1.a. Full Title: CRP gene polymorphism and risk of coronary heart disease and stroke

b. Abbreviated Title (Length 26 characters): CRP polymorphism and CVD

2. Writing Group (list individual with lead responsibility first):

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    Writing group members:
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    (Welcome suggestions for other members)

3. Timeline:
    Begin analysis: September 2004
    First draft: December 2004

4. Rationale:

    CRP is a major acute phase protein produced in the liver in response to interleukin-6 and other cytokine mediators. Measured level of CRP within the normal range (hs-CRP) is an independent predictor incident CHD and stroke in numerous prospective cohort studies [1], including ARIC [2,3](Ballantyne, in preparation). CRP may be more than a non-specific marker of chronic inflammation; there is evidence that it may play a direct role in the pathogenesis of cardiovascular disease [4].

    In the NHLBI Family Heart Study, there was familial aggregation of CRP, consistent with moderate genetic regulation [5]. Heritability of CRP was estimated to be 39% in another study [6]. Statistically significant associations have been reported between circulating CRP level and several single nucleotide polymorphisms in the CRP gene [7-9] and a dinucleotide repeat in intron 1 [10]. Some of these genotypic differences were accentuated following physical exercise, an acute proinflammatory stimulus [9].

    In a cross-sectional study of Pima Indians, a SNP in the 5’ promoter region of the CRP gene (rs2794521) was associated with type 2 diabetes, with prevalences of 62%, 54%, and 39% in
subjects with the TT, TC, and CC genotypes, respectively [11]. To our knowledge, no studies have examined this CRP promoter polymorphism and risk of cardiovascular endpoints, although one study found no association between a synonymous polymorphism in exon 2 and risk of CHD and stroke [7]. Associations between CRP genotypes and cardiovascular disease would suggest that CRP may have direct proinflammatory effects.

5. **Main Hypothesis/Study Questions:**
   Subjects with the TT allele of rs2794521 will have higher levels of hs-CRP at visit 2 and higher rates of incident CHD and stroke post visit 1 compared to subjects with the TC or CC genotypes at this locus. Adjustment for hs-CRP level at visit 2 will attenuate the association between CRP genotype and incident events post visit 2.

6. **Data (variables, time window, source, inclusions/exclusions):**
   CRP genotypes and level (from Table 4); incident CHD and stroke status and time to event; covariates measured at baseline including age, gender, race, center, BMI, WHR, smoking status and pack-years, LDL-c, HDL-c, triglycerides, diabetes, systolic and diastolic blood pressure, anti-hypertensive medication use. Cross-sectional analyses between CRP genotype and hs-CRP level and prospective analyses of incident events post-visit 2 will utilize covariates measured at visit 2 (if available).

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?  ____ 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”?  ____ 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:
   ____ 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)?

    Manuscripts 606 (Folsom) and 889 (Ballantyne) have evaluated hs-CRP level and incident CHD; manuscript 940 (Ballantyne) has evaluated hs-CRP and incident stroke. This
manuscript will include hs-CRP has a possible intermediate in the causal pathway between CRP genotype and incident events.

11. **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.**


