



MURDOCK Update

The Measurement to Understand Reclassification of Disease Of Cabarrus/Kannapolis Study

Studying obesity to predict metabolic health outcomes

By Maggie De Pano

During the past 20 years, excess weight and obesity have emerged as the second leading causes of preventable death in the United States, primarily because of their aggravating effects on high blood pressure, diabetes, and other risk factors for heart disease. Recognized as an “escalating epidemic,” excess weight and obesity affect two-thirds of American adults. In 2007, 30 states reported that more than 25 percent of their residents were obese.

Research shows that people can reduce their risk for heart disease by losing weight, which lowers blood pressure, improves cholesterol, and prevents the development of diabetes. However many who succeed in shedding extra pounds find it difficult to keep them off. Furthermore, not everyone who loses weight experiences the health benefits of weight loss, and there is very little information that can be used to predict who will benefit from the loss. The general assumption that health benefits persist only as long as weight loss is maintained also remains untested.

As part of the multi-tiered MURDOCK study, Duke researchers are working to test these long-held assumptions about weight loss maintenance and improved health. Through the study, researchers are identifying biomarkers associated with weight changes in response to structured behavioral interventions as well as with changes in obesity-related comorbidities such as insulin resistance and lipid abnormalities following weight loss.

Based in Kannapolis, N.C., and funded by a landmark gift from David H. Murdock, the MURDOCK study is a long-term study that is applying modern genomic technologies to identify molecular predictors of outcomes across major chronic diseases and disorders that are some of today’s leading causes of illness and death. It is organized into phases (referred to as “Horizons”). In addition to obesity, the initial phase of the project—Horizon 1—is focused on osteoarthritis, liver disease, and cardiovascular disease.

Testing alternatives

Laura Svetkey, MD, MHS, Professor of Medicine at the Duke University School of Medicine’s Division of Nephrology and Director of Clinical Research at the Sarah W. Stedman Nutrition and Metabolism Center, is confident that a biomarker study of people who lose and regain weight can help address the questions and assumptions about the long-term benefits of weight loss. Biomarkers are biological molecules found in body fluids or tissues. They are used as indicators of normal or abnormal biologic processes.

“[A biomarker study] can help us understand who will succeed at losing weight, who will respond to weight loss with lower blood pressure and cholesterol, and who will most likely avoid or control diabetes by losing weight so we can tailor our recommendations to patients and give them a better idea of what to expect, health wise, if they are able to lose weight,” said Svetkey. “In addition, if we have a better understanding of biological factors that lead to weight regain, we can develop treatments that address these factors and improve long-term weight loss maintenance.”

Svetkey and Svati Shah, MD, Assistant Professor of Medicine at the Duke University School of Medicine’s Division of Cardiology and the Center for Human Genetics (CHG), are leading the obesity component of Horizon 1.

“The purpose of this study is to successfully predict weight loss and weight loss maintenance, as well as identify individuals who will respond best to behavioral interventions for weight loss,” said Svetkey, the study’s principal investigator. “At the same time, we also want to identify patients who will need more than moderate intervention to achieve improvement in obesity-related comorbidities, refine existing treatments for obesity, and clarify novel molecular mechanisms to allow for the potential development of new therapies.”



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School of Medicine’s Division of Nephrology

The Weight Loss Maintenance (WLM) trial will serve as the obesity study’s backbone. Led by Svetkey and sponsored by the National Heart, Lung, and Blood Institute (NHLBI), the WLM is the largest multi-center, randomized, controlled trial to test alternative strategies for weight loss maintenance. It consisted of a six-month weight loss intervention program with 1,685 participants, followed by a 30-month trial that tested participants who lost at least four kilograms during the weight loss phase to see if two alternate maintenance strategies can help them keep the weight off.

Svetkey and Shah’s team has since worked with the WLM Coordinating Center to import WLM data to the CHG for use in the MURDOCK study. It has set up data management procedures for integrating the WLM and CHG databases. It has also shipped tissue samples from the NHLBI biorepository in Bethesda, M.D., to the CHG biorepository and Duke’s Sarah W. Stedman Nutrition and Metabolism Center’s laboratory.

It has completed a data analysis plan that proposes to test the samples of 868 WLM participants. The tests will measure metabolic profiles and satiety hormones on samples that were drawn upon entry into WLM (before weight loss), at the end of the weight loss phase, and after 12 months and 30 months of the maintenance phase.

Metabolic profile measurements include, among others, fasting glucose, fasting insulin, a standard lipid profile (total cholesterol, LDL or “bad” cholesterol, HDL or “good” cholesterol, and triglycerides), and metabolomic profiling. Satiety measurements include leptin (a hormone that plays a key role in regulating appetite and metabolism), ghrelin (a hormone that stimulates appetite), PYY (an amino acid released by the cells in the small intestine and colon in response to food intake), and NPY (an amino acid peptide neurotransmitter).

Seeking predictors

Horizon 1 is finished with its first year. The team’s proposed strategy for the second year—which will end in the third quarter of 2009—focuses on identifying baseline predictors of weight loss and of the outcomes of weight loss, such as changes in insulin resistance and cholesterol. To do this, investigators will run assays on samples from a “test set” of 500 participants, from which they will develop predictive models. Subsequently, the predictive models will be tested in the remaining participants (the “validation set”).

“We will start with factors that have already been identified as predictors—characteristics such as race, sex, age, and behaviors such as dietary intake and physical activity,” said Shah, “but what we seek are predictors that take us beyond these predictors, for example, addressing the extent to which the balance between satiety and hunger hormones influences outcomes, and ultimately, identifying metabolic profiles that predict outcomes.”

Evidence shows that 35 percent of obese people are actually metabolically healthy (i.e., have normal glucose metabolism, lipids, and blood pressure), while 21 percent of lean individuals are metabolically ill. As such, the team expects the most novel results from the project to come from the identification of metabolic profiles that can predict the extent to which weight loss leads to improvements in metabolic health.

“If the ultimate public health goal is long-term weight control, then we need to understand the biological implications of promoting that goal,” said Svetkey. “How big a benefit can we, as a society, expect? The MURDOCK study can help us find out.”

