Title: **Metabolically healthy obesity beginning in childhood and gut microbiota and**

Lead: Shengxu Li

Proposed co-investigators: Wei Chen, Lydia Bazzano

External collaborator: to be identified

Mechanism: NIA R21

Budget: $270K over two years (direct cost)

Deadline: June 16, 2015

Proposed specific aims (see next page)

**Metabolically healthy obesity and telomere attrition**

Obesity prevalence has increased dramatically during recent decades in the United States and around the world. It has become a major public health challenge as a result of its close links to cardiometabolic diseases. However, there exists substantial heterogeneity in the prevalence of cardiometabolic risk factors in obese individuals, i.e., not all obese individuals present adverse metabolic profiles. Obese individuals who do not have an adverse cardiometabolic profile have been referred as “metabolically healthy obesity (MHO)”. Emerging evidence suggests that MHO individuals have reduced risk for cardiometabolic diseases and when challenged with an energy-dense, unhealthy diet show much subdued changes in cardiometabolic profiles. Previous observations on MOH have largely been made in adult populations and longitudinal data, particularly starting from childhood, is lacking. Even for longitudinal studies, MHO is often defined by cross-sectional data, which may suffer from the influence of “regression to the mean”. We have shown MHO begins in childhood and is likely to persist into adult life. Although reduced inflammation, peripheral fat distribution, and genetic factors are poised to play a role in the development of MHO phenotype, determinants of MHO phenotype and underlying mechanisms remain largely unknown. Gut microbiota have been shown to contribute to and modulate human health. Whether gut microbiota contribute to MHO phenotype is an important scientific question.

**The overall objective of the proposed *study*** *is to test the following hypotheses: Adults with an MHO phenotype beginning in childhood have different characteristics in gut microbiota, compared to to other people who is non-MHO, including those who are normal-weight, metabolically healthy, normal-weight, metabolically abnormal, or obese, metabolically abnormal, and such differences may be race- or sex-specific.*

To achieve this objective, we will take advantage of the **Bogalusa Heart Study,** an ongoing longitudinal cohort investigation in which the participants have been followed since childhood**.** It is unique in that it is the only biracial (black-white) community-based longitudinal investigation of the early natural history of atherosclerosis, beginning in childhood. We will examine **60 adults aged 32-54 years** who have been screened multiple times since childhood (at least 2 times in childhood). The study cohort already has data for all traditional cardiometabolic risk variables measured at least 3 times since childhood, and nontraditional cardiometabolic risk variables and subclinical cardiovascular structure/function measured in adulthood. The proposed research is directed towards the following hypothesis-based **Specific Aims:**

1. **Specific Aim 1**: Examine differences in gut microbiota in four groups of adults: normal-weight, metabolically healthy, normal-weight, metabolically abnormal, obese, metabolically abnormal, and obese, metabolically normal (MHO). We hypothesize that MHO individuals have unique gut microbiota profiles.
2. **Specific Aim 2**: Examine differences in gut microbiota in two groups of adults: persistent MHO beginning in childhood and only MHO in childhood but non-MHO in adult life. We hypothesize that Persistent MHO group have unique gut microbiota profiles compared to childhood-only MHO group.
3. **Specific Aim 3**: Examine race and sex contrasts in differences observed in Specific Aims 1 and 2. We hypothesize that differences in Specific Aims 1 and 2 may be race- or sex-specific.

We will use next-generation sequencing technology to examine gut microbiota and apply state-of-the-art statistical analysis to examine differences in comparison groups. Findings from the proposed study will help improve our understanding of MHO development and provide new insights into the underlying mechanisms for childhood to adulthood, which will have implications for planning new, full-scale studies in the same research line.