Each year, the NIH Obesity Research Task Force, consisting of members from many Institutes, Centers, and Offices across the NIH, sponsors seminars held on the main campus in Bethesda, Maryland. These seminars highlight cutting-edge science spanning a broad range of obesity research topics. The posters above advertised the three seminars that were held in 2012.
Obesity

Obesity has risen to epidemic levels in the United States. Individuals who are obese may suffer devastating health problems, face reduced life expectancy, and experience stigma and discrimination. Obesity is a strong risk factor for type 2 diabetes, fatty liver disease, and many other diseases and disorders within the NIDDK’s mission.

Approximately one-third of U.S. adults are considered obese based on body mass index (BMI), a measure of weight relative to height.\(^1\,\text{,}\,\text{2}\) Nearly 17 percent of children and teens ages 2 through 19 are also obese, and thus at increased risk for developing serious diseases both during their youth and later in adulthood.\(^3\) Obesity disproportionately affects people from certain racial and ethnic groups and those who are socio-economically disadvantaged.

The high prevalence of obesity in the United States is thought to result from the interaction of genetic susceptibility with behaviors and factors in the environment that promote increased caloric intake and sedentary lifestyles. Research is providing the foundation for actions to address this major public health problem by illuminating the causes and consequences of obesity, evaluating potential prevention and treatment strategies, and providing an evidence base to inform policy decisions. The NIDDK supports a multi-dimensional research portfolio on obesity, spanning basic, clinical, and translational research. NIDDK-funded studies investigate a variety of approaches for preventing and treating obesity. These span behavioral and environmental approaches in families, schools, and other community settings; medical and surgical interventions; and combinations of these strategies. In parallel, Institute-supported investigations into the biologic processes associated with body weight may spark new ideas for intervention approaches. To help bring research results to health care providers and the public, the Institute also sponsors education and information programs.

The NIDDK also continues to play a leading role in the NIH Obesity Research Task Force. The NIDDK Director co-chairs the Task Force along with the Directors of the National Heart, Lung, and Blood Institute and the Eunice Kennedy Shriver National Institute of Child Health and Human Development. The Task Force includes representatives from these and numerous other NIH Institutes, Centers, and Offices. In 2012, members of the Task Force collaborated with other major research and health organizations and HBO to develop *The Weight of the Nation*, a documentary series and public education initiative that spotlights this urgent public health problem. NIDDK staff and grantees, as well as staff from other NIH Institutes, provided extensive scientific guidance for *The Weight of the Nation* films.

Highlights of recent advances from NIDDK-supported research on obesity are provided in this chapter. These represent examples of NIDDK’s broad spectrum of research efforts toward reducing the burden of obesity so that people can look forward to healthier lives.

\(^3\) Ogden CL, et al: *JAMA* 307: 483-490, 2012. For children and adolescents, obesity refers to a BMI at or greater than the 95th percentile on growth charts (which are based on previous national surveys).
**FOOD ON THE BRAIN**

**Glucose Levels Affect Desire for High-calorie Food:** Scientists have found that blood glucose levels can stimulate or restrain interest in high-calorie food, but that this regulatory mechanism may be lost in the context of obesity. Normally, the body strives to keep blood levels of glucose, the main cellular energy source, within a tight range. In healthy individuals, a transient drop in blood glucose levels, or hypoglycemia, stimulates hunger and food seeking behavior, whereas eating a meal restores blood glucose levels to a normal range (“normoglycemia”) and satiates hunger. However, not just any food will do—during mild hypoglycemia, people preferentially seek out foods high in sugar and fat. The brain is central to many mechanisms driving feeding behavior, but the precise brain pathways driving the motivation to consume high-calorie foods have not been known, nor whether there are differences between obese and non-obese individuals.

In the current study, researchers investigated whether mild hypoglycemia stimulates activity in parts of the brain linked to motivation and reward and if that activity is associated with desire for calorie rich foods. Using an imaging technology called functional magnetic resonance imaging (fMRI), the researchers examined changes in brain activity in obese and non-obese people as they were shown pictures of food. Participants viewed images of high-calorie foods (e.g., ice cream), low-calorie foods (e.g., carrots), and non-foods first while in a normoglycemic state, then while in a mildly hypoglycemic state. As they viewed each image, participants were also asked to rate how much they liked and wanted the item they saw. When compared to their reactions during normoglycemia, people experiencing hypoglycemia showed greater activity in motivation and reward regions of the brain when viewing high-calorie foods, and their desire for them increased. In contrast, low-calorie food images did not provoke the same changes in brain activity and desire during hypoglycemia. Moreover, in non-obese participants, normoglycemia was associated with greater activity in brain regions that reduce motivation for rewarding stimuli—a response that was generally associated with lower desire for any of the foods. However, in obese individuals, this repressive brain activity was lost.

These findings not only help identify brain regions involved in food motivation, but also suggest that higher or lower blood glucose levels can influence susceptibility to high-calorie food cues in the environment—and that persons who are obese may be more susceptible, due to a loss of this regulatory response. While further research is needed, these findings also suggest that it may be possible to develop strategies to reduce desire for high-calorie food by minimizing hypoglycemia between meals.


**Discovery of Factor in the Brain That Regulates Appetite:** Scientists have identified a factor in the brain, called Gpr17, that has a central role in regulation of appetite in mice. It is known that damage to the hypothalamus—a part of the brain that functions to connect the nervous system to the endocrine system—leads to changes in hunger, satiety, and physical activity. Hypothalamic neurons (nerve cells) that produce a protein called AgRP have been directly implicated in promoting feeding behavior: studies have demonstrated that activation of AgRP neurons rapidly increases food intake, while deletion of AgRP neurons causes cessation of feeding and results in starvation.

