

NIDDK

Recent Advances & Emerging Opportunities

Obesity

January 2023

This is a chapter from the NIDDK's Annual Report. The full Report includes highlights of research on these and many other areas across the NIDDK's mission and is available at:

www.niddk.nih.gov/about-niddk/strategic-plans-reports/niddk-recent-advances-emerging-opportunities



U.S. Department of Health and Human Services
National Institutes of Health
National Institute of Diabetes & Digestive & Kidney Diseases



National Institute of
Diabetes and Digestive
and Kidney Diseases

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NIH OBESITY RESEARCH
TASK FORCE SYMPOSIUM:
**THE GLOBAL IMPACT
OF OBESITY**

September 9, 2022

WEBINAR

The trans-NIH Obesity Research Task Force was established to accelerate progress in obesity research across NIH, given the importance of the obesity epidemic as a major public health problem and its relevance to the missions of most of the NIH Institutes, Centers, and Offices. The Task Force is co-chaired by the Director of the National Institute of Diabetes and Digestive and Kidney Diseases, Dr. Griffin P. Rodgers; the Director of the National Heart, Lung, and Blood Institute, Dr. Gary H. Gibbons; and the Director of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, Dr. Diana W. Bianchi. The Task Force holds two seminars each year, covering a broad range of topics. On September 9, 2022, the Task Force convened a symposium on the global impact of obesity where six distinguished scientists highlighted their research from around the world. A summary of this seminar is featured in this chapter.

Obesity

Obesity has risen to epidemic levels in the United States. Individuals who have obesity may develop 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. Nearly 42 percent of U.S. adults are considered to have obesity based on body mass index (BMI), a measure of weight relative to height.¹ Nearly 20 percent of children and adolescents also have obesity, and thus are at increased risk for developing serious diseases both during their youth and later in adulthood.^{1,2} Obesity disproportionately affects people from certain racial and ethnic groups and those who are socioeconomically 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 (social determinants of health) such as a lack of healthy, affordable food and places to exercise in many communities; sedentary jobs; and other conditions that influence what, when, and how much people eat. Diet, activity, and aspects of our environment also may modify biologic factors in ways that promote obesity. 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.

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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 interventions for children and adults in health care, home, community, and other settings using a variety of approaches and technologies, surgical interventions, and combinations of strategies. In parallel, NIDDK-supported investigations into the biologic processes associated with body weight have continued to spark new ideas for intervention approaches.

Nearly 42 percent of U.S. adults and nearly 20 percent of children and adolescents have obesity.^{1,2}

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 to promote collaboration and enhance obesity research across NIH.

NIDDK supports basic, clinical, and translational research to discover how body weight is regulated and to design and evaluate approaches for preventing and treating obesity.

¹ Stierman B, et al. National Health and Nutrition Examination Survey 2017–March 2020 prepandemic data files—Development of files and prevalence estimates for selected health outcomes. Centers for Disease Control and Prevention. National Health Statistics Reports 158, 2021.

² 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).

PEDIATRIC OBESITY PREVENTION RESEARCH

Parenting Program for Obesity Prevention in Firstborn Children Benefits Siblings:

In a recent study, researchers found that a responsive parenting intervention shown to help new parents prevent childhood obesity in their firstborn children also had beneficial spillover effects on the growth of their second-born children years later. The study, called SIBSIGHT, followed an earlier clinical trial—Intervention Nurses Start Infants Growing on Healthy Trajectories (INSIGHT). For the INSIGHT intervention, nurses delivered information in the home to first-time parents, including education on infant feeding, sleep, and play, and responding to the child's needs. The intervention resulted in healthier body weights of the young children, compared to those in a control group whose parents received information about safety.

