ARIC Manuscript Proposal # 1472

PC Reviewed: 02/10/09	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Genome-wide association analysis of age of menarche: the CHARGE Consortium

b. Abbreviated Title (Length 26 characters): Genomewide association of age at menarche

2. Writing Group (ARIC investigators): Ellen Demerath, Nora Franceschini, Aaron Folsom, Eric Boerwinkle

CHARGE participating studies:
Framingham Heart Study, Rotterdam Study I and II, TwinsUK, InCHIANTI, HAPI Heart Study

Other CHARGE WG collaborators and affiliations:

John R Perry1, Lisette Stolk2,3, Kathryn Lunetta5,6,Guangju Zhai7, Patrick McArdle8, Karol Estrada2, David Karasik9, Douglas P Kiel9, Joyce van Meurs2, Fernando Rivadeneira2,3, Nicole Soranzo7,10, Jenny Visser2, Michael Weedon1, Scott Wilson11, Vivian Zhuang6, Elizabeth Streeten12, Anna Murray1, Tim D Spector7, André G Uitterlinden2,3, Joanne Murabito5,13.

1 Institute of Biomedical and Clinical Science, Peninsula Medical School, Exeter, UK

2 Department of Internal Medicine, Erasmus MC, Rotterdam, the Netherlands

3 Department of Epidemiology, Erasmus MC, Rotterdam, the Netherlands

5 The National Heart Lung and Blood Institute's Framingham Heart Study, Framingham, MA

6 Department of Biostatistics, Boston University School of Public Health, Boston, MA

7 Department of Twin Research & Genetic Epidemiology, King's College London, UK

8 University of Maryland School of Medicine, Baltimore

9 Hebrew Senior Life Institute for Aging Research and Harvard Medical School, Boston, MA

10 Wellcome Trust Sanger Institute, Hinxton, Cambridge, UK

11 Endocrinology & Diabetes, Sir Charles Gairdner Hospital, Nedlands, Western Australia, Australia

12 Division of Endocrinology, Diabetes and Nutrition, University of Maryland School of Medicine, USA

13 Section of General Internal Medicine, Department of Medicine, Boston University (JM)

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]**

F**irst author**: **Ellen Demerath, Ph.D.**
Associate Professor,
Division of Epidemiology and Community Health
School of Public Health, University of Minnesota
1300 South Second St., Suite 300
Minneapolis, MN 55454-1015
(612) 624-8231 (phone)
(612) 624-0315 (fax)
email: ewd@umn.edu

Corresponding/senior author (if different from first author correspondence will be sent to both the first author & the corresponding author):
Address: same above

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

4. Rationale:
To conduct a genome-wide association analyses of age of menarche among ARIC participants and a meta-analysis across CHARGE cohorts.

5. Main Hypothesis/Study Questions:
Our goal is to explore the contribution of genetic factors to variation in the age at first menses (menarche) in women of European ancestry. We propose to perform a genome-wide association analyses of age of menarche using the set of genotyped and imputed SNPs in ARIC and to conduct a meta-analysis of the results across 7 CHARGE cohorts.

We also 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, and a CARe DAC on this topic is in preparation.

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: While age at menarche is significantly influenced by genetic factors (heritability ~ 0.50), no specific genetic variants have yet been identified to be associated with this important reproductive health trait. As girls with earlier menarche tend also to be or become obese and of short stature, identification of SNPs associated with age at menarche may point to regulatory mechanisms involved in growth, obesity and chronic disease risk.
Subjects: Women of European ancestry with available measures of age of menarche. Use of GWAS data in African-Americans will follow CARe procedures.

Variables (phenotype): Self reported age at first menses (menarche), which was collected in ARIC at the baseline visit
Exclusions: Age at menarche < 9 years or >17 years, which correspond to approximately the 1st and 99th percentiles of age at menarche among older women of European Ancestry. Exclusions based on participant consent for use of DNA and non-CVD related outcomes will be made. SNPs that failed QC and subjects for whom population stratification PC estimates are not available will be excluded.
Exposure: 2.5 million imputed and measured SNPs included in the Affymetrix 6.0 SNP chip.
Model: Linear regression for analysis of continuous variables, additive genetic model. Due to significant secular trends in age at menarche, analyses will be conducted using birth year as a covariate. We will perform analysis using all available SNPs that pass QC. We will adjust for population stratification using principal components if required.
Transform: Age of menarche is normally distributed so no transformation of the data will be performed.
Covariates: Basic model: birth year and study center adjusted. Age at baseline is highly correlated with birth year (>0.95), so we will not adjust for v1age01 variable.
Statistical significance: Bonferroni correction adjustment (1/ number of tests performed) ($\sim 10^{-7}$)
Meta-analyses: We will perform meta-analysis of parameter estimates and p-values across the 7 cohorts engaged in the CHARGE Aging and Longevity-Reproductive Health Working Group, using fixed effects and the program METAL.

We also explore pleiotropic genetic effects of age of menarche and anthropometric measures in coordenation with the anthropometric CHARGE WG, if appliable.

7.a. Will the data be used for non-CVD analysis in this manuscript?
__X__ 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?
__X__ 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.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)?
no paper proposals related to menarche or genetics of menarche

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.**