The hormones insulin and leptin have been previously shown to inhibit the activity of AgRP neurons, but disruption of insulin or leptin signaling specifically within these nerve cells has mild to no effect on feeding behavior, indicating that neither pathway has sole control over how these cells contribute to appetite regulation. In addition, obesity can lead to insulin and leptin resistance. Scientists sought to identify additional pathways in AgRP neuron-dependent food intake that could potentially be targeted by drug therapy to inhibit the activity of AgRP neurons.
A protein called FoxO1 integrates both leptin and insulin signaling, so the researchers generated genetically engineered mice that lack FoxO1 in AgRP neurons and looked to see if removing this protein affected the appetite of the mice. They found that mice lacking FoxO1 in their AgRP neurons are lean, eat less, and show improved glucose control, as well as increased sensitivity to insulin and leptin. Because FoxO1 is a poor drug target, the scientists sought to determine another target with better therapeutic prospects. To do so, they looked for genes whose activity was reduced in FoxO1-deficient AgRP neurons. They identified the gene encoding Gpr17 as a prominent FoxO1 target and found that inhibition of Gpr17, by injecting a chemical into mice, reduced food intake and increased brain sensitivity to hormones and nutrients.

Gpr17 is also found in humans and is part of a family of proteins that is considered “highly druggable”—a number of existing drugs work through this family. In addition, Gpr17 is abundant in AgRP neurons but not in other neurons, potentially minimizing unwanted drug side effects. Additional research will be necessary to demonstrate whether inhibition of Gpr17 leads to the same outcomes in humans, but these findings reveal a new signaling pathway with potential targets to control appetite and obesity.


Brain Injury Associated with High-fat Diet and Obesity: In people who are obese, and in rodents fed a high-fat diet, researchers discovered damage to an area of the brain that regulates body weight. Previously, scientists had observed inflammation in the brain of rodents with diet-induced obesity. In the current study, a team of researchers further investigated this adverse process. They began with rats and mice that were particularly genetically susceptible to obesity from a high-fat diet. Within a day on a high-fat diet, the rodents’ brains began to react as if they had suffered serious injury. Genes that promote inflammation were activated, and immune cells called microglia hastened to an area of the brain, the hypothalamus, that controls appetite and body weight. Within 3 days, these microglial cells had increased both in number and size. Within a week, astrocytes—another type of brain cell—that had responded as well; the normally discrete projections that branch out from these cells had wrapped into a dense mass. The researchers also observed induction of a protein, Hsp72, known to help protect cells from injury. Although set in motion by a high-fat diet in the present study, these types of brain changes have also been seen in response to brain damage resulting from disruption of blood flow to the brain and even Parkinson’s and Alzheimer’s diseases. Some of the inflammatory and cellular changes were transient at first, as though the brain were attempting to limit adverse effects of the diet, but then reappeared as the high-fat feeding continued; other changes persisted unabated throughout the months of unhealthy eating. Many of the changes began rapidly, even before the animals gained substantial body weight. The researchers then found evidence of brain cell death—specifically of brain cells called POMC neurons, which normally reduce appetite and have other functions that help prevent obesity. With fewer POMC neurons, the likelihood of obesity increases. To see whether similar brain changes occur in people, the researchers analyzed MRI images that had been taken previously. Close inspection of brain images from 34 people revealed differences between lean and obese individuals, with evidence of changes in the hypothalamus of the brain. Thus, this study suggests that obesity and high-fat diet consumption are associated with damage to the brain.


NEW DISCOVERIES ABOUT BROWN FAT

Newly Identified Muscle Hormone May Have Potential for Reducing Obesity and Type 2 Diabetes: Recent research shows that in both mice and humans, exercise induces muscle to release a newly discovered hormone, irisin, and studies in mice show that irisin promotes energy expenditure (calorie burning), and
reduces obesity and type 2 diabetes. The mammalian body contains two kinds of adipose (fat) tissue: white adipose tissue (WAT), which stores fat for energy, and brown adipose tissue (BAT), which “burns” fat to help maintain body heat without shivering—thereby increasing the body’s energy expenditure. Although human brown fat was initially thought to be present only in newborns, recent studies have confirmed its presence and function in adults. A new study has identified a hormone, called irisin, which is produced by muscle tissue and instructs WAT to take on BAT-like characteristics. When irisin was administered to adult mice or added to mouse WAT cells, genes normally found in BAT were turned on, whereas some WAT genes were turned off. The researchers found that in mice and in human study participants, exercise led to an elevation in circulating irisin levels. When the scientists modestly increased the amounts of circulating irisin in a mouse model of type 2 diabetes, this treatment reduced obesity and improved blood glucose control without apparent side effects. These results reveal a hormone that appears to drive many of the physiological benefits of exercise. If irisin in humans works as it does in mice, administration of this hormone could be a potential new therapeutic approach for obesity and type 2 diabetes.


**Ephedrine Does Not Activate Brown Fat:** A recent study has found that in humans, brown fat tissue is activated by mild cold temperature exposure, but not by the drug ephedrine, a decongestant and bronchodilator known to induce weight loss. Many scientists believe that brown adipose tissue (BAT)—a type of fat tissue known to increase energy expenditure, which in turn can promote weight loss—could serve as an ideal target for the development of treatment strategies for obesity. While mild cold temperature exposure is known to activate BAT, safe and effective pharmacological agents could offer a more practical therapeutic approach. Research scientists sought to determine whether ephedrine could induce BAT activation. Ephedrine is known to stimulate the sympathetic nervous system—the portion of the nervous system broadly responsible for the “flight or fight” response and also for the stimulation of BAT. Healthy adult volunteers were either given ephedrine injections, a “cooling vest” set to 57 degrees Fahrenheit, or saline injections as a control. The scientists found that cold

**New Insight into Adult Human Brown Fat Identity:** Scientists have shown that adult human brown fat may actually be “beige” fat—a distinct tissue that burns energy and could serve as a potential target for novel therapies for obesity. The human body has been thought to possess two kinds of fat cells: white fat cells, which store fat molecules; and brown fat cells, found most abundantly in infants, which burn calories and generate heat. However, in mice, for many years scientists have observed, embedded in white fat, a third type of fat cell—now called “beige” fat—that shares characteristics of both brown and white fat. While it was clear that beige fat cells resemble brown fat in appearance and function, little was known about their properties, development, and activity. In a recent study, researchers developed methods to isolate and characterize beige fat cells from certain areas of mouse white fat tissue (subcutaneous white fat), and found that they exhibit unique properties, as well as some characteristics of classical brown fat cells. By isolating these cells, the scientists could then carefully define the set of genes that were turned on specifically in beige fat. The scientists also isolated cells that have the potential to become beige fat—cells called “precursors.” They showed that these beige fat precursors were responsive to the hormone irisin, which is known to convert white fat tissue to a more brown fat-like identity. The researchers then utilized their new knowledge from mice to better characterize adult human brown fat deposits, and found that the fat cells within more closely resembled beige fat than they did classical brown fat cells. This greater understanding of beige cell properties may lead to the development of potential therapies for obesity through the activation of energy-burning adult human beige fat tissue.

exposure, but not ephedrine treatment, activated BAT tissue. In both ephedrine and cold exposure treatment conditions, energy expenditure, basal metabolic rates, and blood pressure increased. However, heart rates were raised with ephedrine treatment, but reduced with cold exposure. These results demonstrated that ephedrine does not induce weight loss through BAT activation. Further research aimed at understanding the brain and molecular pathways that activate BAT upon exposure to cold temperatures may reveal new avenues for the development of anti-obesity therapeutics.


