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Obesity

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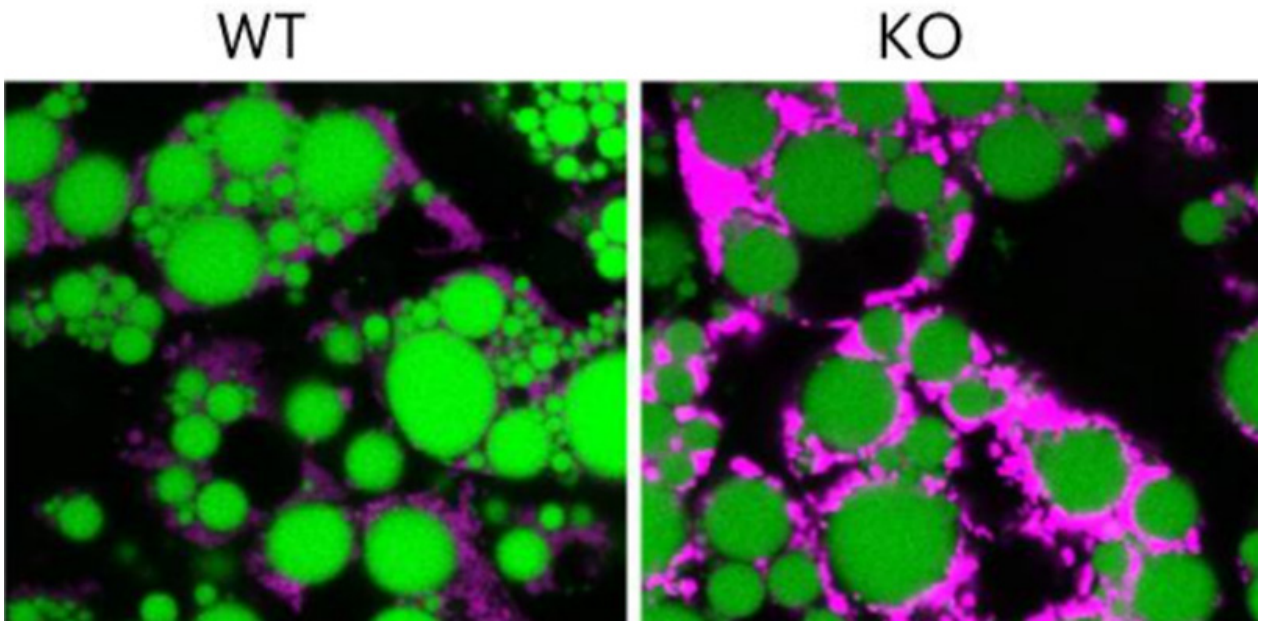

Mitochondria—specialized cellular structures that burn fuel to produce energy—naturally fragment or fuse together as they adjust their activity. Previous research showed that during obesity, fat cells' mitochondria excessively fragment and burn cellular fuel less efficiently. As summarized in this chapter, researchers studying obesity in mice found that the protein RalA is a key link between mitochondrial health and fat cell metabolism. Male mice genetically engineered to lack RalA in their fat cells stayed leaner than their normal counterparts when fed a high-fat diet. The scientists then compared fat cells adapted to cell culture from either normal female mice (labeled above as WT) or female mice engineered to lack RalA (KO). Mitochondrial activity (pink) and fat droplets (green) within the cells were visualized via fluorescent microscopy. As shown above, fat cells from mice lacking RalA had higher mitochondrial activity compared to those from normal mice. Further experiments confirmed that RalA represses fat cell metabolism by disrupting mitochondrial function, shedding new light on how metabolism changes—and how fat accumulates—during obesity.

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 NIDDK's mission. Approximately 40 percent of U.S. adults are considered to have obesity based on body mass index (BMI), a measure of weight relative to height.[1,3] 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.[2,4] 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 biological 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. NIDDK supports a multidimensional research portfolio on obesity, spanning basic, clinical, and translational research. This research is coordinated through NIDDK's Office of Obesity Research and supported by NIDDK's Division of Diabetes, Endocrinology, and Metabolic Diseases and Division of Digestive Diseases and Nutrition. 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.

Approximately 40 percent of U.S. adults and nearly 20 percent of children and adolescents have obesity.

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.

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[1] *Emmerich SD, et. al. September 2024. Centers for Disease Control and Prevention. National Center for Health Statistics Data Brief No. 508.*

[2] *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.*

[3] *Although higher BMI levels generally reflect higher levels of body fat on a population level, BMI does not directly measure body fat or take into consideration age, biological sex, or health risks of populations other than non-Hispanic White.*

[4] *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).*

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.

