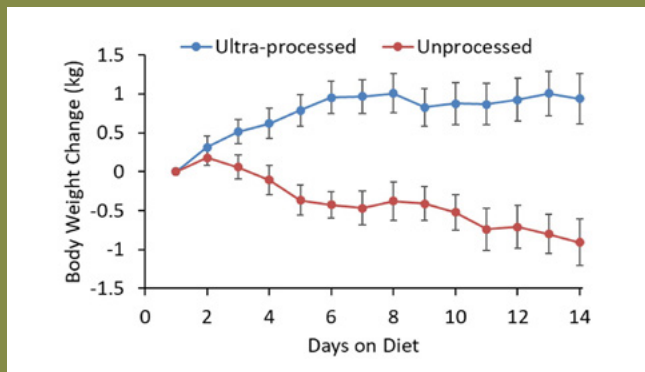


Ultra-processed Diet

Unprocessed Diet



In a recent study described in this chapter, researchers found that a diet of mainly ultra-processed foods—those with ingredients predominantly found in industrial food manufacturing—causes overeating and weight gain. For the study, they recruited 20 men and women to live at the NIH Clinical Center and eat a diet of ultra-processed foods and a diet of unprocessed foods for 2 weeks each, with all meals and snacks provided by the study staff. The ultra-processed and unprocessed meals presented to the participants had the same amounts of calories, sugar, fat, salt, and fiber; and the participants could eat as much or as little of each meal as they wanted. Examples of breakfasts, lunches, and dinners are pictured in this image, along with a graph showing the average changes in body weight. (To match the amount of fiber naturally found in unprocessed foods, many of the ultra-processed meals included fiber supplements dissolved in multiple beverages, shown in the photos.) On the ultra-processed diet, the study participants consumed 500 more calories per day and gained about 2 pounds (0.9 kilograms) on average, while the same individuals lost about 2 pounds during their time on the unprocessed diet. Further studies are needed to understand what aspects of the ultra-processed foods caused overeating and weight gain.

Images courtesy of Dr. Kevin Hall, NIDDK. Reprinted from Cell Metabolism, 30, Hall KD, Ayuketah A, Brychta R,...Zhou M, Ultra-processed diets cause excess calorie intake and weight gain: An inpatient randomized controlled trial of ad libitum food intake, 67-77, Copyright 2019, with permission from Elsevier.

Obesity

Obesity has risen to epidemic levels in the United States. Individuals who have obesity 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. Nearly 40 percent of U.S. adults are considered to have obesity based on body mass index (BMI), a measure of weight relative to height.¹ More than 18 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 that promote increased caloric intake and sedentary lifestyles. Diet, activity, and aspects of our environment may also 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.

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 interventions in families and in health care 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.

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.

Highlights of recent advances from NIDDK-supported research on obesity are provided in this chapter.

COMBATING CHILDHOOD OBESITY

Responsive Parenting—An Early Start Toward Obesity Prevention: In a recent clinical trial, researchers found that educating first-time moms on responsive parenting, with tips on infant feeding, sleep, play, and emotion, resulted in a modest improvement in body weight of the children through age 3 years. The researchers developed the intervention with the hope of setting children on a healthy growth trajectory starting early in life, because childhood obesity can lead to serious diseases during youth and later in adulthood, and rapid and excess weight gain at a young age increases risk for obesity.

The researchers recruited mothers soon after childbirth, randomly assigned them to either the responsive parenting intervention or a control intervention on home safety, and then tracked their children's growth for the next 3 years. In each intervention group, 116 mother-child pairs completed the full study; the participants were mainly white, middle-income families. Both

¹ Hales CM, et al. 2017. CDC. National Center for Health Statistics Data Brief No. 288.