The Quest To Make Visceral Fat Burn Itself: Seeking to learn what sparks the appearance of calorie-burning “brown fat” cells within the body’s visceral fat tissue, researchers have identified their origins, or progenitor cells, in mice, and molecular regulators in both mouse and human tissue that may lead to new therapeutic strategies for obesity and related diseases. Humans and mice harbor different types of fat tissue. Calorie-storing “white fat” tissue is the most abundant, and can be found surrounding internal organs, where it is referred to as visceral or abdominal fat, and just under the skin, a location termed subcutaneous. Brown fat, which burns calories to generate heat, also takes various forms, but is more transient. Babies and rodents have brown fat tissue that, in the case of humans, largely disappears after infancy. However, cells with characteristics of brown fat (sometimes called beige or brite cells) can also appear within patches of white fat tissue, in response to cold or other nervous-system triggers. Typical brown fat tissue develops from progenitor cells that are related to another calorie-burning tissue, muscle, but the origin of brown fat cells that arise within white fat tissue has been unknown. Based on previous reports that suggested a protein called PDGFRα might mark such progenitor cells, scientists tagged visceral fat cells in mice in a way that would mark not only progenitor cells with this protein, but also all cells descending from them. Subsequently, they put some of the mice on a high-fat diet for 8 weeks, and gave the other mice a chemical that stimulates factors in the nervous system (β3-adrenergic receptors) to cause heat generation. Examining the tagged cells, the researchers found that after β3-adrenergic stimulation, the progenitors gave rise to new cells with characteristics of brown fat. By contrast, the high-fat diet led to new white fat cells. Having illuminated two divergent paths for visceral fat progenitor cells, scientists may develop therapies that steer these cells toward brown fat development.

In other recent studies, scientists explored ways to remove molecular barriers to brown fat development within visceral white fat tissue. One team focused on a protein called ActRIIB, which limits muscle mass and regulates fat tissue. Building on previous research, they developed a “decoy” version, ActRIIB-Fc, to subvert the effects of the normal protein, and administered it to mice along with a high-fat diet. Compared with mice that did not receive the decoy, those that did had increased lean tissue (muscle) mass and less fat tissue; they were protected from metabolic effects of a high-fat diet, such as abnormal fat accumulation in the liver; and within their visceral fat were cells that had activated genes characteristic of brown fat. While this study shows that ActRIIB-Fc can prevent diet-induced obesity, future research may determine whether it could help treat mice that are already obese, and whether this approach may work in people. Pursuing an alternate route from white to brown fat, another research team investigated a molecule called retinaldehyde, which is related to vitamin A and is found in white fat, along with an enzyme that processes it, called Aldh1a1. The researchers observed the enzyme in visceral white fat, with higher levels observed in mice fed a high-fat diet and in people who were extremely obese. A chemical inhibitor of this enzyme, when injected into obese mice, limited further weight gain from a high-fat diet; improved their glucose levels, a sign of reduced diabetes risk; and activated brown fat genes in visceral fat tissue.

By revealing previously unknown brown fat progenitor cells and exploring factors that regulate brown fat development, these and other studies may lead to new obesity therapies that coax cells in visceral white fat tissue to burn calories like brown fat.


**Identification of a Protein Controlling Energy Expenditure and Inflammation in Fat Tissue:** Researchers have identified a protein in adipose (fat) tissue of mice that regulates both energy expenditure (calorie burning) and inflammation, making it a promising target for treating obesity and type 2 diabetes. Mammals have two major types of fat tissue: brown adipose tissue (BAT) burns fat and thereby increases energy expenditure, and white adipose tissue (WAT), the more abundant form, stores fat. A promising approach to treating obesity and related diseases is to make WAT take on BAT-like characteristics to increase whole-body energy expenditure. Toward this goal, researchers sought to identify factors that regulate energy expenditure. They identified an ion channel protein, TRPV4, that is found in high levels in WAT. In cells grown in laboratory culture, experimentally blocking TRPV4 made WAT become more like BAT by activating genes that increased energy expenditure. Blocking TRPV4 in fat cells was also found to have an unexpected benefit—it decreased the activity of genes important in promoting inflammation. Obesity is associated with chronic, low-grade inflammation of fat tissue, which contributes to the development of insulin resistance, a condition associated with type 2 diabetes; therefore, identifying ways to reduce inflammation is an important goal. These results suggest that TRPV4 regulates both energy expenditure and inflammation in fat tissue, even though scientists previously thought that the molecular mechanisms regulating those processes were distinct. To see if TRPV4 played this dual role in animals, the researchers conducted experiments using mice that were genetically engineered to lack TRPV4. On a regular diet, the experimental mice weighed the same as control mice. However, when the animals were fed a high-fat diet for 16 weeks, the mice lacking TRPV4 not only gained less fat weight than control mice, but were also protected from fat tissue inflammation and insulin resistance. They also had increased energy expenditure without differences in food intake, physical activity, or body temperature compared to control mice, suggesting that the increased energy expenditure was due, at least in part, to increased fat burning. Because these findings suggest that TRPV4 may be a promising drug target for treating obesity, the scientists next used, as a potential drug, a chemical that inhibits TRPV4 activity in obese mice. Compared to control mice, the treated animals had improved glucose tolerance, and their fat tissue showed increased activation of energy burning genes and decreased activation of genes involved in inflammation. These results suggest that inhibiting TRPV4 gives a two-fold benefit of increasing energy expenditure and reducing inflammation in fat tissue. If these findings are extended to humans, targeting the protein may be a therapeutic avenue for treating obesity and type 2 diabetes.