TIMING MEALS TO IMPROVE HEALTH

When to Eat, Not What to Eat: Time-Restricted Eating Without Calorie Counting for Weight Loss in People With Type 2 Diabetes: In a study to evaluate weight-loss interventions, researchers found that time-restricted eating (TRE)—restricting the time of day for food intake but not the amount or types of food—was effective for weight loss and lowering blood glucose (sugar) levels compared to daily calorie counting in adults with type 2 diabetes and obesity. Weight loss is recommended for people with excess weight and type 2 diabetes, but calorie-restricted diets can be difficult to maintain. Very few TRE studies have been done in adults with type 2 diabetes, and they only followed the participants for short periods of time. Thus, the researchers conducted a 6-month clinical trial comparing the effects of TRE to calorie restriction on body weight and blood glucose levels in a racially diverse group of adults with type 2 diabetes and obesity.

Researchers found that time-restricted eating was effective for weight loss and lowering blood glucose levels compared to daily calorie counting in adults with type 2 diabetes and obesity.

The researchers recruited 75 study participants, most of whom were Hispanic or non-Hispanic Black—two of the racial and ethnic groups with the highest prevalence of type 2 diabetes in the United States. In addition, most participants were women. Participants were randomly assigned to one of three diet groups: a TRE group where participants could eat anything they want, but only between the hours of noon to 8 p.m.; a calorie-restricted group of participants who consulted with a dietician to reduce their calorie intake by 25 percent; and a control group of participants who were instructed to maintain their weight and usual diet and exercise routines. After 6 months, the TRE group lost an average of 3.6 percent of their body weight compared to the control group. By comparison, the calorie-restricted group did not lose a significant amount of weight compared to the control group. Both the TRE and calorie-restricted groups experienced similar reductions (improvements) in blood glucose levels. No adverse events were reported in the study, and the TRE group relayed that their diet was easier to maintain than calorie counting. The researchers note that some medications used to treat diabetes may need to be adjusted while adopting a TRE regimen. Therefore, people considering this dietary approach should consult their physician.

These encouraging results demonstrate the health benefits of adopting a TRE strategy for weight management in adults with type 2 diabetes. Because the research on TRE is still limited, more studies are needed to fill critical knowledge gaps to improve the health of all people with type 2 diabetes, especially the health of groups with a particularly high prevalence of the disease.

Pavlou V, Cienfuegos S, Lin S,...Varady KA. Effect of time-restricted eating on weight loss in adults with type 2 diabetes: A randomized clinical trial. JAMA Network Open 6: e2339337, 2023.

INVESTIGATING MECHANISMS UNDERLYING EFFECTS OF OBESITY MEDICATIONS

New Discovery Could Help Reduce Side Effects of Next-Generation Obesity Medications: By studying the effects of next-generation obesity medications on the brain in mice, researchers discovered that the therapeutic benefits of the medications can be uncoupled from the side effects because different populations of brain cells control food intake and nausea. The most effective weight-loss drugs are the long-acting "GLP-1 receptor agonists," such as semaglutide (marketed as Ozempic® and Wegovy®) and tirzepatide (marketed as Mounjaro® and Zepbound®), which can result in an impressive reduction in body weight that is thought to occur, in part, via the drugs' actions in the brain to suppress food intake. However, nausea is by far the most common side effect of GLP-1 receptor agonists, with up to 60 percent of participants in clinical trials reporting this adverse event, and many people discontinue the medications because of it despite their effectiveness at reducing appetite and increasing fullness. Since it is unknown whether the unpleasant side effects contribute to the drugs' efficacy, the researchers investigated the physiological relationship between feeling satisfied after a meal versus food avoidance due to feeling nauseous.

In a series of sophisticated experiments in male and female mice, the researchers found that two areas in a part of the brain called the hindbrain have protein receptors on cells that become activated in response to GLP-1-based drugs. Because GLP-1 receptor agonists cause both a feeling of satisfaction after eating and nausea, they analyzed responsivity to a nutrient-rich food source or a nausea-inducing agent in different groups of mice. Unexpectedly, they discovered that individual cells mediating the two effects are different. Using imaging techniques in live, anesthetized mice, they found that most individual cells in these areas react to nutrient-rich stimuli or unpleasant stimuli, but not both. Moreover, the researchers found that cells in one of the two areas respond more to unpleasant stimuli, while cells in the other area respond to food stimuli. By separately manipulating the two different groups of cells to understand their effects on behavior, they found that stimulating cells in one area led to the mice feeling full (waiting longer between meals) with no nausea, while stimulating cells in the other area caused a strong adverse reaction. Importantly, the obesity drugs reduced food intake even when the cells that respond to unpleasant stimuli were inhibited, meaning that the two different pathways can be successfully separated.

By studying the effects of next-generation obesity medications on the brain in mice, researchers discovered that the therapeutic benefits of the medications can be uncoupled from the adverse side effects because different populations of brain cells control food intake and nausea.

This study demonstrates that separate brain regions mediate different effects of the same drug. And because nausea is a side effect of many treatments for multiple diseases, this concept could be applied to investigate therapies beyond those for obesity with a goal of developing more targeted drugs that treat disease but avoid negative side effects.

Huang KP, Acosta AA, Ghidewon MY,...Alhadeff AL. Dissociable hindbrain GLP1R circuits for satiety and aversion. Nature 632: 585-593, 2024.