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).

interventions included home visits by research nurses, study participant visits to the research center, and other components. The responsive parenting intervention focused on responding to a child's needs in a prompt and age-appropriate way and provided a wealth of information helpful to new parents. This included tips on recognizing when infants are hungry or full, using alternatives to feeding to soothe infants who are fussy but not hungry, serving age-appropriate portion sizes of food, putting infants to bed and other sleep-related information, establishing routines, and interactive play. When the children were 1 year of age, those in the responsive parenting group were less likely to be overweight than those in the control group, a promising result reported previously. The research team has since found that, at age 3 years, children in the responsive parenting group had significantly healthier body weights than those in the control group, as assessed by "BMI z score," a measure of weight relative to height that also reflects how far a child's weight is from average. Although the effect was modest, it was within the range considered clinically meaningful. Interestingly, the intervention had a greater effect on girls' weight than on boys' weight, though the reasons are unclear. Research staff also monitored the children to see whether any were not gaining enough weight and found no significant differences between groups in this potential side effect.

This study thus provides hope that a parenting intervention, begun in infancy, may help reduce excess weight gain during childhood. To determine longer-term effects, the researchers plan to evaluate the children's weight and eating behaviors up to age 9. They also initiated a study of a similar intervention for obesity prevention in a different population, African Americans in low socioeconomic areas in the rural South, with the goal of improving the health of more children.

Paul IM, Savage JS, Anzman-Frasca S, ... Birch LL. Effect of a responsive parenting educational intervention on childhood weight outcomes at 3 years of age: The INSIGHT randomized clinical trial. JAMA 320: 461-468, 2018.

COMPARING BARIATRIC SURGERY IN TEENS AND ADULTS

Age Is More Than Just a Number: Early Weight-loss Surgery May Lead to Better Health Outcomes: Researchers have found that, despite similar weight loss, teens who underwent a form of bariatric surgery called Roux-en-Y gastric bypass were

significantly more likely to have remission of type 2 diabetes and high blood pressure compared to adults who underwent the same procedure.

Bariatric surgery can be an effective tool for treating severe obesity, leading to significant weight loss and improved health outcomes for both adolescents and adults. However, whether results vary depending on the age of the patient at the time of surgery was unclear. In this analysis that utilized data from two related but independent studies, researchers evaluated outcomes of gastric bypass surgery in 161 adolescents (ages 13-19) with severe obesity and compared them to outcomes in 396 adults (ages 25-50) who reported having obesity since they were teens and who underwent gastric bypass surgery during adulthood. Five years after surgery, the two groups had achieved significant weight loss that was similar in magnitude. While the number of participants with type 2 diabetes declined in both groups after surgery, adolescents were more likely to have their diabetes resolve. In fact, no teens in the group needed diabetes medication 5 years post-surgery. Moreover, among those participants with high blood pressure prior to surgery, teens were 50 percent more likely than adults to have their blood pressure return to normal and no longer require medication. Although teens had better health outcomes in certain areas compared to adults, they also experienced increased risks in other areas, including needing subsequent abdominal surgeries and exhibiting low iron and vitamin D levels, the latter of which could possibly be explained by nonadherence to vitamin supplements. Bariatric surgery risk is further highlighted by the fact that deaths occurred in both groups within 5 years post-surgery (3 teens, 7 adults). Two of the adolescent deaths were related to substance use, which merits attention given that a previous study had found an increased risk of substance use disorders following bariatric surgery in adults.

This study demonstrates that bariatric surgery at a younger age may provide significant health benefits like remission of type 2 diabetes and high blood pressure, in addition to substantial weight loss, potentially avoiding adverse effects of prolonged severe obesity into adulthood. While this study contributes important information about the reversal of obesity-related conditions post-surgery, the procedure is not without risk, and lifetime risk remains unknown. Future research can help to shed light on the best timing of bariatric surgery and the

most effective treatments for people with obesity and its related conditions.

Inge TH, Courcoulas AP, Jenkins TM,...Helmrath MA; Teen-LABS Consortium. Five-year outcomes of gastric bypass in adolescents as compared with adults. *N Engl J Med* 380: 2136-2145, 2019.

RESEARCH TOWARD IMPROVING HEALTH IN PREGNANCY

New Evidence-based Recommendations for Calorie Intake in Pregnant Women with Obesity:

Researchers have provided, for the first time, evidence-based recommendations for energy intake (caloric intake) in pregnant women with obesity, making this a pioneering study in its field that can potentially help improve obstetrical care.