**CELLULAR TARGETS FOR REDUCING OBESITY AND METABOLIC SYNDROME**

Getting Rid of Body Fat by Targeting Its Blood Supply: Results of recent research suggest it may one day be possible to achieve weight loss by targeting cells in the blood vessels of body fat. In previous work with mice, the researchers used a molecule called “adipotide” that binds only to blood vessels in white adipose tissue, which accounts for the great majority of fat in the body. The molecule triggers cell death specifically in the cells to which it binds. Although the mice given adipotide lost a great deal of weight,
and seemed to suffer no obvious ill effects from the treatment, numerous previous weight loss methods that seemed promising in mice have failed to prove effective in humans. In the new research, therefore, scientists tested the approach in obese monkeys—an animal model that more closely mimics human obesity. Just as with humans, some monkeys become overweight or obese when given an abundant supply of whatever food they want to eat, while others do not. Also, as with humans, obesity in monkeys can lead to insulin resistance, type 2 diabetes, and other metabolic and cardiovascular problems. The scientists injected obese monkeys with doses of adipotide or placebo daily for 4 weeks, and then followed the animals for an additional 4 weeks. The monkeys receiving adipotide began to lose a significant amount of weight within the first week of treatment, and continued to lose weight for 3 weeks after treatment ended, losing a total of about 15 percent of their body weight in 7 weeks. Tests of body composition revealed that almost all of the weight lost was body fat, although mild dehydration did also occur. (In a separate experiment, the researchers showed that lean monkeys treated with adipotide did not lose weight, indicating that the drug works selectively on fat tissue.) The obese animals receiving adipotide ate less than their counterparts, although they seemed to continue to like their food. In other respects, their behavior was normal, during and after treatment. Adipotide-treated monkeys produced more urine than did control animals, and had significant but not serious increases in urine glucose and protein levels that reverted to normal after treatment. Notably, adipotide treatment also improved insulin sensitivity. Of some concern, the treatment also led to an elevation of serum creatinine, a sign of kidney damage. The elevated creatinine levels seen in the adipotide-treated monkeys fell during recovery, but remained slightly higher than in control animals. Direct examination of the kidneys revealed signs of slight damage which appeared to be reversible, but which suggests a possible side effect to watch for in potential future human trials. These results validate the general approach of reducing body fat by attacking its blood supply. Future research will determine whether adipotide or a similar agent would be safe and effective for weight loss in humans.


Working Out the Health Benefits of Autophagy:
Researchers have discovered that an intracellular protein degradation system may be crucial to normal metabolism and the response to exercise. To help get rid of imperfect proteins and aging cellular components, and in some cases to modulate levels of intracellular factors, a cell can engulf portions of itself, target the damaged contents for breakdown, and recycle undamaged components for reuse. This process is called autophagy. While autophagy occurs at a basal level under normal circumstances, it is also stimulated by starvation and other stressors, enabling cells to adapt to changing conditions and needs. Scientists studying this process in mice recently found that muscle cells turn up autophagy in response to exercise. Intriguingly, when mice with mutations that hinder such stimulus-induced autophagy ran on a treadmill without prior exercise training, they showed lower endurance than normal mice. Also, while strenuous exercise normally induces changes in skeletal muscle that help it use glucose more efficiently, the autophagy-deficient mice did not show those changes. Autophagy was particularly important for achieving the metabolic benefit of long-term exercise training, in the context of obesity. Researchers found that while exercise protected normal mice from elevated glucose levels induced by a high-fat diet, it did not give autophagy-deficient mice the same protection. The autophagy-deficient mice also did not show exercise-induced improvements in levels of cholesterol and triglycerides (a type of fat) that were seen in normal mice. These findings suggest that autophagy plays a role in conferring the health benefits of exercise.

In addition to evidence that autophagy helps the body respond to exercise, researchers found it is also needed to produce a signal that the body has consumed enough food. Scientists studied the role of autophagy in the hypothalamus, the region of the brain central to control of energy balance—regulating energy intake (as food calories) and expenditure (burning calories to maintain basic body functions, do work, or generate heat).
Certain cells in the hypothalamus generate the hormone \(\alpha\)-melanocyte-stimulating hormone (\(\alpha\)-MSH) that signals the brain to curtail eating and promote calorie burning. Mice genetically engineered to lack autophagy in just these brain cells showed altered levels of molecular factors important to energy balance, including reduced levels of \(\alpha\)-MSH. These mice gained more fat weight than normal mice when fed a high-fat diet, and appeared to have problems with mobilizing fat from fat cells for use as an energy source when fasted. They also showed impaired glucose tolerance. Similar problems with brain-derived hormone levels and with fat mobilization occur with older age in mice—raising the possibility that some of the metabolic problems associated with aging may be due partly to loss of autophagy.

Together, these papers suggest that autophagy, already known to help protect against cancer and some other diseases, also has a key role in counteracting some of the dangerous metabolic consequences of obesity, including type 2 diabetes risk. If borne out through further research, strategies to mimic or manipulate autophagy may prove beneficial in preventing or treating these conditions.


