1.a. **Full Title:** Meta-analysis of genome-wide association data in relation to circulating lipoprotein-associated phospholipase A2 concentrations in white adults of European descent: CHARGE Consortium

b. **Abbreviated Title (Length 26 characters):** Lp-PLA2 Meta-analysis of GWAS data in Whites

2. **Writing Group:**
   Maja Barbalic, Eric Boerwinkle, Christie Ballantyne, Ron C. Hoogeveen, Gerardo Heiss Josef Coresh, plus authors from other cohorts

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. __EB__ [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:** All genotyping is complete. Analyses to begin immediately.

4. **Rationale:** Markers of inflammation such as lipoprotein-associated phospholipase A2 (Lp-PLA2) have been associated with increased risk for coronary heart disease (CHD) events (Tsmikas 2008). In the ARIC cohort, Lp_PLA2 was associated with incident CHD levels after adjustment for age, sex, and race (Ballantyne et al 2004). Lp-PLA2 hydrolyzes oxidized fatty acids to generate lysophosphatidylcholin and oxidized fatty acids, which have proinflammatory properties (Ballantyne et al 2004). With the availability of genome-wide collection of single nucleotide polymorphisms, it is now possible to identify the genes responsible for inter-individual variation in Lp_PLA2 levels and to contribute to the understanding of mechanisms leading to CHD.

5. **Main Hypothesis/Study Questions:** Investigate the association of genome-wide genetic variation with inter-individual variation in Lp-PLA2 levels in adults of European ancestry
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).

General Analysis Approach:

Subjects: European/European-American subjects with Lp-PLA2 levels available

Exposure: 2.5 million HapMap genetic variants identified in CEPH trios

Outcome: Lp-PLA2 levels

Exclusions: those without consent for genetic research

Primary statistical approach: Additive linear regression model (1 df) with robust variance estimates adjusted for sex, age

Meta-analysis: all resulting p-values

Validation and Replication: Possible validation genotyping for selected findings; correlation of findings with those from existing databases

Major Phenotypes to Analyze: Lp-PLA2 levels

Cohorts Included in Analysis: CHS, FHS, Rotterdam, and ARIC

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 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

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 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.  ____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)?

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 primarily the result of an ancillary study (list number* _2006.03_?)
B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* __________ __________ __________)

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.

References