Excess gestational weight gain occurs in two-thirds of pregnancies and can lead to metabolic impairments in the mother and increased risk for obesity in the child. There have been several trials to evaluate the effectiveness of lifestyle interventions for pregnant women with overweight/obesity, but only half have resulted in substantially reduced weight gain during pregnancy. Moreover, current recommendations for energy intake during pregnancy have been based only on studies in women without obesity or have been based on subjective, self-reported assessments, which are prone to recall bias. To enhance the understanding of caloric needs during pregnancy and characterize factors leading to excess gestational weight gain in women with obesity, researchers analyzed energy intake and energy expenditure (calories burned) in 54 pregnant women with obesity during the second and third trimesters using technologies and methods for rigorous, objective measurement. Applying the 2009 Institute of Medicine guidelines for gestational weight gain, 8 women from the study group gained the recommended amount of weight during the study period (approximately 4.5 kg or 9.9 lbs.) while 36 women gained an excess amount of weight (approximately 10.3 kg or 22.7 lbs.); 10 women experienced inadequate weight gain. The investigators determined that differences in weight gain were not related to differences in physical activity, physiological factors such as hormone activity, or factors such as diet quality. To understand other aspects of pregnancy-related weight gain, the researchers measured amounts of body fat in the women, as well as amounts of fat-free body tissues and fluid and calculated their

energy expenditure. The women who gained the recommended amount of weight had gained that weight in fluid and fat-free body mass (including the fetus and tissues such as the placenta), while actually losing a small amount of body fat. In those who gained excess weight, the extra weight was from increased fat tissue. The researchers' findings suggest that pregnant women with obesity should not consume extra calories during the second and third trimesters and that the energy needs of the fetus are met by mobilizing maternal fat mass to achieve healthy delivery of the infant. Importantly, these findings challenge the current recommendations for women with obesity, which advise consuming an additional 200-300 calories/day after the first trimester.

This study is unique in its use of objective methods to assess energy requirements in pregnant women with obesity and it has the potential to improve obstetrical patient care for better maternal and infant outcomes. However, it is limited by its small sample size, and evaluation of the longer-term effects on the children's development will be important. Future research could lead to the implementation of new, evidence-based recommendations for calorie intake in pregnant women with obesity.

Most J, Amant MS, Hsia DS,...Redman LM. Evidence-based recommendations for energy intake in pregnant women with obesity. *J Clin Invest* 130: 4682-4690, 2019.

ULTRA-PROCESSED FOODS AND WEIGHT GAIN

Diets of Ultra-processed Foods Cause Overeating and Weight Gain: Comparing effects of a diet of ultra-processed food with a diet of unprocessed or minimally processed foods, researchers found that people consumed more calories per day and gained weight on the ultra-processed diet, while losing weight on the unprocessed food diet. Ultra-processed foods, as defined by a classification system called NOVA, are those with ingredients and additives predominantly found in industrial food manufacturing, such as hydrogenated oils, high-fructose corn syrup, flavoring agents, and emulsifiers. Past research had shown a correlation between ultra-processed foods and worse health, but it was not known whether ultra-processed foods actually caused people to eat too much and gain weight, or whether the correlation was the result of other factors. Thus, a team of NIDDK intramural

scientists and colleagues decided to test this with a small group of people in a rigorously controlled study.

The research team recruited volunteers, 10 men and 10 women, to live at the NIH Clinical Center for a month and eat a diet of ultra-processed foods and a diet of unprocessed foods for 2 weeks each. All meals and snacks were provided by the study staff, and the participants could eat as much or as little of each meal as they wanted. The researchers designed the ultra-processed and unprocessed meals to have the same amounts of calories, sugar, fat, salt, and fiber. The diets were also similarly palatable, as rated by the participants. (Examples of the meals are shown at the beginning of this chapter.) On the ultra-processed diet, the study participants ate an average of 500 more calories per day and gained about 2 pounds, while they lost about 2 pounds during their time on the unprocessed diet. They also ate faster (more calories per minute) when on the ultra-processed diet. What attributes of the ultra-processed foods might have caused these effects? Among the differences between the diets, the ultra-processed foods contained more saturated and other unhealthy fats; added sugars, rather than only sugars naturally occurring in foods; and industrially processed ingredients. There were also slight differences in amounts of protein between the two diets, which the researchers note could explain as much as half the difference in calorie intake. However, it is not yet clear whether these or other factors led to the effects of the ultra-processed diet.