Diet-induced Changes in Fat Tissue—Role of the *FGF1* Gene and Link to Type 2 Diabetes: Scientists discovered that the *FGF1* gene plays a key role in “remodelling” body fat tissue in rodents in response to dietary changes. These findings may ultimately lead to new treatments for type 2 diabetes and for reducing the elevated glucose levels often found in obese individuals. Body fat tissue typically changes to accommodate the influx of nutrients encountered following re-feeding after an overnight fast, or after a switch from a normal to a high-fat diet. In experiments to understand how these metabolic changes occur, researchers discovered that the *FGF1* gene was activated in the fat tissue of mice that ate normal chow compared to those that had fasted overnight, and *FGF1* induction increased even more when the mice were given a high-fat diet. The *FGF1* gene was turned on by the master regulator of fat tissue, a protein called PPAR\(\gamma\). To gain further insights, the research team compared normal mice to those genetically engineered to lack *FGF1*. When allowed to eat as much as they wanted of a high-fat diet, mice lacking *FGF1* gained the same amount of weight as normal mice, but otherwise their health was far worse. They developed severe type 2 diabetes; their livers were enlarged and contained excess fat; and, potentially at the root of these problems, their visceral fat tissue was abnormal. Although excess nutrients usually cause fat tissue to expand, the visceral fat of *FGF1*-deficient mice did not; it instead showed structural defects and more inflammation than that of normal mice. Conversely, when switching mice from a high-fat diet to healthier fare, the researchers also found that *FGF1* helped fat tissue adapt accordingly. These new findings suggest that *FGF1* helped mitigate such problems by directing fat tissue to adjust to feeding, fasting, and—at least to some extent—a high-fat diet. Although *FGF1* had been implicated in other biological processes, its crucial functions in fat tissue were initially surprising to the researchers because in previous studies, mice without *FGF1* seemed perfectly fine. However, until this new study, scientists had not examined *FGF1*-deficient mice on a high-fat diet. The new study suggests that in mice, as in people, genetic susceptibility to type 2 diabetes and other metabolic problems may only become apparent when on an unhealthy diet, particularly one that leads to obesity. These new findings point to *FGF1* as a potential target for developing novel type 2 diabetes therapies.


**RESEARCH ON THE EFFECTS OF BARIATRIC SURGERY**

Bariatric Surgery Reduces Blood Glucose Levels: A recent study has shown that bariatric surgery can help control type 2 diabetes more
effectively than medical therapy alone, and can help reduce the need for medications to lower glucose, lipids, and blood pressure. To understand the potential health benefits of bariatric surgery for people with obesity and poorly controlled type 2 diabetes, researchers compared outcomes achieved through intensive medical therapy (which included lifestyle counseling, weight management programs, frequent home glucose monitoring, and the use of diabetes medications) to those obtained with intensive medical therapy in combination with bariatric surgery. Of the many available forms of bariatric surgery, researchers tested two specific procedures: a variation of gastric bypass surgery, called Roux-en-Y surgery, in which the top portion of the stomach is connected directly to a lower portion of the small intestine; and sleeve gastrectomy, in which the majority of the stomach is removed, leaving a comparatively narrow “sleeve.” After 12 months, blood glucose was reduced to levels below the diabetic range in only 12 percent of participants that received medical therapy alone, compared to 42 percent in the gastric bypass group and 37 percent in the sleeve gastrectomy group. Indeed, many of the patients in the two surgery groups who achieved these good glucose levels within a year of surgery did so without further use of diabetes medications. Overall, the use of medications to treat cholesterol and blood pressure, as well as to lower blood glucose levels, decreased sharply in both surgical procedure groups, whereas medication use modestly increased in the group that was given medical therapy alone. Longer studies will be needed to determine whether the metabolic improvements observed in the surgery patients will be durable. Further, determining whether these results apply equally to various racial/ethnic groups with obesity and type 2 diabetes will require a larger study, with a more diverse cohort. However, this study adds to existing evidence that bariatric surgery may be a reasonable approach for treating some patients with obesity and uncontrolled type 2 diabetes.


Health Benefits 6 Years After Bariatric Surgery: While the long-term health risks of extreme obesity have been well documented, a recent study has provided important new information on long-term health benefits of a major form of treatment—bariatric surgery. People who have extreme obesity typically do not gain sufficient health benefits from lifestyle intervention alone or from lifestyle plus drug treatment, and thus many turn to bariatric surgery. Although researchers have reported that bariatric surgery can lead to significant weight loss and improvements in type 2 diabetes and other metabolic conditions over the short term, there has been only limited information on long-term effects. To gain more data on risks and benefits over the longer term, a team of researchers assessed health outcomes 6 years after surgery. For the study, they recruited over 400 individuals who were extremely obese and who had Roux-en-Y gastric bypass surgery, a common type of bariatric surgical procedure. For comparison, the researchers also recruited several hundred individuals who were similarly obese but did not undergo surgery. A majority of the study volunteers were women. The surgery led to a number of health benefits that persisted for years. Individuals who had surgery experienced better weight-loss maintenance, with a majority (76 percent) having kept off 20 percent of their initial body weight for 6 years after surgery. Among participants who had type 2 diabetes at the beginning of the study, those receiving surgery had a 62 percent rate of disease remission 6 years later, compared to only a 6 to 8 percent remission rate seen in those who did not have surgery. Among participants who did not have diabetes at the outset of the study, those who had surgery were less likely to develop the disease. Other outcomes seen after surgery included higher levels of “good” cholesterol (HDL), lower levels of “bad” cholesterol (LDL) and triglycerides, and better blood pressure. Although the overall effects of surgery were beneficial, some of the individuals (approximately 8 percent) required further hospitalization after surgery, and there were four suicides reported. The reasons for the small number of suicides, which was significantly higher than in the control population, are unknown, but this finding indicates a need for greater attention to patients’
psychological health before and after surgery. Taken together, the findings from this study add important long-term data to the current knowledge about bariatric surgery and will help individuals and their health care providers with treatment decisions. Future research may show whether the results are similar in diverse racial/ethnic groups, as most of the participants in this study were non-Hispanic white. Finally, although the participants’ health was tracked over 6 years, the entire study took over a decade to complete, demonstrating the value of long-term research efforts.


