I. New Knowledge on Lung, Blood and Cardiovascular Disorders

a. Relative effects of smoking and sedentary lifestyle on lung function.

This study examined the relative effects of smoking and sedentary lung function on African Americans in the JHS and provided evidence that individuals who are non-smokers and have a non-sedentary lifestyle have better lung function than individuals who are smokers and have a sedentary lifestyle. Of these two risk factors, smoking was found to have a more deleterious effect on lung function than sedentary lifestyle. The findings from this research underscore the importance of healthy lifestyle behaviors for maintaining good lung function.


b. Inflammation and subclinical cardiovascular disease.

Systemic inflammation has been implicated as an early marker for subclinical cardiovascular disease, but the evidence for this association has been less consistent in studies of African-Americans. This research found that among African Americans in the Jackson Heart Study there was evidence of an association between a biomarker of systemic inflammation, C-reactive protein (CRP), and increased risk of subclinical cardiovascular disease as measured by the presence of aortic valve calcification and peripheral arterial disease but not with carotid intima-medial thickness. These findings suggest that systemic inflammation may also be an early marker of subclinical cardiovascular disease among African-Americans and of potential use in identifying at risk individuals who might benefit from education and or prevention recommendations.


c. Elevated pulmonary artery systolic pressure as a risk factor for heart failure hospitalization.

Although elevated pulmonary artery systolic pressure is associated with heart failure, it is not known if elevated pulmonary artery systolic pressure is a risk factor for heart failure hospitalizations, especially in African Americans who are at increased risk for heart failure. This research focused among JHS participants found that elevated pulmonary artery systolic
pressure predicts heart failure hospitalizations among African Americans and may aid in early identification of at-risk subjects for aggressive risk factor modification.


d. Research participants’ opinions on genetic research and reasons for participation.

This focus group research evaluated the willingness of an African American community to participate in genetics research, given the past history of bioethical misconduct in ethnic minority communities. This research identified several reasons for participants’ interest in research in general and genetics research in particular, including: interest in individual and family health; interest in new health information that might be disclosed; hope for better health for participants’ current and future families; interest in the common good; interest in research that might benefit African Americans throughout the country; and confidence and trust in the study leadership and staff. This research also examined participants’ knowledge about genetics research. Training on genetic issues was developed for the Jackson Heart Study community and staff.


e. “Good” cholesterol and risk of coronary heart disease.

In the blood, cholesterol is carried by different types of proteins, called lipoproteins. These lipoproteins are called high density lipoproteins (HDL), low density lipoproteins (LDL), and very low density lipoproteins (VLDL). The form of cholesterol that is associated with lower risk of heart attacks and blockages in the arteries is called “good” cholesterol or HDL cholesterol. HDL cholesterol in the blood occurs as smaller, higher dense particles as well as larger but less dense particles. This study showed that higher blood levels of the smaller, denser HDL cholesterol were associated with a lower risk of heart disease in African Americans in the Jackson Heart Study, while levels of the larger, less dense HDL cholesterol were not associated with risk of heart disease. In contrast, the two types of “good” cholesterol were found to be associated with lower risk of heart disease among participants in the Framingham Heart Study Offspring participants. Findings from this study suggest possible differences between African American and white populations with regards to heart disease and “good” cholesterol that warrant further evaluation.

f. Age-related blood cancers and adverse outcomes.

Mutations in certain genes are associated with blood cancers like leukemia. However, it is not known whether such mutations increase with age or whether such mutations may be associated with illness or death. This study found that as people get older they have progressively increased numbers of mutations in genes that are associated with blood cancers, and that people who get mutations in these genes are at increased risk of getting blood cancers or of dying from heart attack, stroke, or other causes.


g. Sickle cell trait and chronic kidney disease.

Hemoglobin is the protein that carries oxygen in red blood cells. Many people in the United States, especially African Americans, carry a mutation in their genes that leads to an abnormal hemoglobin called sickle hemoglobin. People who have two copies of this mutation have sickle cell disease, and those who have only one copy have sickle cell trait. People with sickle cell disease can develop many problems including attacks of bone pain, repeated infections, anemia (low blood count), and poor kidney function. Sickle cell trait, on the other hand, has always been considered to be fairly harmless. In the kidney, sickle cell trait is known to cause minor problems like blood in the urine but large and careful studies of sickle cell trait and kidney function have not been conducted until now. The Jackson Heart Study and other studies in the United States have done genetic tests that can identify which participants are likely to have sickle cell trait. This research examined whether study participants with sickle cell trait were more likely than others to get kidney disease using five different studies including the Jackson Heart Study. Study participants with sickle cell trait were more likely to develop kidney disease than participants without sickle cell trait even after accounting for factors such as age, diabetes, and high blood pressure. This increased risk of kidney disease was seen in each of the five studies separately and when the
results were combined. These findings contradict the long-held view that sickle cell trait is largely benign, and suggest the need for extensive additional studies to assess whether early detection and intervention can alter the course of CKD in persons with sickle cell trait.