The results of this study suggest that limiting consumption of ultra-processed foods could help prevent excess weight gain. However, ultra-processed foods are ubiquitous in the United States, inexpensive, highly convenient, have a long shelf-life, and do provide needed nutrients. By contrast, less-processed foods typically take more time and expense to prepare. Future research could lead to strategies for developing diets with the convenience of ultra-processed foods and the weight-related health benefits of unprocessed foods.

Hall KD, Ayuketah A, Brychta R, ...Zhou M. Ultra-processed diets cause excess calorie intake and weight gain: An inpatient randomized controlled trial of ad libitum food intake. Cell Metab 30: 67-77, 2019.

GUT MICROBIOME AND BODY WEIGHT

Networking Gut Bacteria and Their Role in Body Weight: A recent study has shown that women

with lean body types who eat high-fiber diets have complex, highly interactive bacterial networks in their gut microbiomes, and subsequent experiments in mice showed that these bacteria can impart resistance to obesity for several weeks on a high-fat diet. The human gastrointestinal tract is home to a thriving community of bacteria. Studies have shown that some of these bacteria are associated with leaner body types, suggesting that they may protect against obesity. One way that they might do this is by breaking down dietary fiber to produce short-chain fatty acids (SCFAs), which are molecules believed to play an important role in regulating metabolism. The overarching properties of the microbiome that may encourage SCFA production and protect against obesity are unclear, however. For example, little is known about how the many different types of bacteria in the gut interact with each other—one type of bacteria might rely upon another to survive while aggressively competing against other types of bacteria for space and nutrients. Recognizing relationships such as these would allow scientists to conceptualize an ecological network in the gut, wherein a type of bacteria is “connected” to another if it affects its ability to thrive. Scientists could then determine how changes to this microbial network affect health.

In a recent study, scientists sought to gain understanding of human gut microbial networks by analyzing the gut microbiomes of 50 women from rural Ghana and 50 African American women from an urban area of the United States. Roughly half the participants—some from each country—were women who had obesity, while the others had lean body types, allowing the researchers to compare not only the microbiomes between different geographical areas, but also between people with different body types. Sequencing the microbial genetic material from the participants’ microbiomes (obtained from fecal material), the scientists identified the types of bacteria that were inhabiting the women’s guts, along with their relative amounts. They then compared the microbiomes from all the women to gain an understanding of how the types of bacteria relate to each other—whether their quantities tend to increase or decrease in parallel from sample to sample, or if their abundances appear to be unrelated. They found that the Ghanaian women with lean and obese body types—all of whom tended to eat more starches and fiber-rich foods than the U.S. women—had more diverse microbiomes and

higher amounts of detectable SCFAs than their respective U.S. counterparts who ate diets higher in protein and lower in fiber. Also, the Ghanaian women with lean body types had microbiomes that formed the most densely interconnected bacterial networks compared to the rest of the study population; the researchers also estimated, with computer modeling, that the Ghanaian microbiomes were more stable and resistant to disruption. To determine how this affects health, the researchers inoculated male mice, which had been treated with antibiotics to deplete their native gut bacteria, with samples of the microbiomes from each group of women (those from the United States or Ghana, and with lean or obese body types). The mice that were given samples of the microbiome from a Ghanaian woman with a lean body type were significantly more resistant to weight gain when fed an obesity-inducing high-fat diet for 6 weeks, compared to the mice harboring the microbiomes from the other groups of women. These obesity-resistant mice also made higher levels of a molecule that interacts with SCFAs, suggesting that bacterial-derived SCFAs may be involved in preventing weight gain in these mice.

Rather than pointing to individual types of bacteria, this was the first study to implicate the characteristics of the entire microbiome network—including how the many types of bacteria in the microbiome relate to each other—in metabolic conditions like obesity. This could be important for future studies to determine the best ways to manipulate the microbiome to improve health.