Weight-loss Surgery Increases Risk for Alcohol Use Disorders Over Time: A recent study showed that adults who had Roux-en-Y gastric bypass (RYGB) bariatric surgery to lose weight had a significantly higher risk of alcohol use disorders (AUD) 2 years after surgery compared with before surgery. Researchers investigated alcohol consumption and AUD symptoms in 1,945 participants from the Longitudinal Assessment of Bariatric Surgery (LABS), a prospective study of patients undergoing weight-loss surgery at one of 10 different hospitals across the United States. Within 30 days before surgery and again 1 and 2 years after surgery, study participants completed the Alcohol Use Disorders Identification Test (AUDIT), a validated and reliable alcohol use screening method, to identify symptoms of AUD. Study participants were categorized as having AUD if they were positive for at least one symptom of alcohol dependence or alcohol-related harm, or if their total AUDIT score was at least 8 (out of 40). Among participants who had the RYGB procedure, 7.0 percent reported symptoms of AUD prior to surgery. There was no significant increase in AUD 1 year after surgery. However, by the second postoperative year, 10.7 percent of patients reported symptoms of AUD, a relative increase of more than 50 percent compared to pre-surgical rates. Patients who underwent another common type of weight-loss surgery, laparoscopic adjustable gastric banding (LAGB), did not report an increase in symptoms of AUD. About 70 percent of the study participants had RYGB surgery, another 25 percent had LAGB surgery, and about 5 percent of the patients had other, less common weight-loss surgeries. AUD prior to surgery was one of the strongest predictors of postoperative AUD, although more than half of the study participants with AUD after surgery did not report having the condition during the year before surgery. In addition, patients with less social support or who reported preoperative recreational drug use or smoking were more likely to report symptoms of AUD after surgery. Men and younger adults were also more likely to develop AUD. Depressive symptoms, mental health treatment, and binge eating prior to surgery were not independently related to an increased likelihood of AUD after surgery. The study results suggest that clinicians should be aware of the importance of monitoring for signs and symptoms of AUD and consider counseling after bariatric surgery, particularly in patients who undergo gastric bypass.


**INSIGHTS INTO DIET AND ACTIVITY—STRATEGIES AND HEALTH BENEFITS**

Weight Loss and Increased Fitness Slow the Decline of Mobility in Adults: New research has shown that weight loss and increased physical fitness reduce the risk of losing mobility in overweight or obese adults with type 2 diabetes. Older adults with type 2 diabetes are more likely to have reduced mobility than those without this disease, and obesity increases the risk for mobility-related health problems. As part of the Look AHEAD (Action for Health in Diabetes) clinical trial, researchers investigated whether a lifestyle intervention program could slow the reduction of mobility. Look AHEAD is determining whether a lifestyle intervention designed to promote weight loss can improve health outcomes in overweight or obese people with type 2 diabetes. Participants were randomly assigned to either an intensive lifestyle intervention group (ILI) or a diabetes support and education group (DSE). Among
the tests done in the trial, the researchers measured participants’ weight, and they assessed the participants’ fitness with a treadmill test. When the Look AHEAD trial began, nearly two-thirds of participants reported mild, moderate, or severe restrictions in mobility. After 4 years of the study, participants in the ILI group did not lose as much mobility as those in the DSE group. The ILI intervention slowed decline in mobility by 48 percent compared to DSE. Moreover, 20.6 percent of ILI participants reported severe disability compared to 26.2 percent of participants in the DSE group. Similarly, 38.5 percent of those in the ILI group reported good mobility, whereas the rate was 31.9 percent in the DSE group. Weight loss was a slightly stronger predictor of better mobility than was improved fitness, but both contributed significantly to the observed reduction in risk. These results are consistent with previous analyses, which showed that participants in the ILI group lost significantly more weight than did those in the DSE group, and also had improved fitness, glucose control, blood pressure, and HDL cholesterol with less use of medication. These findings show that intensive lifestyle intervention programs can slow the decline of mobility in overweight or obese people with type 2 diabetes, and have significant implications for improving quality of life as people age.

In September 2012, the intervention was discontinued when it was found that intensive lifestyle intervention in overweight/obese adults with long-standing type 2 diabetes did not reduce cardiovascular events such as heart attack and stroke. Although the intervention did not reduce cardiovascular events, Look AHEAD has previously shown other important health benefits of the lifestyle intervention, including decreasing sleep apnea, reducing the need for diabetes medications, improving quality of life, and helping to maintain physical mobility (as shown in this advance). Although the intervention was discontinued, follow-up of all study participants will continue to evaluate their long-term health and effects of the weight loss intervention.


Physical Activity and Reduced Risk for Obesity in Adults with FTO Gene Variants: Although we cannot change our genome sequence, we can influence some of the effects of our genes. Researchers found that in adults, physical activity may reduce the risk for obesity associated with certain variants of the FTO gene. Knowing that people can have different forms of the FTO gene, which vary slightly in their gene sequences, the researchers compared people who have a form of the FTO gene that increases risk for obesity with individuals who have another form of the gene. Because previous reports had conflicting results as to whether physical activity can attenuate this risk, the team of researchers decided to analyze more people. To do this, they compiled information on FTO gene sequences and physical activity for over 218,000 adults who had participated in a variety of other studies. For the new analysis, the researchers defined adults as “inactive” if they had sedentary jobs and less than an hour per week of moderate-to-vigorous activity during leisure time or commuting, or if their activity levels were otherwise particularly low compared to other participants of their respective study. Those with higher activity levels were considered “physically active.” Overall, they found that people with the adverse FTO gene variant were more likely to be obese than those with the other form of the FTO gene. Encouragingly, physical activity reduced this risk by 27 percent. In a similar analysis of over 19,000 children, the researchers found that physical activity, which was defined slightly differently for this age group, did not seem to attenuate FTO-specific risks for obesity, and it did not correlate with the children’s body mass index (a measure of weight relative to height). However, physical activity did appear to be helpful for children in general, as those who were physically active had less body fat and a smaller waist circumference than inactive children. Other studies of the FTO gene have found that adverse FTO variants seem to drive people to eat more, particularly high-fat foods. It is not clear how, in adults, physical activity may reduce obesity risk conferred by the FTO gene, or whether the reduced risk may be due to a combination of lifestyle factors. For example, adults who are physically active might also tend to have healthier eating habits than those who are sedentary. These results offer hope of reducing obesity risk for the
many people with this FTO gene variant, and emphasize the value of both individual behaviors and environments that promote healthy lifestyles, regardless of one’s genetic predisposition.


Reducing Sugary Drinks Could Reduce Obesity:
Recent studies have shown that, for some people, limiting the consumption of sugar-sweetened beverages leads to weight loss or reduced weight gain. Over the past few decades, the prevalence of obesity has increased significantly, leading many researchers to seek behavioral changes that might have played a causal role in the development of this public health epidemic. During that time, a dramatic rise in the consumption of sugar-sweetened beverages, such as some sodas, and sports, energy, and juice drinks, has paralleled the rise in obesity. Based on this observation, many scientists believe that sugar-sweetened beverage intake has contributed to the obesity epidemic and could be a potential target behavior for obesity prevention intervention strategies—an idea that was tested in a series of recent studies.

