. We will adjust for population stratification using principal component methods.

**Subgroups:** In secondary analyses, we will perform stratified analysis by behavior factors as described above.

**Transform:** For quantitative measures with nonnormal distribution, we will perform log transformation to reduce kurtosis.

**Covariates:** Basic model: age, age2, sex and center adjusted, interaction covariate: cigarette smoking (current, past, never) and alcohol intake (current, never/past).
We will consider multivariable analysis, restricting to "top hits" identified in the interaction analyses. These analyses will adjust for age, age2, sex, BMI, total cholesterol,
HDL cholesterol, lipid lowering therapy, type 2 diabetes and measures of population stratification.

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

**Validation and Replication:** We will pursue validation/replication of the top hits within the Framingham study and possibly the CHARGE hypertension/BP group.

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?  ___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.csec.unc.edu/ARIC/search.php](http://www.csec.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 # 1408: CHARGE GWAS for BP (SBP and DBP) at first visit

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.