Dugas LR, Bernabé BP, Priyadarshini M,...Layden BT. Decreased microbial co-occurrence network stability and SCFA receptor level correlates with obesity in African-origin women. [Sci Rep](#) 8: 17135, 2018.

BRAIN DEVELOPMENT AND BODY WEIGHT

Wired for Obesity: How Genes Involved in Brain Development Affect Body Weight: Researchers have identified key genes that guide brain circuit development and link this process to body weight regulation. It is known that a part of the brain called the hypothalamus plays a critical role in body weight regulation. But, the exact molecules involved remain unclear.

In this study, scientists investigated the role of a group of molecules called semaphorins, which are

abundant in the hypothalamus during development and are released by brain cells, allowing them to communicate with other brain cells. The researchers first tested DNA samples from children and adults (male and female) and found that individuals with severe early-onset obesity had mutations in several genes involved in semaphorin signaling pathways. These mutations are rare, but, collectively, appeared more frequently in the people with severe early-onset obesity than in healthy individuals. To investigate the role of semaphorins further, they used a zebrafish model to test whether altered semaphorin signaling in the hypothalamus influenced body weight. They found that deletions in seven of the genes that code for semaphorins, or proteins they interact with, caused weight gain and/or an increased percentage of body fat. In addition, deletion in two other genes decreased zebrafish body fat percentage. These results suggest that disruption of semaphorin signaling pathways has an impact on energy balance, or the relationship between calories consumed and calories burned. Next, studying mouse hypothalamic cells in laboratory culture dishes with other cells that had normal or mutant semaphorin genes, they found that several semaphorin gene variants stunted the outgrowth of projections from the hypothalamic cells, preventing cells from growing properly and forming appropriate cellular connections. Lastly, the researchers genetically modified mice to deplete the protein “receptor” on the surface of hypothalamic brain cells on which semaphorins exert their effects. Hypothalamic cell cultures from the male mice that were studied showed that genetic loss of semaphorin action through loss of the receptor blocked the outgrowth of cell projections, suggesting a role of semaphorin signaling in the formation of connections between cells in the brain. Moreover, the genetically modified mice had significantly higher body weights and reduced energy expenditure (calorie burning) compared to their normal littermates.

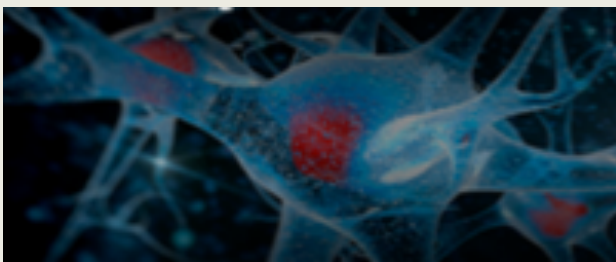
Taken together, these results suggest that semaphorin signaling plays a role in the connections between different brain regions and the development of brain circuitry that governs body weight. Further studies on human semaphorin gene variants could inform our understanding of obesity in people and possibly lead to prevention and treatment strategies.

van der Klaauw AA, Croizier S, Mendes de Oliveira E,...Farooqi IS. Human semaphorin 3 variants link melanocortin circuit development and energy balance. [Cell](#) 176: 729-742, 2019.

Beyond the Scale: Understanding Weight Gain—and Regain—from Studies of Body and Mind

NIDDK convened experts from across the country for three workshops in 2019 on challenges and opportunities in obesity research. An April workshop focused on novel technologies for brain imaging, to understand the brain's complex roles in obesity and diabetes. At a workshop in May, researchers explored challenges in measuring body fat and other tissues in infants and young children. At a June workshop, researchers presented studies of both body and mind that are illuminating why it is so difficult to maintain a healthier weight after weight loss.

Neuroimaging and Modulation in Obesity and Diabetes Research 10th Anniversary Meeting, April 16-17, 2019: Focusing on cutting-edge technologies for brain imaging and related studies, researchers at the workshop reviewed the progress over the past 10 years, new technologies on the horizon, and potential future directions. The broad range of topics included, for example, the roles of different parts of the brain in appetite suppression and motivation for eating, deep brain stimulation as a potential therapy for a particular type of overeating, obesity-associated impairments in memory and cognition, and brain imaging studies of appetite in children.

