

ARIC Manuscript Proposal # 1474

PC Reviewed: 2/10/09
SC Reviewed: _____

Status: A
Status: _____

Priority: 2
Priority: _____

1.a. Full Title: Genome-wide association study of age at natural menopause and reproductive lifespan: the CHARGE Consortium

b. Abbreviated Title (Length 26 characters): GWAS of age at menopause

2. Writing Group: Ellen Demerath, Nora Franceschini, Aaron Folsom, Eric Boerwinkle, other welcome

CHARGE WG collaborators and affiliations:

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

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3. Timeline: Analyses will begin when all genotyping and QC is completed.

4. Rationale:

To conduct a genome-wide association analysis of age of natural menopause and reproductive lifespan among ARIC women of European ancestry and a meta-analysis across CHARGE cohorts.

5. Main Hypothesis/Study Questions:

To explore the contribution of genetic factors to age of natural menopause (ANM) and reproductive lifespan among women of European ancestry, we propose to perform a genome-wide association analysis of ANM using the set of genotyped and imputed SNPs in ARIC and to conduct a meta-analysis across 7 CHARGE cohorts. We will also perform analysis of Chromosome X SNPs after proper QC is applied.

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).

Introduction: Later age at natural menopause is associated with longer lifespan, while early menopause is associated with increased morbidity and mortality, possibly secondary to the loss of estrogen. Age at natural menopause is significantly heritable (e.g., $h^2 = 0.50$ in the FHS) but few specific genetic variants associated with this important marker of senescence have been identified and none have been replicated.

Subjects: Women of European ancestry with available self-reported information regarding age at menopause and GWAS data.

Variables (phenotype): Self reported age of natural menopause defined as the age at the last menstrual period, after at least 12 consecutive months of amenorrhea (as derived from questionnaire data). In ARIC, this variable was derived primarily using the following existing ARIC variables: MENOPSA01 (menopausal status), RHXA08 (age at menopause) and RHXA09 (cause of menopause), among others. If a woman was pre- or peri-menopausal at visit 1, the next visit data were examined, and so on until the first report of natural menopause was obtained.

Inclusion: all White women with age at natural menopause (ANM)

Exclusions: Women were excluded if they reported hysterectomy and/or bilateral ovariectomy prior to natural menopause (surgical menopause), if they reported menopause due to chemotherapy or radiation (other non-natural menopause), were pre-menopausal or peri-menopausal at Visit 4, or if the cause of menopause (natural, surgical, or other non-natural) could not be deduced from the questionnaire responses, were of a race other than White, had ANM < 40 years or > 60 years.

Exposure: 2.5 million imputed HapMap SNPs typed using the Affymetrix 6.0 SNP chip.

Models:

Primary analysis: Analysis of imputed data (using the HapMap Caucasian information) for all women with ANM 40-60 yrs. Linear regression analysis using an additive genetic model. Basic model: We will perform analysis using all available SNPs that pass QC, with adjustment for center/site within cohort, and for population stratification (assessed using principal components (PC) analysis) where PCs that are significantly associated with the trait will be included.

The meta-analysis will include the following studies: ARIC, Framingham Heart Study, Rotterdam Study I and II, TwinsUK, InCHIANTI, HAPI Heart Study (Amish study).

Secondary analyses:

- Adjustment of models for additional covariates (final list to be decided by WG, but may include diabetes status prior to menopause or at baseline (Visit 1), cigarette smoking status or pack-years at baseline, BMI at baseline, presence or absence of unilateral oophorectomy, hormone-replacement therapy, age at recall of age at menopause, and habitual physical activity (in ARIC using the Sport Index of the Baecke)
- Analyze data from all women with data on natural menopause (no age exclusion)
- Analyze data from women with natural menopause < 40 yrs as cases with possible premature ovarian failure compared to controls with natural menopause occurring > 45 years of age.
- Analyze women with menopause > 60 yrs as cases with extreme late menopause.
- Analyze reproductive lifespan as an alternative phenotype using the same models as above. Reproductive lifespan (years) = age at natural menopause – age at menarche.

Transform: Age of menopause is normally distributed so no transformation of the data will be performed. The distribution of the other phenotypes will be evaluated.

Covariates: (listed above under Secondary analyses)

Statistical significance: Genome-wide significant: $p\text{-value} \leq 5 \times 10^{-8}$. Suggestive significance if $p\text{-value}$ below threshold of 5 expected false positives ($p\text{-value} \sim 5/2,200,000 = 2.3 \times 10^{-6}$). Top findings with $p\text{-value} < 10^{-5}$ will also be listed.

Meta-analyses: We will conduct meta-analysis of cohort-specific $p\text{-values}$ within the CHARGE Aging and Longevity—Reproductive Health WG, using fixed effects and the program METAL.

7.a. Will the data be used for non-CVD analysis in this manuscript?

☐ Yes ☒ 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.csc.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 Proposal # 1368. Analysis of single nucleotide polymorphisms from genome-wide association data for adiposity traits. Kari North; Keri Monda; Ellen Demerath; Linda Kao; Eric Boerwinkle; Braxton Mitchell (with the OOA Study); Caroline Fox (with the FHS); Tamara Harris (with the AGES Study)

(other genome-wide association studies have been proposed, but none on age at natural menopause)

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)

____ 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.csc.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.**