For the SIBSIGHT study, the researchers recruited INSIGHT participants who had a second child, including those who had received the responsive parenting intervention and those from the control group. The SIBSIGHT study was only observational; that is, the participants did not receive any further training on responsive parenting when their second children were born, even though it had been an average of 2.5 years since the birth of their first children. Monitoring the growth of 117 second-born infants based on body mass index (BMI), a measure of weight relative to height, the researchers found that at age 1 year, second-born children whose parents received the intervention with their first child had a significantly lower BMI, by 0.36 units, compared to those whose families were in the control group. This weight-related benefit of the intervention for second children was similar to that observed in the firstborn children at the same age. Because the study participants were mostly White, middle-income families, further research would be needed to determine the benefits to children from other backgrounds.

A responsive parenting intervention shown to help new parents prevent childhood obesity in their firstborn children also had beneficial effects on the growth of their second-born children years later.

This study demonstrates that an intervention of responsive parenting for obesity prevention in firstborn children has a continuing benefit for second-born children. The findings provide hope that a parenting strategy,

taught once when first children are infants, could help with setting those children and their future siblings on a healthy growth trajectory starting early in life.

Savage JS, Hochgraf AK, Loken E,...Paul IM. INSIGHT responsive parenting educational intervention for firstborns is associated with growth of second-born siblings. Obesity 30: 183-190, 2022.

STUDYING OUTCOMES OF BARIATRIC SURGERY FOR OBESITY TREATMENT

Weight Loss from Bariatric Surgery Compared to Nonsurgical Care for People with Severe Obesity:

Researchers found that bariatric surgical procedures, including gastric bypass surgery and sleeve gastrectomy, led to significantly more weight loss than nonsurgical care for people with severe obesity—information that could help with treatment decisions. Although past research demonstrated that bariatric surgery leads to substantial weight loss, only a few long-term studies compared weight loss from nonsurgical care to that from surgery, and there has been less information on sleeve gastrectomy, though it is currently the most common bariatric procedure.

To better understand the effects of surgery, researchers analyzed electronic medical records and other data from women and men of diverse race and ethnicity with severe obesity in a large health care system, including 13,900 people who had sleeve gastrectomy (SG), 17,258 who had Roux-en-Y gastric bypass (RYGB), and 87,965 people who did not have surgery. Those in the nonsurgical group received usual medical care, which in general did not include specific obesity treatment. On average, 1 year after surgery, people in the RYGB group had lost 28 percent of their weight, and those who had SG lost 23 percent of their weight. At a similar time point, those in the nonsurgical group had lost 0.2 percent of their weight. Longer-term follow-up data were available for a majority of the people. At 5 years, the people who had surgery regained some weight, but those who had RYGB still maintained an average 22 percent weight loss, and those in the SG group still maintained 16 percent weight loss, or approximately 60 pounds and 43 pounds lost, respectively. Some regained enough weight to be within 5 percent of their initial weight, however, including 1 of every 10 people who had SG and 1 in 27 who had RYGB. Those who didn't have surgery had lost approximately 2 percent of their weight, or about 6 pounds. At 10 years, those who had RYGB were still on average 20 percent below their

pre-surgical weight, and those in the nonsurgical group had lost approximately 5 percent of their weight. (There were not enough data to analyze weight loss 10 years after SG.)

Researchers found that, compared to nonsurgical care for people with severe obesity, bariatric surgical procedures—including gastric bypass surgery and sleeve gastrectomy—led to substantially greater weight loss that was maintained for years, based on 10 years of follow-up data for gastric bypass surgery and 5 years of data for sleeve gastrectomy.

This study provides important information that people with severe obesity and their health care providers can use when considering bariatric surgery. The findings also suggest a need for additional care for people who experience weight regain after surgery. Future research could explore other long-term effects of bariatric surgery on health.

Arterburn DE, Johnson E, Coleman KJ,...Haneuse S. Weight outcomes of sleeve gastrectomy and gastric bypass compared to nonsurgical treatment. *Ann Surg* 274: e1269-e1276, 2021.

IDENTIFYING A LINK BETWEEN EXERCISE AND FOOD CONSUMPTION

An Exercise-induced Molecule Reduces Obesity in Mice:

Scientists discovered that a molecule produced during exercise by various mammals, including people, can reduce food consumption and obesity in mice.