In one study, researchers sought to determine if genetics could influence whether sugar-sweetened beverage consumption affects risk for obesity. The scientists took advantage of existing data sets, collected as a part of three large-scale health surveys, which included physical, behavioral, and other characteristics from more than 30,000 U.S. men and women of European ancestry. They examined variations within 32 regions of each person’s genome, which previous analyses have shown to be associated with body mass index (BMI, a measure of weight relative to height). The three health surveys also detailed sugar-sweetened beverage consumption, allowing the researchers to tease apart any association between these genetic and behavioral factors in obesity risk. The combined results from all three surveys were significant and clear: for individuals with many genetic risk variants predisposing them to obesity, there was a relatively greater association between consuming sugar-sweetened beverages and subsequent increases in BMI, particularly at higher levels of consumption.

In another study, researchers examined the effects in adolescents of an intervention substituting sugar-sweetened beverages with non-caloric beverages in their homes. The study included overweight and obese teenagers who regularly consumed sugar-sweetened beverages. For 1 year, participants received an intervention strategy designed to reduce intake of sugar-sweetened beverages in their homes: delivery of non-caloric beverages, motivational telephone calls with their parents, and periodic check-in visits. At the end of the year, sugar-sweetened beverage consumption was significantly reduced compared with a control group that did not receive the intervention. In addition, BMI increased less in the intervention group than in the control group during the intervention. A year after the intervention stopped, there was no longer a difference between groups overall in BMI, but Hispanic adolescents from the intervention group still showed less of a BMI increase. These results add to previous data suggesting a link between sugar-sweetened beverage consumption and excess weight gain, which may be greater in some individuals.


A study on an intervention involving reducing sugar-sweetened beverage consumption in younger children, not funded by NIDDK, was published in the same journal as the preceding studies. In this intervention study, conducted in the Netherlands, researchers reported strong evidence that replacing sugar-sweetened beverages with non-caloric substitutes in schools significantly reduces weight gain in children (N Engl J Med 367:1397-1406, 2012), findings that complement those from the above U.S. studies.
DISEASES ASSOCIATED WITH CHILDHOOD OBESITY

Increased Gallstone Disease in Obese Children and Adolescents: Researchers have identified another health consequence of obesity in youth—increased risk for gallstones. A common, costly, and often painful condition in adults, gallstones were thought to be rare in children and adolescents. However, as with other adult diseases that are now developing at earlier ages in parallel with the childhood obesity epidemic, gallstones may also become more prevalent in youth. Previous studies had suggested a link between obesity and gallstones in children, as is the case in adults, but those studies had analyzed only a few individuals. To investigate further, researchers in the current study reviewed the electronic health records of over 500,000 youth, ages 10 to 19, who were participating in the Kaiser Permanente Southern California Children’s Health Study. The researchers assessed whether the children and adolescents were underweight, normal weight, overweight, moderately obese, or extremely obese, and they identified 766 youth who had gallstone disease diagnosed within 2 years of enrollment in the study. The results showed that being overweight is associated with increased risk for gallstone disease, and that obesity and extreme obesity further heighten this risk. Gallstones were more common among girls than boys, particularly among obese girls, a finding that mirrors the increased risk for gallstones among obese women. The researchers also found that Hispanic youth were more likely to have gallstones than were individuals of other races/ethnicities. These results highlight the importance of further research to address both obesity and health disparities in childhood. Additionally, this study can inform current medical practice, as pediatricians may need to be increasingly aware that their young patients, particularly those who are obese, may develop gallstone disease.

The Weight of the Nation –
The NIDDK Collaborates on HBO Obesity Project

One-third of American adults are obese. Another third are overweight. How did this happen? And how can we, as a nation, return to a healthy weight?

To help illustrate the answers—and to show the science of obesity and NIH’s efforts to combat the obesity epidemic—the NIDDK and other components of the NIH collaborated with HBO and major research and health organizations to develop The Weight of the Nation, a documentary series and public education initiative that spotlights this urgent public health problem.

“If we don’t succeed in turning this epidemic around, we are going to face, for the first time in our history, a situation where our children are going to live shorter lives than we do,” said NIH Director Dr. Francis Collins, who appears in the full-length films. “It takes diverse and rigorous research to understand the causes of obesity and to identify interventions that work in the real world. The results from federally funded research, as seen in these films, can help to prevent and treat obesity and its complications.”

The project consists of four documentary films originally aired on HBO in May 2012; a 3-part series for families; 12 short films, including one on NIH; and a nationwide community-based outreach campaign. An HBO crew spent 2 days on the NIH campus, documenting how researchers are trying to understand, prevent, and treat obesity. “When it comes to America’s health, there are problems which must be confronted, even if they make us uncomfortable, frighten us or are so daunting we don’t know where to begin,” said HBO producer John Hoffman, who previously worked with the NIH on HBO’s The Addiction Project and The Alzheimer’s Project. “With The Weight of the Nation, HBO is again proud to stand together with the NIH, as we step forward to…hopefully reverse the obesity epidemic.”

HBO also filmed several NIDDK grantees at universities, as well as people struggling with obesity and its associated diseases, representatives from local governments, health care providers, and many others.

Leaders of the NIH Obesity Research Task Force from the NIDDK; the National Heart, Lung, and Blood Institute; the Eunice Kennedy Shriver National Institute of Child Health and Human Development; and the National Cancer Institute provided scientific guidance for The Weight of the Nation films and screening kits, which are available in English or Spanish. Health centers, community groups, and others who sign up on the HBO web-site will get copies of the films and guidance on how the project can assist in their organizations’ weight-control efforts. The films can be viewed online for free on the HBO web-site.