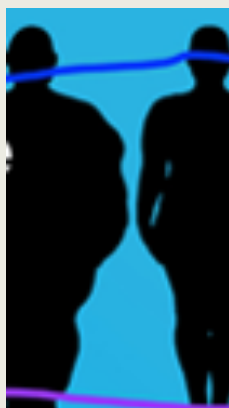


Body Composition Measurements from Birth through 5 Years Workshop, May 30-31, 2019: Because obesity often begins in childhood, it is critical to be able to measure body composition—the amounts of fat, other tissues, and water in the body—in very young children. Such measures are useful for understanding and predicting health risks and evaluating potential therapies. However, a simple scale does not give sufficient information, and

there are unique challenges to body composition measurements in very young children. For example, babies and toddlers typically cannot stay still long enough for accurate measures using technologies that measure fat and lean tissue. At this workshop, researchers discussed emerging technologies and research opportunities.

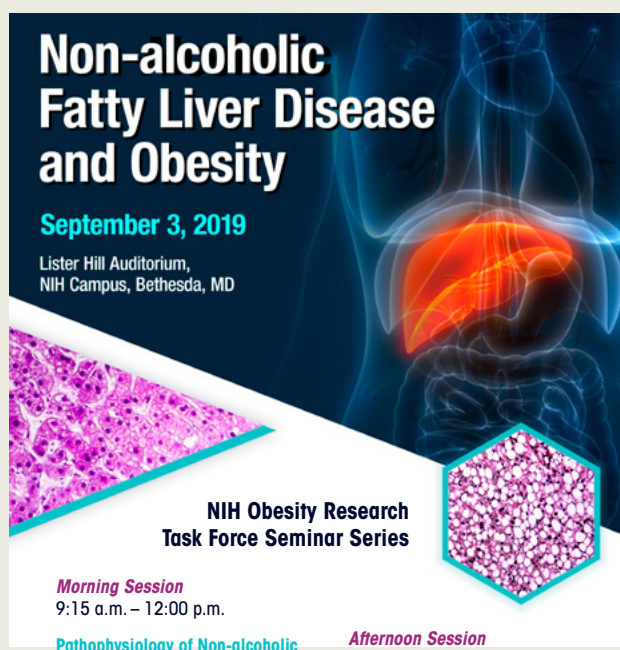


The Physiology of the Weight Reduced State Workshop, June 3-4, 2019: While many people can lose some excess weight over the short term, a majority have trouble maintaining that weight loss, even with persistent efforts. While some challenges come from living in an environment that promotes unhealthy eating and sedentary behavior, there are also physiological changes that occur after weight loss that lead to increased appetite and reduced calorie burning. At the workshop, researchers presented studies of molecular and cellular pathways in the brain and body that contribute to regain of lost weight;



potential strategies to reduce weight regain after lifestyle interventions, bariatric surgery, and weight-loss medications; and differences between individuals in weight loss and regain. The researchers also explored opportunities for future research that could lead to more effective and lasting obesity treatments.

NIH Seminar Series: Nonalcoholic Fatty Liver Disease and Obesity



The liver is the largest internal organ and a true workhorse within the body. Among its many jobs are converting food into fuel, processing fat from the blood, and clearing harmful toxins. Due to its central role in metabolizing nutrients, this hard-working organ is also susceptible to a condition called nonalcoholic fatty liver disease (NAFLD). NAFLD is a condition in which excess fat is stored in the liver of people who drink little to no alcohol. It is rapidly becoming the most common form of chronic liver disease worldwide, due in part to the increasing prevalence of obesity, although not all people with overweight or obesity develop this condition. Approximately one-third of adults in the United States have NAFLD, and the majority of this group have a condition called simple fatty liver, in which fat has accumulated in the liver, but there are no signs of inflammation or damage.¹ However, in some people with NAFLD, the condition progresses to a more dangerous form called nonalcoholic steatohepatitis, or NASH, that is characterized by inflammation and liver cell damage that can lead to cirrhosis or liver cancer.