h. APOL1 risk alleles and risk of cardiovascular diseases

Two risk alleles in the gene encoding apolipoprotein L1 (APOL1), a major component of high-density lipoprotein, that confer protection against African sleeping sickness are also associated with an increased risk for chronic kidney disease. Because approximately 14% of Americans with African ancestry carry these two APOL1 risk alleles, these APOL1 risk alleles may also account for some of the excess burden of chronic kidney disease among African Americans. This study found that these two APOL1 risk alleles also confer a two-fold increase in risk of cardiovascular disease (CVD). Thus two variants of this gene that provide protection from African sleeping sickness account for a proportion of the increased burden of CVD among African Americans compared to other ethnic groups.


i. Gene-environment interactions involving low serum potassium and risk of ventricular arrhythmias

Analyses in JHS identified a gene-environment interaction in which low serum potassium interacts with the African ancestry-specific 1103Y variant of SCN5A to prolong the duration of ventricular repolarization. This work may help to identify persons of African ancestry who are at increased risk of ventricular arrhythmias and sudden death when treated with certain medications, such as thiazide diuretics.

j. Loss of function mutations and reduction in serum lipids and risk of coronary heart disease.

As part of NHLBI’s Exome Sequencing Project, JHS investigators participated in studies showing that loss-of-function mutations in APOC3, whose gene product, APOC3, resides on the surface of triglyceride-rich lipoproteins, are associated with approximately a 40% reduction in serum triglyceride levels and a 40% reduction in risk of coronary heart disease (CHD). These studies provide evidence that circulating triglyceride-rich lipoproteins contribute to CHD risk and suggest that therapies to reduce the concentrations of these lipoproteins may be valuable in primary or secondary prevention of CHD.


Through the Exome Sequencing Project and additional exome sequencing the JHS participated in studies showing that loss-of-function mutations in the Niemann-Pick C1-like 1 (NPC1L1) gene, including several mutations that are African ancestry-specific, are associated with reduced LDL cholesterol levels and a 53% relative reduction in the risk of CHD. The NPC1L1 gene product mediates the transport of dietary cholesterol from the gut lumen into intestinal enterocytes, and is targeted by the drug ezetimibe, which can reduce dietary sterol absorption by about 50%. These studies show that life-long reduction of the function of the NPC1L1 protein results in reduced CHD risk, and argue that ezetimibe is likely to be of value in the primary or secondary prevention of CHD.

k. Loss of function mutations and lower risk of type 2 diabetes

JHS investigators participated in studies in which loss-of-function mutations in SLC30A8 were found to be protective against type 2 diabetes (T2D). Overall, carriers of disruptive variants in SLC30A8 had a 65% reduction in T2D risk. These studies identify the product of this gene, ZnT8, which is a zinc transporter that is expressed in pancreatic islet cells, as a therapeutic target for the prevention of T2D.


l. Mutations that result in higher lipid levels and risk of myocardial infarction

Through the Exome Sequencing Project, JHS investigators participated in exome sequencing and follow-up genotyping showing that rare non-synonymous mutations in the LDLR and APOA5 genes contribute to increased risk of myocardial infarction (MI). Compared with non-carriers, LDLR mutation carriers (4.2-fold increased risk of MI) had higher plasma LDL cholesterol, whereas APOA5 mutation carriers (2.2-fold increased risk of MI) had higher plasma triglycerides. These studies confirm that disordered metabolism of both LDL cholesterol and triglyceride-rich lipoproteins contributes to MI risk.


m. P-selectin levels and genetic variant associated with diabetic retinopathy

JHS investigators examined the prevalence and risk factors for retinopathy in African Americans with impaired fasting glucose (IFG) and type 2 diabetes in the Jackson Heart Study and whether plasma levels of the protein P-selectin plasma levels were independently associated with retinopathy in this population. This study found that the prevalences of any
retinopathy among participants with IFG and type 2 diabetes were 9.4% and 32.4%, respectively, that higher P-selectin levels were associated with any diabetic retinopathy, but that individuals who were minor allele homozygotes for the variant rs6128 were less likely to develop diabetic retinopathy.