Exercise is a powerful tool that can help protect against obesity and obesity-associated diseases such as type 2 diabetes and cardiometabolic disease. Physical activity results in many molecular changes in the body, but the extent to which each molecular alteration contributes to health benefits, including obesity prevention, is not well understood. A team of researchers analyzed blood samples from male mice before and after an intense bout of exercise running on a treadmill and looked for molecules that increased following exercise. The researchers found the largest increase was in a compound called *N*-lactoyl-phenylalanine, or Lac-Phe, which is a molecule of unknown function. Interestingly, the team found similar increases in Lac-Phe in blood samples following exercise in thoroughbred racehorses

and humans, suggesting exercise-induced production of Lac-Phe is not unique to mice. When the researchers gave an injection of Lac-Phe to obese mice on a high-fat diet, the mice reduced their food intake by half over 12 hours even though circulating levels of the molecule fell to baseline within 1 hour, suggesting long-lasting benefits. Obese mice treated with Lac-Phe for 10 days lost weight and had lower blood glucose (sugar) levels than obese mice that did not undergo treatment. In contrast, Lac-Phe treatment had no effect on food consumption in lean mice on a normal diet. Previous research has shown that Lac-Phe is synthesized by the enzyme CNDP2, found in many cell types including immune cells and cells that line the surfaces of organs. In the current study, the researchers confirmed in cultured cells that Lac-Phe production requires this enzyme, and that Lac-Phe is secreted from the cells. CNDP2 requires the molecule lactate to generate Lac-Phe. Lactate is produced in the body during strenuous exercise, causing the burning sensation in exhausted muscles. In the cultured cells, increasing the lactate supply increased Lac-Phe production. Lastly, the research team examined mice that were genetically engineered to lack CNDP2 and were thus deficient in Lac-Phe; these mice had increased food intake and weight gain while on a daily exercise regimen, compared to mice with CNDP2.

Scientists discovered that a molecule produced during exercise by various mammals, including people, can reduce food consumption and obesity in mice.

Taken together, these results suggest that regular exercise increases production of Lac-Phe, which helps to regulate food intake and body weight. More research is needed to unmask how Lac-Phe may be acting in the brain to suppress feeding and obesity, which may provide new therapeutic opportunities to capture the benefits of physical activity for human health.

Li VL, Yang H, Contrepois K,...Long JZ. An exercise-inducible metabolite that suppresses feeding and obesity. *Nature* 606: 785-790, 2022.

INSIGHTS INTO FAT TISSUE-BRAIN COMMUNICATION

A Direct Line of Communication Identified Between Fat Tissue and the Brain: Researchers have discovered sensory nerve cells that send messages from fat tissue to the brain in mice. This finding challenges the conventional notion that circulating hormones in the blood are the sole messengers sending information related to stress and metabolism between fat tissue and brain cells.

In mammals, fat tissue stores energy (calories) and releases this energy when the body needs it. Fat tissue also regulates hormones and signaling molecules that update the brain on fullness, hunger, and metabolism. Disruption of these critical functions can contribute to several diseases including diabetes, obesity, and fatty liver disease. Researchers have known that nerve cells contact fat tissue. However, they suspected that they were part of a network of nerves responsible for the body's "fight-or-flight" response that activates fat-burning pathways during stress and physical activity—not sensory nerve cells that carry data directly to the brain. Until now, a lack of suitable laboratory tools and techniques prevented scientists from identifying the function of nerve cells contacting fat tissue. The team of researchers leading this study developed new techniques to overcome these obstacles.

First, they used an imaging technique they had recently developed that turned fat tissue transparent so they could visualize the nerve cells that extend into the

tissue. Surprisingly, in experiments in male mice, they discovered that nearly half of the nerve cells were not part of the fight-or-flight response network, but rather connected to an area of the brain where sensory cells originate. Next, the team used a genetic tool, developed previously and that they optimized, to analyze the function of the sensory nerve cells by selectively removing these cells within the fat tissue. The experiments demonstrated that destroying sensory input from fat tissue to the brain in mice results in elevated body temperatures and the generation of "beige fat," a type of fat tissue that breaks down other fat molecules to produce heat. These results suggest that the two types of nerve cells extending into fat tissue, cells in the fight-or-flight network and sensory cells, have opposing functions: the former act as a "gas pedal" for burning fat, and the latter act as the "brake". When the brake was removed, a response reminiscent of fight-or-flight was activated (fat-burning, body temperature increase).

