ARIC Manuscript Proposal #1940

1.a. Full Title: Modification of PM-Associated Heart Rate Variability

b. Abbreviated Title (Length 26 characters): Modification of PM Associated HRV

2. Writing Group:
   Writing group members: Candidates currently include co-investigators who have been involved in the planning, execution of, or assembly of data for ARIC AS#2009.08 and its WHI CT sister study AS#264: Avery CL, Chasse S, Heiss G, Li Y, Liao D, Limacher M, Lin D, North KE, Quibrera PM, Smith RL, Tinker L, Vernon M, Wilhelmsen K, Yan S, and Zhang Z

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

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ARIC author 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:**
First pass analyses will begin as soon as requisite electrocardiographic, environmental, genetic and covariate data have been assembled.

4. **Rationale:**
Several measures derived from the resting, supine standard twelve-lead electrocardiogram (ECG) reflect influences of the autonomic nervous system on the heart. These measures include the median duration of the RR interval (RR) across all twelve leads (or equivalently, heart rate), the standard deviation of all normal-to-normal RR intervals (SDNN), and the root mean square of successive differences in normal-to-normal RR intervals (RMSSD).\(^1\) The repeatability, accuracy, and predictive validity of these short-term, time domain measures of heart rate variability (HRV) have been described by members of the writing group,\(^2\) as has the association of HRV with ambient particulate matter air pollution (PM) concentrations.\(^5\) Although others have suggested that HRV is heritable\(^6\) the great majority of genome-wide association studies (GWA) studies in this area have focused on heart rate, not measures of its variability.\(^9\) As such, the genetic basis of short-term, time domain measures of HRV remains incompletely characterized. Even less is known about how genes modify associations between HRV and environmental factors like PM.

5. **Main Hypothesis/Study Questions:**
We therefore propose a GWA study to examine (1) gene-by-PM effects as they relate to the above HRV measures and (2) consistency of these interactive effects among race and gender groups. \[Genetic main effects are addressed by manuscript #1780.\]

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).**
The proposed study will be conducted in the ARIC and Women’s Health Initiative clinical trial (WHI CT) cohorts, based on the foundation provided by ARIC Ancillary Study #2009.08, “Modification of PM-Mediated Arrhythmogenesis in Populations” (R01-ES017794; Whitsel, PI) and two WHI Ancillary Studies: #140 “The Environmental Epidemiology of Arrhythmogenesis in WHI” (R01-ES012238 Whitsel, PI) and #264 “Genetic Modification of PM-Mediated Arrhythmogenesis” (R01-ES017794; Whitsel, PI). The focus will be on approximately 26,000 uniformly well-characterized and consenting participants living within the contiguous 48 U.S., U.S. Environmental Protection Agency (EPA) Regions 1-10, and 500 mi of their exam site who had one or more high quality ECGs between 1987 and 2004 and no condition that affects availability or accuracy of HRV measures. The population will include seven distinct subpopulations: (1) black women, (2) Hispanic women, and (3) white women in the WHI CT; and (4) black women, (5) white women, (6) black men, and (7) white men in ARIC. The seven subpopulations will be used to independently identify gene-by-PM interactions for HRV using imputed data from the Affymetrix 6.0 platform and daily mean ambient PM concentrations spatially interpolated at geocoded participant addresses.
To identify them, we propose a stratified, longitudinal analysis of HRV. The initial strategy is to longitudinally model the average of repeated outcomes as we have done in AS #2009.10 and thereby facilitate estimation of time-varying environmental exposure effects by increasing power. We will stratify the longitudinal analyses by study, race, and within the ARIC study, gender. All analyses will be appropriately adjusted for both ancestral admixture and multiple comparisons. Conventional, generalized estimation equations (GEE) will be used to estimate gene-by-PM interactions. A compound symmetric correlation structure will be used to account for the correlation of repeated observations made on the same participants over time, although other structures can be accommodated, if necessary.

More powerful tests of gene-by-PM interaction across ancestral populations will be based on an extension of kernel machine regression (KMR) methods that aggregate SNP-level score test statistics within genes. Such methods are particularly useful in genetically diverse populations where different SNPs may be in linkage disequilibrium with causal SNP(s). They also can accommodate complex SNP interactions, permit covariate adjustment, and do not penalize SNPs with opposing associations within a gene. We anticipate that important gene effects will be shared across subpopulations, but we will examine heterogeneity among them as a function of study, race, and gender. Although we expect modest power to detect heterogeneity, meta-analytic methods will be used to combine gene-level results across subpopulations, when appropriate.

The replication plan described above relies on identical electrocardiographic, genetic and environmental data in the ARIC study and WHI CT, i.e. the same ECG measures estimated by the same ECG reading center using the same methods; approximately 10⁶ SNPs genotyped on the same Affymetrix 6.0 platform and imputed to the same HapMap reference panel; and daily mean PM concentrations estimated at all geocoded participant addresses using the same kriging methods. Although issues related to phenotype and genotype harmonization have been minimized by design, opportunities for replication of genes implicated in gene-by-PM interaction analyses outside the ARIC study and the WHI CT may be limited to those populations with comparable measures, e.g. the Multiethnic Study of Atherosclerosis.

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 ICTDER03 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 ICTDER03 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?  

   _____ 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 ICTDER03 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)?

#1780  - Genome-Wide Association Analyses of Respiratory Sinus Arrhythmia / Heart Rate Variability. However, the lead author of #1780 is the same as the lead of this proposal (Whitsel), the focus of #1780 is on longer duration time and frequency domain measures of HRV, and SNP main (not gene-PM interactive) effects.

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*_ #2009.08 _)  

_____  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/

12a. 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.

12b. The NIH instituted a Public Access Policy in April, 2008 which ensures that the public has access to the published results of NIH funded research. It is your responsibility to upload manuscripts to PUBMED Central whenever the journal does not and be in compliance with this policy. Four files about the public access policy from http://publicaccess.nih.gov/ are posted in http://www.cscc.unc.edu/aric/index.php, under Publications, Policies & Forms. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to Pubmed central.
References