1. Title:
Multiple Metabolic Syndrome and Lower Extremity Arterial Disease (LEAD)

2. Writing Group:
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3. Timeline:
Analysis will be done immediately. A draft manuscript will be ready by June 1995.

4. Rationale:
Multiple metabolic syndrome has been described in several studies. Evidence of insulin resistance predating the other metabolic abnormalities has been found. Obesity (measured as waist-hip ratio and body mass index), fasting insulin, dyslipidemia (increase of triglycerides and decrease of HDL-C), hypertension and hyperuricemia have been the abnormalities more currently described to be associated (Haffner et al. 1992, Mitchell et al. 1992, Schmidt et al. MS #27 unpublished). LDL-C levels seem to be independent of levels of insulin resistance (Schmidt et al, deFronzo and Ferrannini 1991).

All these abnormalities are traditional risk factors for arteriosclerotic cardiovascular disease (ASCVD). It is not known if, when present in clusters, the risk of cardiovascular disease (CVD) is greater than expected on the basis of their added independent effects. This is currently being assessed int he aRIC study in relation to carotid atherosclerosis by one of the co-authors (MIS).

Another manifestation of ACSVD, LEAD, also shares with CVD most of the same risk factors. Some differences in respect of risk influence and magnitude of the effect have been reported: lipid levels may have more modest effects, while smoking is described as a strong risk for LEAD. Diabetes was also strongly associated, although serum insulin did not have a consistent relationship with LEAD (Dobs et al. MS #121, Fowkes et al. 1992). This contrasts with the fact that atherosclerotic occlusion in the lower extremities is a frequent complication of diabetes mellitus (Hiatt et al, 1990). Increasing levels of fibrinogen were associated with popliteal wall thickness in the ARIC population (Dobs et al, MS #121), and results are inconsistent for obesity.

5. Hypotheses:
1) Risk factors of CVD are present in clusters that are associated with a greater risk of LEAD than expected on the basis of their independent effects. We will assess the presence of clusters of abnormalities and their effect on LEAD (measured as intermittent claudication, ankle-brachial index (ABI) and popliteal wall thickness), estimating the possible excess of risk due to clustering.
2) Glucose has an independent role: the risk of LEAD associated with fasting glucose levels exceeds the risk expected by the presence of clusters.

6. Data:
Analyses will be done in the entire visit 1 cohort.
1) Evaluate the existence of clusters of abnormalities on LEAD, assessing the existence of interaction due to clustering. The presences of effets beyond those expected using both additive and multiplicative models will be evaluated.
2) Effect of the clusters of factors (independent) in popliteal thickness, ABI and Intermittent claudication (dependent) adjusting for age, sex, race, smoking, use of medication, LDL-C and fibrinogen levels. 

3) Effect of diabetes (glucose levels) (independent) in popliteal thickness, ABI and intermittent claudication (dependent) adjusting for age, sex, race, smoking, use of medications, LDL-C, fibrinogen and presence of clusters.

7. REFERENCES