These findings fill an important knowledge gap on how the brain regulates different fat tissue functions, highlighting the importance of this newly discovered avenue of brain-body communication. Future research could lead to new therapeutic strategies to treat obesity and other metabolic diseases.

Wang Y, Leung VH, Zhang Y,...Ye L. *The role of somatosensory innervation of adipose tissues.* *Nature* 609: 569-574, 2022.

Symposium Held To Explore the Global Impact of Obesity

The epidemic of obesity in adults and children is not limited to the United States. Obesity prevalence is increasing globally and can co-exist with malnutrition and chronic undernutrition. Given the global impact of obesity, the research community recognizes the need to accelerate development of new and innovative prevention and treatment strategies, close knowledge gaps with the goal of translation into more effective patient care, and explore lessons the United States and international communities can learn from each other toward developing creative and integrated approaches to obesity prevention and treatment. To that end, six leading scientists highlighted their research from around the world at a September 2022 virtual symposium organized as part of the NIH Obesity Research Task Force Seminar Series. The research presented was supported by NIDDK and other NIH Institutes.

Dr. Francesco Branca of the World Health Organization presented on the topic of the dual burden of malnutrition (DBM). DBM, defined as the simultaneous manifestation of both undernutrition (micronutrient deficiencies, underweight, childhood stunted growth) and overweight/obesity, affects most low- and middle-income countries. DBM can occur at the country, household, and individual levels. While progress has been made worldwide toward exclusive breastfeeding of infants as well as reductions in childhood stunted growth, increases in overweight/obesity continue. Dr. Branca outlined opportunities for action to address DBM globally including scaling up health services; redesigning social safety nets and educational programs; and expanding agricultural development to make nutritious foods available, affordable, and appealing.

Dr. Lara Dugas of Loyola University presented her research on sleep timing, gut microbiota, and

cardiometabolic risk. The Modeling the Epidemiologic Transition Study (METS) has six sites worldwide in low-, middle-, and high-income countries, including in Africa, Caribbean countries, and the United States. Through self-reporting methods, METS researchers tracked sleep timing and dietary habits in study participants. The longest sleep durations and highest dietary fiber intake were reported in Ghana, while the shortest sleep durations and lowest dietary fiber intake were reported in the United States. Longer sleep durations are associated with a lower prevalence of obesity and cardiometabolic risk. High-fiber intake is associated with a rich and diverse gut bacterial ecosystem.

Dr. Marcella Nunez-Smith of Yale University presented her research on obesity and cardiometabolic disease in understudied Eastern Caribbean populations with a high burden of chronic disease morbidity and mortality. The objectives of the Eastern Caribbean Health Outcomes Research Network (ECHORN) cohort study are to expand clinical research to include these minority populations, address the need for regional research infrastructure, and increase regional capacity to translate research into policy and practice. ECHORN consists of several initiatives including diabetes, hypertension, and childhood obesity subprojects. All data collected through the ECHORN cohort study are publicly available to the research and policy communities on a data-sharing platform.

Dr. Franco Sassi of the Imperial College Business School presented on The Science and Technology in childhood Obesity Policy (STOP) project in European countries. The STOP project aims to develop a measurement framework for epidemiological surveillance, establish new evidence on childhood obesity determinants and impacts of policies and interventions, and design toolkits for policy

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implementation. New STOP analyses have provided evidence in support of fiscal and regulatory policies, social marketing interventions, physical education and physical activity interventions, and food reformulation programs. In ongoing efforts, a primary care-led, family-based approach for addressing obesity in children under the age of 5 is currently being tested in a randomized controlled trial in several countries.

