# The Revolution in Risk Assessment and Disease Detection Made Possible with Non-invasive Imaging: Implications for Population Science

The ability to quantify subclinical disease to assess cardiovascular disease is greatly enhanced by modern medical imaging techniques that incorporate concepts from biomedical engineering and computer science. These techniques' numerical results, known as quantitative phenotypes, can be used to help us better understand both health and disease states. In this report, we describe our efforts in using the latest imaging technologies to assess cardiovascular disease risk by quantifying subclinical disease of participants in the Jackson Heart Study. The CT and MRI exams of the Jackson Heart Study have collected detailed information from approximately 3,000 participants. Analyses of the images from these exams provide information on several measures including the amount of plaque in the coronary arteries and the ability of the heart to pump blood. These measures can then be added to the wealth of information on JHS participants to understand how these conditions, as well as how clinical events, such as heart attacks and heart failure, occur in African Americans. (*Ethn Dis.* 2012; 22[Suppl 1]:S1-24–S1-27)

**Key Words:** Jackson Heart Study, Biomedical Imaging, Cardiovascular Disease, Obesity, Coronary Artery Disease, Atherosclerosis, Pericardial Fat, Myocardial Fat

## Introduction

Heart disease and stroke have worldwide impact on human health but are particularly relevant to individuals living in the southeastern United States, who experience excess mortality from both cerebral-vascular disease and cardiovascular disease.[1] Understanding the root causes of cardiovascular diseases in the African American communities of the southeastern United States is a major goal of the Jackson Heart Study, supported by the National Heart, Lung and Blood Institutes (NHLBI). To help achieve this

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goal, the National Institute of Biomedical Imaging and Bioengineering (NIBIB) joined with the Jackson Heart Study to add advanced non-invasive imaging to the Jackson Heart Study protocol. In this article, we review the scope of the problem of cardiovascular disease in African Americans (AA), provide examples of subclinical cardiovascular disease that can be derived from medical imaging tests and discuss how this information can be integrated with the extensive existing data in the Jackson Heart Study to reduce excess deaths and improve the cardiovascular health of African Americans in the southeastern United States.

Disparities in cardiovascular health negatively impact the African American community. Mensah et al reported that nationally, hypertension has a prevalence of 40% in African Americans, Black women had the highest prevalence of obesity (47%) and deaths from cardiovascular diseases tended to be highest in AA of all ages.[2] Life expectancy in women overall is 5 years longer than men and a comparable 5 year difference is seen between White and Black Americans.[2] Death rates from heart disease and stroke are especially high in the southeastern United States. Obesity rates, like cardiovascular diseases, also greatly impact the people, especially African Americans, of this region of the United States. Data from the CDC and its National Center for Health Statistics indicate that, in 2008, the prevalence of a body mass index > 30 was more than 35% among the Black Non-Hispanic citizens of every state in the southeastern US.[3] The impact of obesity on increased rates of hemorrhagic stroke, ischemic stroke and ischemic heart disease was demonstrated in a collaborative study of over 300,000 individuals in the Asian-pacific basin.[4] While much can be learned from basic

measures of height and weight, non-invasive imaging provides a means to look inside healthy people as well as precisely measure how much fat tissue is found in specific areas (eg, the abdomen). The potential for the combined use of non-invasive imaging variables, blood biomarkers, genetic information and standard measures of health from the results of the Jackson Heart Study can help us better understand the causes and potential relationship between obesity and heart disease in African Americans. The ultimate goal is to use this new knowledge to develop specific tools and interventions that improve health.