Given how common NAFLD is and that the only recommended therapy is weight loss through diet and exercise, the research community recognizes the need to accelerate development of new and innovative treatments for NAFLD and obesity and to close knowledge gaps with the goal of translation

into more effective patient care. To that end, four leading scientists highlighted their research on NAFLD and obesity at a September 2019 symposium at the NIH campus in Bethesda, Maryland. Dr. Averell Sherker from the NIDDK moderated a panel discussion following the presentations. The research presented was supported by NIDDK among other Institutes. The seminar was organized as part of the NIH Obesity Research Task Force Seminar Series.

Dr. Natalie Torok from Stanford University presented her research focusing on the molecular mechanisms behind the development of NASH and the role of factors such as age and diet in disease processes. Her group studies young and older mice fed either a typical chow diet or a diet that mimics a fast-food diet consumed by humans that can induce insulin resistance and/or liver disease. In this model, Dr. Torok's team found that specific molecules become activated in the livers of older mice on a fast-food diet; these molecules are known to mediate "oxidative stress" pathways that can cause cell and tissue damage. This discovery could lead to future therapies that specifically target these molecules and pathways.

Dr. Hashem El-Serag from the Baylor College of Medicine summarized his studies on the epidemiology of NAFLD in U.S. adults. Through research conducted using data from the national Veterans Affairs health care system, Dr. El-Serag and his team determined that the prevalence of NAFLD more than doubled from 2003-2011.² Dr. El-Serag went on to describe how NAFLD is more common in Hispanics and less common in African Americans. There are several established risk factors, including obesity, hypertension, metabolic syndrome, and type 2 diabetes—in fact, globally, NAFLD is estimated to affect more than half of people with type 2 diabetes.³ Due to the rising prevalence of NAFLD, cirrhosis and liver cancer are also on the rise. Future research could help to ameliorate this trend.

¹ Spengler EK and Loomba R. *Mayo Clinic Proceedings* 90: 1233-1246, 2015.

² Kanwal F, et al. *Clin Gastroenterol Hepatol* 14: 301-308, 2016.

³ Younossi ZM, et al. *J Hepatol* 71: 793-801, 2019.

NAFLD does not just affect adults, but also children. Research suggests that 10 percent of U.S. children ages 2-19 years have NAFLD; prevalence is higher in males.⁴ Dr. Jeffrey Schwimmer from the University of California San Diego has focused his research on the prevalence, diagnosis, and treatment of this condition in children and teens. Like adults, obesity and type 2 diabetes are risk factors for children, and Dr. Schwimmer's research suggests early screening and diagnosis are crucial for better outcomes in adulthood. Moreover, his research indicates that diet plays a big role: a low-sugar diet compared to a standard diet resulted in significant improvement in liver disease in a group of adolescent boys. These findings are preliminary, and further research is necessary to evaluate long-term outcomes.

Dr. Yaron Rotman from the NIDDK Division of Intramural Research concluded the series of presentations by describing his research on current and emerging therapies to treat NAFLD. Lifestyle interventions through healthy diet and exercise remain the standard of care, although there is little consensus among health care providers about which diet to recommend for this condition.

In fact, a 10 percent reduction in body weight can resolve NASH. For this reason, bariatric surgery is also an effective option. Dr. Rotman went on to describe several investigational pharmacological therapies, many of which target liver-specific proteins and pathways. While some treatments currently in development result in some positive outcomes, they also raise concerns such as insulin resistance, increased blood lipid profiles, and safety at effective doses. This remains an area of research that is ripe for innovation, and the "magic pill" could possibly involve a combination of medication and lifestyle changes tailored for an individual's needs—personalized medicine.

The seminar concluded with a discussion among participants of current challenges and opportunities in this field. Continued research in this important area can potentially reveal better ways to prevent, diagnose, and treat this increasingly common and chronic form of liver disease.

⁴ Schwimmer JB, et al. *Pediatrics* 118: 1388-1393. 2006.