Dr. William Dietz of the Milken Institute of Public Health at George Washington University presented an overview of the global syndemic (concurrent epidemics) of COVID-19, obesity, food and nutrition insecurity, and climate change. Dr. Dietz highlighted the impact of many contributing factors, such as increased greenhouse gas emissions that affect weather and food production, food costs, transportation systems, structural racism and related social determinants of health, physical inactivity, and other factors. The COVID-19 pandemic resulted in increased hospitalization, severity of infection, and death in people with chronic diseases such as obesity, diabetes, and cardiovascular disease and in people of color. The pandemic also led to food and nutrition insecurity secondary to food supply chain failures and job loss. Moreover, COVID-19 lockdowns resulted in dramatic increases in childhood obesity. Dr. Dietz put forth his suggestions to address this syndemic with actions to build and strengthen resilient, sustainable,

plant-based food systems that shift reliance away from ultra-processed foods; address physical activity; and many other actions to help combat obesity, diabetes, and COVID-19 mortality.

Dr. Jonathan Wells of University College London presented his research on the evolution of human adiposity (excess fat tissue) and obesity. His talk explored how body fat tissues are regulated, how they develop over the life course, what biological functions they serve, and how they may have evolved. There is substantial evidence that human adiposity is not merely a buffer against the threat of starvation but is also a resource for meeting the energy (calorie) costs of growth, reproduction, and immune function. However, human metabolism is sensitive to environmental cues. Readily available, inexpensive, and palatable ultra-processed foods, as well as economic forces such as product placement, television advertising, and celebrity endorsements, could be contributing to the current obesity epidemic.

The seminar included a lively discussion among speakers and participants on current challenges and opportunities. Continued research could reveal better strategies to prevent and treat obesity on a global scale, thereby preventing many adverse health outcomes.

Workshop on Housing and Obesity: Gaps, Opportunities, and Future Directions for Advancing Health Equity



November 14–15, 2022



Workshop Held To Explore the Relationship Between Housing Insecurity and Obesity

Many important aspects of our health are shaped by the environment and conditions in which we live. A serious health challenge across the United States is the rise in housing insecurity, including inability to afford rent and utilities, experiencing frequent moves, living in low-quality housing or overcrowded conditions, and residing in under-resourced neighborhoods. Studies have implicated housing insecurity as an important risk factor for obesity (along with its comorbidities like diabetes) due to obstacles such as limited availability of healthy and affordable food, lack of safe green spaces to encourage physical activity, mental stress, and inadequate means of transportation for health care visits. Housing insecurity is also rooted and sustained in historical systemic racism and is a driver of present-day residential segregation, disparities in home ownership, housing inequality, and wealth inequalities. These challenges underscore housing insecurity as a barrier to health equity and a critical social determinant of health.

As part of ongoing efforts to advance health for all people, NIDDK, along with other NIH Institutes and Centers, the Centers for Disease Control and Prevention, and the U.S. Department of Housing and

Urban Development, co-sponsored a multi-agency workshop to explore the role of housing insecurity in obesity-related health disparities, review the evidence for housing-related interventions to overcome these disparities, and identify future research directions to advance health equity. The overall goal of the workshop was to accelerate research on the role of housing insecurity—including housing affordability, quality, and stability—on behaviors and pathways that increase risk for obesity-related health disparities across the lifespan. The workshop also aimed to propel research on interventions to address housing insecurity.

The meeting brought together a diverse group of researchers, leaders, and experts from a range of disciplines, including housing and the neighborhood environment, obesity, health disparities, health equity, public health, and other relevant fields. The participants discussed existing research that links housing policies and programs with obesity, methods for housing and obesity research, and interventions that address housing as a social need and a core social determinant of health. The workshop also included discussions to identify critical research questions

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and opportunities for creating research partnerships and collaborations across federal, regional, and local housing programs.

This workshop serves as an integral component of NIDDK's endeavors to achieve health equity by advancing understanding of social determinants of health, both as causes of disease and as targets for intervention. A summary of the workshop will be made available to the public.