## The Cardio-metabolic Profile and Beyond BMI: It's Not Just about Weight

Weight and body mass index (BMI) are important measures of health but they are insufficient for us to explain completely the underlying association with cardiovascular diseases. Wildman et al explored how serum biomarkers could further influence our understanding of the cardiometabolic risk related to obesity.[5] Using data gathered from the NHANES survey of the US population between 1999-2004, Wildman found that among non-Hispanic Whites, non-Hispanic Blacks and Mexican Americans, 21% to 32% of those of normal weight had an abnormal metabolic profile. Among those at the highest quartile of BMI, nearly 30% to 34%, depending on ethnic group, had a normal metabolic profile. The biomarkers are indicating that more than height and weight of an individual are influencing the metabolic profile and future cardiovascular disease risk. Understanding where the fat and lean mass are located in the body may provide greater insight into those at both high and low

risk for developing cardiovascular diseases.

The Jackson Heart Study provides us the opportunity to answer the questions: "How can we explain an individual with "normal" weight / BMI and abnormal cardiometabolic profile? How can we explain an individual with obesity and a normal cardiometabolic profile?

## JACKSON HEART STUDY – OPPORTUNITY TO PROVIDE ANSWERS TO THE AFRICAN AMERICAN COMMUNITY

To answer these important questions, the Jackson Heart Study (JHS) set out to determine how body composition factors over the lifespan affect cardiovascular disease among African Americans in the southeastern United States. We are measuring not only how much fat but also its location in the abdomen. In addition, we are measuring subclinical coronary atherosclerosis and other conditions affecting liver, heart and aortic function. From approximately 2,800 CT scans of JHS participants, we have completed extensive phenotyping and collected data on weight and adipose tissue in various body compartments, including the visceral fat in the abdomen, which has been associated with increased risk of cardiovascular events. Initially, these CT scans provide measurement of total fat, subcutaneous fat and visceral fat compartments of the abdomen and help develop a preliminary understanding on how they related to risk factors for numerous diseases. Moving forward, these same measurements can be used to better understand why some individuals develop diabetes, heart attacks and strokes.

### Background

Research from Ding and colleagues suggests that, even after adjusting for other risk factors, fat tissue around the heart and arteries can indicate a person's risk for heart attack or other cardiovascular events.[6,7] Previous work in mammals and humans indicates that fat cells around the heart have may have properties that impact the functioning of the heart and coronary arteries.[8,9]

Understanding how these fat cells work and how the fat tissues around the heart and coronary arteries may impact an individual's risk for heart disease was an aim of our research in the NHLBI's Multi-Ethnic Study of Atherosclerosis (MESA). In MESA, we found that, among study participants, those who were in the upper quartile for amount of pericardial fat had a two-fold increase in their hazard ratio for "hard" clinical events, ie, cardiovascular death or myocardial infarction and that the amount of pericardial fat was independently associated with both subclinical coronary atherosclerosis and incident coronary heart disease events after adjusting for BMI and other risk factors.

Approximately 14 million Americans have coronary artery disease (CAD) and, among Blacks, the incidence, prevalence, manifestations and response to therapy for CAD vary significantly.[4] The cardiac CT scans obtained in JHS provide high resolution images of coronary arteries showing plaque build up of calcified plaque. Calcified plaque in the coronary arteries has previously been shown to be highly predictive of death and myocardial infarction, the so called "hard coronary heart disease events." Based on the amount of calcified plaque burden shown by CT, the likelihood of an individual having a heart attack increased significantly; this was true for the four ethnic groups studied – Chinese Americans, Hispanic Americans, African Americans and White Americans, all of whom demonstrated a very similar risk for hard CHD events based on the calcified plaque burden.[5] While knowing the coronary calcium score is one measure that can predict CHD, the ability to predict future cardiovascular events is strengthened if this measurement is coupled with other traditional risk factors such as, age, sex, the patient's Framingham risk score, etc. In other words, by getting information about traditional risk factors and combining it with information about the amount of disease in the coronary arteries, we can increase the ability to predict future heart attacks and death in all four ethnic groups.