For more information, please visit the HBO web-site at http://theweightofthenation.hbo.com and the NIH project web-site at http://www.nih.gov/health/NIHandweightofthenation/
Childhood Obesity Prevention Through Solution-oriented Research

Dr. Thomas N. Robinson

Solution-oriented Research: A Complementary Approach

The predominant paradigm for health science research, Dr. Robinson noted, is to identify the underlying causes of and risk factors for disease, with the ultimate goal of using that knowledge to develop strategies for treatment and prevention. This “problem-oriented” research paradigm has produced numerous successes that have improved health, but it inherently emphasizes a somewhat reductionist view of complex diseases and does not always produce the evidence, rapidly enough, to address key questions for clinical and public health practice: “what works, and how to do it?” In his presentation, Dr. Robinson offered a complementary research approach. Multi-factorial conditions such as obesity, he argued, do not necessarily require a detailed understanding of their causes in order to develop effective treatment or preventative strategies. “Solution-oriented” research focuses on identifying the causes of improved health, positive outcomes, and reduced risk for disease.1 This conceptual shift could have a significant impact on how a scientist generates hypotheses and studies. Solution-oriented research is based on the assumption that it is not always necessary to know the causes of a problem first in order to determine how to prevent or treat it effectively. This approach recognizes that the preceding, causal, or

contributing factors for complex diseases may no longer exist or may not be susceptible to change. Solution-oriented approaches focus on testing the efficacy of intervention strategies; such research questions are likely to be more relevant for clinical and public health practice and policy, and may shorten the time needed to translate research findings to improved public health.

Obesity is a condition well suited for solution-oriented research. Scientists generally accept that weight gain results from a disruption in energy balance, but numerous factors (e.g., biological, social, psychological, economic, policy) likely have contributed to today’s high levels of obesity. While research may help illuminate each individual factor’s contribution to obesity, efforts to test treatments or prevention strategies, even in the absence of such knowledge, may ultimately yield more practical results. For example, in children, screen time (e.g., television viewing, videotape viewing, video game use) is linked to obesity, but the reasons for this connection are unclear. Potential hypotheses for this link include: the effects of advertising, increased food consumption while viewing television, and the reduction in physical activity accompanying screen time. Most previous studies were observational, and study designs were complicated by inaccuracies in measuring screen time. Furthermore, even if a study proved that screen time contributes to obesity, that knowledge would not provide information on what to do, that is, how to reduce screen time or whether screen time changes will improve weight. The complementary approach would be to test an intervention to limit screen time and measure the resulting effects on the study participants’ weight. This experimental approach was conducted by Dr. Robinson’s research team. They found that in third- and fourth-grade students over a 6 month span, the average reduction of several hours of screen time per week led to approximately half the increased body mass index (BMI, a measure of weight relative to height) and waist circumference as was observed in children who did not alter screen time viewing. Thus, the solution-oriented intervention reduced obesity in children, without knowing the specific causal factors linking screen time to obesity. In another study, Dr. Robinson and colleagues extended their analyses to younger children and assessed effects of screen time reduction over 2 years. In a trial with 4 to 7 year-old children with high BMIs, reducing screen time by 50 percent, compared to a control group, led to sustained improvement in BMI over a 2 year period.

Stealthy Interventions, Healthy Outcomes

Can the idea of health benefits alone motivate children to change their behavior? Perhaps in some cases, but improved health may not be a potent factor driving many to become more physically active or to reduce calorie intake. Dr. Robinson proposed that a study design in which the target behavior of the intervention is intrinsically motivating, but its “side effects”—such as increased physical activity, reduced sedentary behavior, or dietary changes—would improve health. These types of solution-oriented “stealth interventions” could improve obesity-related behaviors without the appearance of health education. To test this concept, Dr. Robinson’s research team explored using dance in pre-adolescent girls as a fun target behavior, involving

---

participation in a group, cultural awareness, and the thrill of performance. They first tested whether hip-hop and other types of dance programs could improve BMI in fifth-graders, mostly of African American and Mexican American ethnicities. After 12 weeks, the girls who participated in the dance program maintained their BMIs, whereas BMIs rose in those who took standard physical education classes during the same time period. In a separate study, an intervention that included a culturally tailored dance program (hip-hop, step, and traditional African dance) and reduced television viewing time was compared with a nutrition education program in African American girls from California. Over a 12-week period, the BMIs and waist circumferences of the girls from the dance program and reduced television viewing group increased about half as much as those of the girls from the nutrition education group. When the trial was extended to 2 years, they encountered challenges in program implementation, and BMIs did not change significantly. However, a number of obesity-related factors did improve in the girls in the dance and reduced television viewing group, including total cholesterol, LDL (“bad”) cholesterol, depressive symptoms, and fasting insulin levels.

Dr. Robinson described results from another “stealth intervention” trial—after-school sports programs for overweight children. Many aspects of team sports are highly motivating for children: participating on a team, receiving mentoring, developing friendships with young adult coaches, displaying skills to friends and family, and even having the opportunity to wear a uniform—“you’d be amazed how motivating shin guards are,” Dr. Robinson explained. In the study, overweight children either participated in a soccer program or received health or nutritional education. After 6 months, the children who played soccer had significantly reduced BMIs, as well as increased physical activity measures, compared with those enrolled in the education programs. These findings show that although the contribution of each potential motivating factor is unknown, after-school team sports programs for overweight children could serve as effective interventions for weight control.

Taking Stealth Interventions to the Next Level
Any obesity prevention or treatment strategy will require individuals to change their behaviors, but what will motivate people to act? The answer is likely different for each person. Dr. Robinson posits that because social and ideological movements drive many people to enact changes within their lives, they may provide opportunities to design stealth interventions for obesity prevention and treatment. Many such movements motivate large numbers of people to act: environmental sustainability/climate change, food safety, human rights/social justice, animal protection, and cause-related fundraising, to name just a few areas for potential stealth interventions. The issue of environmental sustainability/climate change inspires many people to change their behaviors, for example, walking or biking instead of driving. In the example of cause-related

fundraising, people may train for and participate in races, such as half-marathons, to raise money for charities. In both examples, improved health is not the motivating factor behind the behavior change, but it is a side effect. Dr. Robinson’s current research investigates whether these and other social and ideological movements could be co-opted to serve as sources of effective interventions.

**Conclusions**

In presenting his team’s ongoing research, Dr. Robinson makes the case that solution-oriented research, particularly through stealth interventions, could identify obesity prevention and treatment avenues for motivating people to change their individual behaviors. He proposes a litmus test for solution-oriented research: a study should only be done if the researchers know what to conclude from any possible result (positive, negative, or null) and if the findings may change intervention strategies to address obesity (or other public health problems). Dr. Robinson makes clear that problem-oriented research has enormous value; solution-oriented research adds an alternative and complementary methodology for tackling complex public health challenges like childhood obesity.