**The Role of the Gut Microbiota in CVD Risk: The Bogalusa Heart Study**

The human gut hosts a vast array of microbes collectively known as the microbiota. Although influences of the gut microbiota on human health have been hypothesized for some time, technological advances have only recently made it feasible to characterize host microbial communities and examine their associations with disease states. The cross-sectional relationships of the gut microbiota with cardiovascular disease (CVD) risk factors including obesity, type 2 diabetes, and dyslipidemia have already been well documented in population based studies. Recently, strong evidence of a link between gut microbiome metabolites and CVD in human subjects was reported. These data provide strong support for a role of gut microbiota in the development and progression of CVD. *However, no comprehensive epidemiologic investigations into the association between gut microbial communities and longitudinal CVD risk have been conducted previously. Such work could provide novel etiologic insights and yield innovative strategies for CVD prevention and treatment.*

***The overall objective of the proposed study is to examine the role of gut microbiota on longitudinal CVD risk among black and white participants of the Bogalusa Heart Study.*** We hypothesize that gut microbial communities influence development of CVD in human subjects. To test our hypothesis, gut microbial communities and their metabolites will be characterized among black and white Bogalusa Heart study participants selected from the current follow-up study based on longitudinal measures of CVD risk factors and subclinical atherosclerosis. Such work will allow us to directly and agnostically identify CVD-related gut microbiota and metabolites. Promising metabolites will then be measured from blood samples collected at least 5 years prior to the current follow-up study to examine their associations with longitudinal changes in CVD risk factors and subclinical measures of atherosclerosis. This analysis will be conducted among all Bogalusa Heart Study participants with previously collected blood samples who are currently undergoing follow-up study (N=400). The proposed work will take advantage of the rich resources of the Bogalusa Heart Study, a cohort that has been extensively characterized for CVD related traits over the lifespan. To achieve our overall objective, we will pursue the following specific aims:

**Specific Aim 1: To examine the association between gut microbiota and longitudinal CVD risk among Bogalusa Heart Study participants.** The 100 white and 100 black Bogalusa Heart Study participants with highest CVD risk will be matched by age and gender to the 100 white and 100 black participants with the lowest risk, respectively. CVD risk will be determined based on multiple longitudinal measures of CVD risk factors and subclinical atherosclerosis collected throughout childhood and young adulthood. We will take advantage of state-of-the-art 16S rRNA sequencing technologies to characterize gut microbial communities among Bogalusa Heart study participants. The composition and quantities of gut microbiota will be compared across CVD risk groups in blacks and whites, separately. *This research will be among the first to directly explore microbiota-longitudinal CVD risk associations.*

**Specific Aim 2: To identify gut microbiota related metabolites which may contribute to CVD risk among Bogalusa Heart Study participants.** *Despite tremendous advances in characterizing gut microbial communities, relatively little is known about the metabolic products which contribute mechanistically to their important health consequences.* Among those participants whose gut microbiota were characterized in **Specific** **Aim 1**, we will conduct untargeted metabolomic quantification of plasma samples collected during the follow up study. We will examine the associations between gut microbiota and metabolomic profiles to identify and characterize gut microbiota related metabolites. Gut microbiota related metabolites will also be examined for association with longitudinal CVD risk in blacks and whites, separately.

**Specific Aim 3: To determine whether promising gut microbiota related metabolites predict longitudinal changes in CVD risk factors and measures of subclinical atherosclerosis among Bogalusa Heart Study participants.** *Previous studies examining associations of gut microbiota with CVD risk factors have been primarily cross-sectional by design, limiting causal inference. The proposed research could provide critically needed information regarding the temporality of the relation between microbiota and CVD risk.* We will conduct targeted metabolomic quantification of promising gut microbiota related metabolites identified in **Specific Aim 2** using stored blood samples from 400 Bogalusa Heart Study participants who are currently undergoing follow-up study. We will examine the associations of these gut microbiota related metabolites with longitudinal changes in multiple CVD related risk factors and subclinical measures of atherosclerosis*.*

By leveraging longitudinally measured data on CVD-related traits, the proposed research provides an outstanding opportunity to explore the relation of the gut microbiome with CVD risk in an extremely cost-effective manner. Findings from this study may be used to identify individuals at high risk for CVD development. Based on this information, targeted therapeutic strategies aimed at altering identified gut microbiota could be developed, providing additional strategies in the prevention and treatment of CVD.