Other studies that support this finding include research by Lakoski and colleagues who looked at the role of coronary atherosclerosis among women in the MESA study who were identified as low-risk for cardiovascular events based on traditional risk factors.[10] Even for those women considered at low risk of CVD events, the researchers found that those with higher coronary calcium scores had a significantly increased number of heart attacks.[10] Likewise, the Rotterdam Heart Study[11] found more reasons to link coronary calcium score to cardiovascular events, despite the traditional risk factor of age. In this study, older adults with no coronary artery calcium had a 3% rate of heart attack and death vs those with extensive calcium artery calcium (CAC) who had a 12% event rate during a four-year period.

## JACKSON HEART STUDY DATA – DIABETES, METABOLIC SYNDROME AND CORONARY ARTERY DISEASE

Obesity, diabetes and the metabolic syndrome are inter-related conditions that dramatically impact the risk of cardiovascular disease in African Americans. To demonstrate how imaging of subclinical disease in healthy people can help us understand the development of heart disease over decades, we examined the relationship of coronary artery calcium to diabetes and metabolic syndrome in the JHS. In a preliminary analysis of the JHS participants, grouped by normal, presence of metabolic syndrome,

presence of diabetes or the presence of metabolic syndrome and diabetes, we looked at the prevalence of CAC as measured by CT exam. For both African American men and women, the presence of metabolic syndrome and diabetes, as expected, increased the prevalence of subclinical coronary artery disease (CAC by CT). Among those with both metabolic syndrome and diabetes, 65% of women and 75% of men had calcified plaque in the coronary arteries, which can be compared to 28% and 42% for those without either of the two conditions, respectively. These findings remained significant after adjustment for other variables. Thus, it becomes clear that non-invasive imaging of subclinical disease can help us understand how conditions, such as obesity and diabetes, influence subclinical disease and are precursors of the clinical conditions that commonly cause death and disability.

## Cardiac MRI a Powerful Tool for Understanding How the Heart Beats

In a subset of JHS participants, we are using a state-of-the-art cardiac MRI scan to measure not only the size of the heart but how well it is pumping blood. This exam takes advantage of advanced techniques to model the size and motion of the heart through each heart beat. These quantitative models of the left ventricle of the heart provide precise estimates of numerous parameters of cardiac function. As a next step, we are going beyond the MRI images of the heart to convert the images into mathematical equations that incorporate the 3 spatial dimensions (length, width and height) as well as time so that we can better understand how well the heart is beating in very precise terms. In addition, we are utilizing a special MRI technique to look for local areas of decreased performance. These cardiac maps of ''strain'' have the potential to identify areas of the heart muscle that are relatively weak and perhaps more likely to fail prematurely. The hope is that

techniques like this could, in the future, allow us to identify individuals at high risk for heart failure and identify treatments that could slow, or even prevent, the condition before the damage becomes irreversible. This powerful information can improve our understanding of how the heart pumps blood and, when coupled with the blood pressure measurement of the JHS, it will help us understand how hypertension affects the heart throughout adult life.

## Aortic Function

The aorta, the main blood vessel that supplies blood to all the arteries in the body, could be called the interstate freeway of the vascular system. Yet, the aorta is more than just a pipe. It has elastic properties that allow it to catch and store the energy of the heart and aid in the efficient movement of the blood throughout the body. The aorta and changes in the aorta are closely associated with the development of high blood pressure. Using data from the JHS MRI and CT exams, we hope to be able to determine changes in the aorta that may precede the development of clinical high blood pressure. In the MRI exam, JHS participants have special images of the aorta that measure not only how thick the wall of the aorta is but also how fast the blood is flowing through the aorta. The MRI can thus follow pulse-wave velocity (ie, the movement of blood through the aorta), to determine the precise measure of how the wave energy moves from the top to bottom of the aorta. These data will provide new insight into the aging of the aorta and the clinical development and progression of hypertension, as well as heart failure in JHS participants.

