

## ARIC Manuscript Proposal # 1371

PC Reviewed: 05/13/08  
SC Reviewed: \_\_\_\_\_

Status: A  
Status: \_\_\_\_\_

Priority: 2  
Priority: \_\_\_\_\_

**1.a. Full Title:** Association of the NOS3 Glu298Asp SNP with hypertension and possible effect modification of dietary fat intake.

**b. Abbreviated Title (Length 26 characters):** NOS3, hypertension and dietary fat

**2. Writing Group:** Pascal L. Kingah, MD; Hung Luu, MD, MPH; Kelly Volcik, PhD; Alanna Morrison, PhD; Eric Boerwinkle, PhD; Jennifer Nettleton, PhD.

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

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**3. Timeline:** Genotyping for the NOS3 Glu298Asp SNP (rs1799983) is complete for the entire ARIC cohort. Statistical analysis will begin immediately, with a first draft manuscript prepared by August 2008.

**4. Rationale:**

In the United States, 1 out of every 3 persons aged 20 and older has hypertension, with more than 100 million people having either pre-hypertension or definite hypertension (1-2). Both human and animal studies have revealed evidence of hypertension due to the loss of the effect of

nitric oxide, which acts as the endothelium derived relaxing factor (3). Nitric oxide is catalyzed by endothelial nitric oxide synthase (eNOS), an enzyme with multiple genetic variants that might confer risk for hypertension (4). Three SNPs in the NOS3 gene have been shown to be associated with hypertension, including Glu298Asp, T786C, and a base pair VNTR in intron 4 (5). However, inconsistent findings on the relationship between NOS3 polymorphisms and hypertension have been observed in previous studies, with significant associations reported from Japan (6) and Singapore(7) , but no associations observed in China(8) and Australia(9). In a recent meta-analysis by Pereira et al, the association between the NOS3 Glu298Asp SNP and hypertension was shown to be modified by specific dietary patterns (e.g. diets rich in saturated fat) and conditions (e.g. hypercholesterolemia) (10). This meta-analysis included studies comprised of subjects from Europe, China and Japan, but did not include subjects from the United States. Apart from publication bias, one of the most common limitations among these previously reported studies is the low power to detect the strength of association due to small sample sizes.

Being a cohort with a large sample size, the ARIC study offers an opportunity to determine stronger effect measures between NOS3 and hypertension in both whites and blacks, with additional analyses of possible gene-diet interactions. Studies have shown that the impact of n-3 fatty acids on endothelial function depends on eNOS genotype with the influence of n-3 fatty acid level being greater in Asp298 carriers.(11) Interactions between cholesterol and regulatory mechanisms of blood pressure are poorly understood and the role of individual fatty acids in blood pressure regulation remains unclear.(12,13,14). We propose to evaluate the association between the NOS3 Glu298Asp SNP (rs1799983) and hypertension, as well as the possible effect modification of dietary fat intake (saturated fat, monounsaturated fat, polyunsaturated fat).

## **5. Main Hypothesis/Study Questions:**

- 1- Determine the frequency distribution of the NOS3 Glu298Asp SNP in the ARIC study. If allele frequencies are markedly different with respect to race, all subsequent analyses will be stratified by race.
  
- 2- Using logistic regression, evaluate the independent effect of the NOS3 Glu298Asp SNP on hypertension status. Models will be adjusted for age, gender, race, BMI, smoking status, diabetes and physical activity.
  
- 3- Evaluate whether dietary intake modulates the independent effect of the NOS3 Glu298Asp SNP on hypertension status. Models will be adjusted for age, gender, race, BMI, smoking status, diabetes and physical activity.

## **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).**

Hypertension status at visit 1 will be the primary dependent variable (HYPERT05). The usual DNA restriction, ethnic group and missing data exclusion criteria will be used. Exclusions will include the following: 1) prohibited use of DNA, 2) ethnic background other than white or

African American, as well as African Americans not from Jackson or Forsyth. Independent variables include but are not limited to NOS3 genotype status and traditional risk factors such as age, gender, smoking, BMI and diabetes.

For the analyses of gene-diet interaction, we will focus on dietary intakes of saturated fat (SFAT), monounsaturated fat (MFAT) and polyunsaturated fat (PFAT). We acknowledge that diet is notoriously measured with error, and we will explore the effects of bias due to this error. If we feel the degree of bias is large, we will explore methods to correct for some degree of the error in reported dietary intake.

**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

**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"?**  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.**  
 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)?**

**MS#950, North** – Association of the NOS3 Glu298Asp SNP with non-invasively measured atherosclerotic burden and/or risk of adverse CVD events

**MS#1131, Bielinski** – Association of the NOS3 Glu298Asp SNP with serum levels of inflammation biomarkers and possible effect modification of dietary antioxidants

**MS#1228, Bressler** – Association of the NOS3 Glu298Asp SNP with diabetes and possible effect modification of obesity

**11. a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data?** \_\_\_ Yes  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)\* \_\_\_\_\_)**

**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. Agree**

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