1.a. Full Title: Association of a SNP (rs1800630) in the regulatory region of tumor necrosis factor-alpha (TNFα) and the risk of cardiovascular disease

b. Abbreviated Title (Length 26 characters): TNFα and CVD risk

2. Writing Group:
   Writing group members: Linda Kao, Lin, Zhang, Josef Coresh, Jim Pankow, Aaron Folsom, Eric Boerwinkle

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3. Timeline: Genotyping data is already available in Table 4. We project that analyses and manuscript preparation will take place over the next year.

4. Rationale:
   TNFα is a multifunctional cytokine produced by adipocytes that is both an immunomodulator and a neuromodulator\textsuperscript{1,2}. It has been hypothesized that variations in the gene encoding TNF-α may play a role in the risk of vascular diseases, including CHD and stroke. In fact, previous prospective epidemiologic studies have shown that serum TNF-α levels are predictive of
cardiovascular events\textsuperscript{3-5}, with higher serum TNF-α levels being associated with increased risk of cardiovascular events. In addition, there is evidence that expression of TNF-α is determined by variations in the gene encoding the protein, particularly the C→A polymorphism at position -1042 of the promoter of the gene (this SNP is also known as the -863 C/A SNP; rs1800630). One previous study examined the functional effects of various SNPs in the promoter region of the TNF-α gene\textsuperscript{6} and demonstrated that the A allele of rs1800630 was significantly associated with reduced basal rate of transcription of the TNF-α gene; furthermore, in 156 healthy, middle-aged men, carriers of the A allele had significantly lower serum TNF-α concentrations. The aim of this proposal is to investigate association between rs1800630 and the risk of CHD and stroke in the ARIC study.

5. **Main Hypothesis/Study Questions:**
   The A allele of rs1800630 is associated with lower risk of CHD and stroke.

6. **Data (variables, time window, source, inclusions/exclusions):**
   For individuals in Table 4, the following variables will be needed for these analyses: age, sex, race, center, IMT thickness, blood pressure, diabetes, history of CHD, body mass index, waist-to-hip ratio, smoking status, and fasting insulin and lipid levels.

   Analyses will assume the following steps:
   1. Hardy-Weinberg equilibrium among genotypes will be checked by calculating expected frequencies of genotypes and using the chi-square goodness-of-fit test.
   2. All analyses will first be stratified by ethnicity to test for interaction. If no interaction is detected, pooled analyses will be performed.
   3. CHD and stroke will be analyzed as separate outcomes. Genotype of rs1800630 will be coded as 0 (zero copies of the candidate allele), 1 (one copy of the candidate allele), or 2 (two copies of the candidate allele). An additive genetic model will be assumed unless indicated otherwise by results of the analysis or unless the allele frequency of a given candidate variant is low, in which case, a dominant model combining the risk of heterozygotes and homozygotes will be used. Analysis will use the Barlow Macro for analysis of case-cohort data following the design layout in Table 4.
   4. General linear regression will be performed to assess the association between genotype of rs1800630 and quantitative cardiovascular risk factors, including IMT thickness, blood pressure, body mass index, waist-to-hip ratio, and fasting insulin and lipid levels in the cohort sample of the ARIC case-cohort design.

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 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.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)? MS682, MS967, MS941

11. a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data?  ____ Yes    __X__ No

11.b. If yes, is the proposal

___    A. primarily the result of an ancillary study (list number* __________)
___    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.