1.a. Full Title:

*Genome-Wide Association Study of Alcohol Consumption in the CHARGE consortium*

b. Abbreviated Title (Length 26 characters):

*CHARGE alcohol GWAS*

2. Writing Group:

Writing group members:

*The following proposal derives from the CHARGE consortium and currently plans to include data from ARIC along with six other cohorts: Framingham, AGES, CHS, Rotterdam, Health ABC, and WGHS*

Sarah R Preis (lead)
ARIC co-authors and collaborators from other cohorts are listed below:

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Collaborators</th>
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| Framingham Heart Study | Daniel Levy  
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| Health ABC          | Annemarie Koster  
Tamara Harris |
| WGHS                | Daniel Chasman  
Brendan Everett  
Paul Ridker |
I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. ___SRP___ [please confirm with your initials electronically or in writing]

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ARIC author(s) 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).

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3. Timeline: Each cohort will complete their GWA and upload their results to the CHARGE alcohol Share Space as soon as possible. Subsequently, analysts from FHS and Rotterdam will conduct the meta-analysis.

4. Rationale:

Heavy alcohol consumption exacts a high burden of morbidity and mortality worldwide.\(^1\) In contrast, moderate drinking has been shown to be associated with reduced risk for cardiovascular disease.\(^2\) Prior work has suggested that there is a genetic component to alcohol dependence.\(^3\) Twin studies have shown heritability estimates of 50-60\%.\(^3\) Candidate gene studies have revealed an association of polymorphisms in acetaldehyde dehydrogenase (ALDH1, ALDH2) with alcohol dependence.\(^4\) Individuals with a variant in the ALDH2 gene, common in Asians, have reduced clearance of the alcohol metabolite acetaldehyde, and a lower risk of alcohol dependence.\(^4\) Polymorphisms at loci involved in GABAergic neurotransmission, specifically GABRA2, have been shown to be associated with alcohol dependence, although there is a lack of consistency as to the specific polymorphisms in GABRA2 that are associated with alcohol dependence.\(^3,5\) Other candidate gene studies have focused on the role of variants in the D\(_2\) dopamine receptor DRD2 but no consistent results have emerged.\(^3\) There has been only one GWAS of alcohol dependence to date.\(^6\) In a case-control study of 487 males with alcohol dependence and 1358 population-based controls, two SNPs reached genome-wide significance (rs7590720, \(p=9.7E-09\); rs1344694, \(p=1.7E-08\)). Both of these SNPs are located in the chromosome region 2q35 which has been identified in prior linkage studies of alcohol dependence. Confirmation of these GWAS results is needed.
It is hoped that the identification of additional polymorphisms through GWAS will provide insight into the etiology of alcohol addiction and potentially to identify new pharmacologic therapies. It is envisioned that the CHARGE Consortium studies will provide an adequate sample size to detect associations with modest effect sizes.


5. Main Hypothesis/Study Questions:
The main aim of the proposed investigation is to characterize genetic polymorphisms associated with alcohol consumption.

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).

Phenotypes – to be defined at each study’s baseline exam
1.) Continuous phenotype: Drinks per week at baseline examination (with In-transformation)
   a. Drinks per week, with drink defined by the following units (following the derived variable definitions in ARIC):
      i. 1 beer (DTIA97) = 12 oz = 13.2 gm ETOH
      ii. 1 glass wine (DTIA96) = 4 oz = 10.8 gm ETOH
      iii. 1 drink of spirits (DTIA98) = 1.5 oz = 15.1 gm ETOH

2.) Dichotomous phenotype: Heavy vs. light drinking – based on categorization of ‘drinks per week’ variable
   a. Heavy drinking is defined as ≥21 drinks per week in men, ≥14 drinks per week in women
   b. Comparison group is ≤14 drinks per week in men, ≤7 drinks per week in women
      i. If information available, also include current non-drinkers who are former drinkers of ≤14 for men or ≤7 for women
   c. Exclusion: men reporting >14 to <21 drinks per week and women reporting >7 to <14 drinks per week (i.e., “moderate” drinkers excluded)

Main Exclusions
1.) Missing data on alcohol consumption
2.) Not current drinkers (drinks per week = '.' Or '0')
3.) Missing data on covariates
4.) Non-white race
**Covariates**

- Age (years) – at baseline visit
- Sex
- Study site

**GWAS**

1.) Primary analysis
   Additive genetic model test for association between genotyped/imputed genotype and alcohol consumption per week will be applied for each study combining data for both men and women (except WGHS which has only women).
   
   i. Continuous outcome: drinks per week (with ln-transformation)
      - For the continuous trait of “drinks per week,” a linear regression model will be constructed using sex-specific residuals and will be adjusted for age, and study site.
   
   ii. Dichotomous outcome: heavy versus light drinking
       - For the dichotomous trait of “heavy versus light drinking,” a logistic regression model will be constructed and will be adjusted for sex, age, and study site.

The results for both traits will be meta-analyzed across studies using inverse variance weights. A p-value of 5.0E-08 will be considered statistically significant.

2.) Secondary analysis: sex-specific GWAS for each study
   All models will be run separately for each sex. The results for both traits will be meta-analyzed across studies using inverse variance weights.
   
   i. Continuous outcome: drinks per week (with ln-transformation)
      - For the continuous trait of “drinks per week,” a linear regression model will be constructed for each sex and will be adjusted for age, and study site.
   
   ii. Dichotomous outcome: heavy versus light drinking
       - For the dichotomous trait of “heavy versus light drinking,” a logistic regression model will be constructed for each sex and will be adjusted for age, and study site.

A CHARGe Sharespace site will be created for uploading each study’s GWAS results. The format of the GWAS result data file should follow the CHARGe Protocol for file sharing.

7.a. Will the data be used for non-CVD analysis in this manuscript?  
    **NO**

7.b. Not applicable
8.a. Will the DNA data be used in this manuscript?
   
   YES

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

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
   
   YES

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)?

   1098: Interaction effects of HDL metabolism gene variation and alcohol consumption on CHD risk (Volcik)
   1138: Influence of ApoE polymorphism and alcohol intake on HDL concentrations (Pankow)
   1513: GWAS of blood pressure using genotype-by-smoking and genotype-by-alcohol intake interactions (Franceschini)

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

   YES

   GWAS via STAMPEDE & GENEVA, #2006.03

11.b. If yes, is the proposal primarily the result of an ancillary study (list number* 2006.3)

   ARIC is one of 7 cohort studies contributing data to the CHARGE -based meta-analysis. Since this work is a product of CHARGE which utilizes GWA data, ancillaries related to STAMPEDE & GENVA are also acknowledged.

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.

   The authors understand and will comply with this expectation.