## Coronary Artery Disease and Cardiac Function

Combing the data from the CT and MRI exams, we sought to determine how coronary artery disease might negatively influence the ability of the heart to pump. We wanted to answer

the question, ''For African American men and women with coronary artery disease, do their hearts pump as well as those without CAD?'' Preliminary findings indicate that the presence of coronary calcium, indicating CAD, resulted in degraded myocardial performance as measured by cardiac MRI strain techniques. Likewise, for fat around the heart and coronary arteries, our initial analyses indicate an association between the pericardial fat and global left ventricular function. The greater the amount of fat around the heart, the lower the cardiac function was found to be; this relationship remained significant even after accounting for visceral fat in the abdomen and other risk factors such as age, smoking, hypertension, diabetes, and serum cholesterol. Interestingly, body mass index and pericardial fat had a modest correlation. That is, there were individuals who are relatively lean but had a lot of pericardial fat and, conversely, relatively overweight people with very little pericardial fat. This marker of central adiposity varies for reasons not completely understood. However, with the imaging techniques discussed herein and other avenues of the JHS research, we will draw a more complete picture of the factors that influence whether an individual accumulates adipose tissue around the heart and how that might influence risk of heart disease and heart failure.

Also underway is a JHS effort that will examine silent heart attacks by using an MRI technique that utilizes a dedicated MRI contrast agent called gadolinium. This MRI technique, much like the conventional ECG, can identify individuals and localize small areas of heart muscle damage caused by previous heart attacks both large and small. The number of small heart attacks in African Americans that go unrecognized is unknown. The JHS will be able to provide some of the first information on these silent heart attacks in African Americans. Understanding small and

silent heart attacks may be important to understanding the high risk of heart disease discussed earlier among African Americans in the southeastern United States.

## NEXT STEPS IN BIOMEDICAL IMAGING FOR THE JACKSON HEART STUDY

The JHS offers the medical community a tremendous opportunity to couple clinical, biomarker, genomic and imaging data to help address the observed health disparities in African Americans. The imaging component of the JHS, working in conjunction with the National Institute of Biomedical Imaging and Bioengineering (NIBIB), is leading the way in taking very complex cardiac structure and function data and putting it into a framework that allows secure analysis to authorized researchers, now and in the future. In addition, precisely linking the imaging data to the other robust data being gathered as part of the JHS – from bioarrays to genomic sequencing – will allow the contributions of the JHS participants to have greatest scientific impact for improving health. Already, the JHS investigators are contributing to collaborative studies that have the potential to dramatically change our understanding of cardiovascular diseases. The high quality and unique nature of the JHS make it an important study to add to our knowledge of both health and disease. Thus, we need to organize the extensive data to allow comparisons and collaborations with other NIH studies as well as national/international databases (eg, the American Heart Association) when appropriate. To achieve this goal, the CT and MRI Reading Center have arranged and organized the imaging data and results so as to maximize their current and

future use. Researchers at the Reading Center are members of the NHLBI's Cardiovascular Research Grid (http://cvrgrid.org/) where the experience of the JHS in performing cardiac MRI and CT exams is being shared to help develop the next generation platform for cardiovascular research. The goal of this platform, informed by JHS experience, is to make secure storage and access of data possible to facilitate research needed to reduce the burden of heart disease on African Americans.

## CONCLUSION

The JHS continues to make great progress in understanding the complex nature of cardiovascular disease in African Americans. State-of-the-art biomedical imaging techniques and processes improve our understanding of how obesity and diabetes influence the development of both coronary artery disease and heart failure. With each new answer, we gain greater insight but also develop new questions and a more refined understanding of how we can best help people lead the most healthy and productive life possible. Through collaborations between investigators across the United States and internationally, Jackson Heart Study investigators are helping to develop the tools that allow integration and analysis of the vast amounts of data that have and will continue to be collected through the generosity of our participants who volunteer their time and bodies. Increasingly, we are making significant strides in understanding the interaction between genes, environment and organs such as the heart. The knowledge made possible by the JHS will allow current and future researchers to more precisely identify and prevent heart and other related diseases to improve health among African Americans.

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