1. Title: Predictors of carotid artery wall thickness in those with high and low plasma lipid levels. II. HDL-cholesterol levels.

2. Writing group: Hwang, Sharrett, Hutchinson, Schreiner, Wu, Smith, and Boerwinkle

3. Timeline:
All data has been collected. Only analyses and manuscript preparation remain.

4. Rationale:
Numerous studies have provided strong evidence that low levels of plasma HDL-cholesterol are associated with the occurrence of coronary heart disease. However, it is not clear whether high levels of HDL-cholesterol are protective of coronary heart disease regardless of the presence of other risk factors (e.g. high levels of LDL-cholesterol). In this manuscript we will test the hypothesis that the relationship between established CHD risk factors is the same between two groups defined as having low and high HDL-cholesterol levels. It is an accepted but still provocative concept that certain risk factors act in a multiplicative manner. Therefore, we expect to define variables whose predictive relationship with carotid artery wall thickness is altered in the high HDL-cholesterol group, relative to the low HDL-cholesterol group. The analyses will begin with an exploratory component to define the predictors of carotid artery wall thickness within each group, and then proceed to testing the heterogeneity of this predictive relationship between groups.

5. Primary null hypotheses:
(1) Using univariable methods, the relationship between each variable and carotid artery wall thickness is the same among the three groups defined by plasma HDL-cholesterol levels.
(2) Using multivariable methods, the relationship between the vector of predictor variables and carotid artery wall thickness is the same among the three groups defined by plasma HDL-cholesterol levels.

6. Sample: The entire ARIC cohort at visit one will be used. The low group will be defined as the lower 25 percentile of HDL-cholesterol. The high group will be defined as the upper 25 percentile of HDL-cholesterol. These percentiles were selected based on statistical power calculations in the African-Americans. All analyses will be carried out separately in males and females, and in African-Americans and Non-hispanic whites. \textit{A posteriori} power calculations will be carried out.

7. Data requirements:
ARIC visit one data will be used. The derived variable \text{sum45_2} will be used to measure carotid artery wall thickness. Data requirements: The list of primary predictor variables includes: age at visit 1, body-mass index, lipid (LDL-cholesterol, lipoprotein(a), HDL cholesterol, triglyceride), fasting glucose, fasting insulin, nutrient (keys score), hemostatic factors (active partial thromboplastin time (APTT), factor VIII:C, fibrinogen, factor VII, antithrombin III, protein C), lifestyle (pack of cigarettes times years of smoking, usual ethanol intake in gram/per week), physical activity (sport index higher than 2.5 or not), had hypertension or not. For those significant predictor factors in either low or high LDL-cholesterol group and were tested
equally distributed in the two groups, we then tested for significant heterogeneity of the relationship between groups. The most parsimony model that explains the variability of carotid wall thickness in the study population was then presented for low and high LDL-cholesterol groups.