1. Title: Different predictors of carotid artery wall thickness in those with high and low plasma lipid levels. I. LDL-cholesterol levels.

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

4. Rationale:
Despite publicity championing a role for plasma cholesterol as a predictor of coronary heart disease, it is widely accepted that only a portion of coronary heart disease cases can be accounted for by elevated cholesterol levels. The majority of plasma cholesterol is carried in the LDL fraction. This manuscript will explore the relationship between carotid artery wall thickness and potential predictor variables in those with low and high levels of plasma LDL-cholesterol. It is likely that variables thought not to be predictors of disease in the general population are, in fact, highly significant predictors of disease in subsets of the population defined by plasma LDL-cholesterol. We expect to define variables whose predictive relationship with carotid artery wall thickness is increased in the high LDL-cholesterol group (relative to the low LDL-cholesterol group). One biologic explanation for such a positive interaction is that the two factors (i.e. LDL-cholesterol and the second risk factor) act synergistically in the atherosclerotic process. Therefore, we expect to define a set of risk factors that interact multiplicatively with plasma LDL-cholesterol to affect atherosclerosis. Conversely, we also expect to define variables whose predictive relationship with carotid artery wall thickness is decreased in the high LDL-cholesterol risk group (relative to the low LDL-cholesterol group). A biologic explanation for such a negative interaction is that the effect of LDL-cholesterol is masking a role of the second risk factor.

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 LDL-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 LDL-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 LDL-cholesterol. The high group will be defined as the upper 25 percentile of LDL-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. A posteriori power calculations will be carried out.

7. Data requirements:
ARIC visit one data will be used. The derived variable 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.