A Link Between Weight-Loss Medication and the Hormone Leptin: Seeking insight into how some obesity and diabetes medications work, researchers discovered that the diabetes and obesity drug liraglutide directly reduces levels of the hormone leptin, and that leptin reduction may be a prime mechanism underlying the subsequent weight loss and improved blood glucose (sugar) and liver measures in mice. This finding may lead to the development of new therapies that specifically target leptin reduction. Previous research showed that leptin is secreted by fat cells, and among its many functions, leptin, at normal levels found in lean individuals, regulates hunger to help limit food intake to what the body needs. However, there can be too much of a good thing—leptin levels are proportional to fat mass and are very high in obesity, but the elevated levels of this hormone do not dampen appetite; instead, the body becomes resistant to leptin. In fact, scientists recently found that very high leptin levels may help drive weight gain in mice, and, surprisingly, reducing leptin levels leads to weight loss.

For the current study to examine leptin levels during liraglutide treatment, the researchers gave a high-fat diet to male mice to induce obesity, and then administered liraglutide to some of the mice. Compared to mice that did not get the drug, those on liraglutide ate less, lost weight, and had lower leptin levels. To determine whether leptin reduction was a cause or result of weight loss from the drug, the researchers adjusted leptin levels by other means. With one experimental technique, they reduced the amount of leptin even further in mice given liraglutide, and they found that these mice lost even more weight. Conversely, when they used another technique to keep leptin levels abnormally high even in the presence of liraglutide, the mice did not lose as much weight. The researchers concluded that leptin reduction was a mechanism by which the drug caused weight loss. In other analyses, they found that reducing leptin levels in the mice also improved blood glucose levels and markers of liver fat and fibrosis—conditions associated with obesity. Additionally, the researchers saw similar leptin-dependent effects when they treated obese mice with a different weight-loss agent (a drug candidate under development).

This study in mice demonstrates that reducing high leptin levels is key to the benefits of an approved weight-loss and diabetes drug (liraglutide) and one under development. If future research shows similar effects in people, this study may lead to new strategies to target leptin for treating obesity and related metabolic disease.

Zhao S, Li N, Xiong W,...Scherer PE. Leptin reduction as a required component for weight loss. Diabetes 73: 197–210, 2024.

EXPLORING NEW, PRAGMATIC APPROACHES TO TREAT OBESITY

Automated, Online Obesity Treatment and Weight Maintenance Program for Primary Care: Researchers found that adults with overweight or obesity achieved and maintained modest but clinically significant weight loss over 2 years using an automated, online behavioral treatment program that was implemented in a primary care network without need for clinician involvement. Behavioral weight-loss programs, with strategies for modifying diet and physical activity, are a first-line treatment for obesity and are also recommended to accompany obesity medication or surgery. However, many clinicians do not have the training, time, or resources for such programs, and people often regain pounds they lost.

For the current study, the researchers designed and tested an automated, online combination of weight-loss and weight-maintenance programs that did not require interactions with clinicians or the researchers, and thus could be implemented broadly in primary care practices. They recruited adults with overweight or obesity from a large primary care network. The average age of the study volunteers was about 53 years old; 71 percent were women, and 94 percent were White. All participants were first offered a 3-month online weight-loss program, which included goals for calorie intake and physical activity; weekly video lessons on problem solving and other strategies; self-monitoring of weight, calories, and physical activity; and automated feedback. Subsequently, the researchers randomly assigned participants to one of three online, 9-month weight-maintenance programs: Two involved different schedules of lessons and self-monitoring, and the third was a control program with newsletters. The researchers tracked participants' weights from electronic medical records. They also monitored usage of the online programs, and found that 253 participants, or just under half of those who had volunteered, used both the weight-loss and weight-maintenance programs. These participants lost an average of 13.6 pounds from the 3-month weight-loss program, and by the end of the 2-year study, individuals in the control maintenance group had gained back about 9.6 pounds, while those in the weight-maintenance programs with lessons and self-monitoring regained only 3 to 5 pounds. Further analyses showed that participants who viewed more of the online lessons and self-monitored for more days had less weight regain.

Researchers showed that adults with overweight or obesity lost a modest but clinically significant amount of weight over 2 years from a combination of automated, online weight-loss and weight-maintenance programs implemented in a large primary care practice.

This pragmatic study shows that an automated online weight-loss program followed by a weight-maintenance program for adults leads to modest but clinically significant weight loss over 2 years, among those who continued to engage with the maintenance program, without need for healthcare provider involvement in delivering the programs. Future research could explore approaches for reaching more diverse populations and for increasing use of this type of online weight-loss and weight-maintenance program.

Thomas JG, Panza E, Goldstein CM,...Wing RR. Pragmatic implementation of online obesity treatment and maintenance interventions in primary care: a randomized clinical trial. JAMA Intern Med 184: 502-509, 2024.

UNDERSTANDING MOLECULAR REGULATORS OF METABOLIC HEALTH

Researchers Elucidate Pathway Linking Obesity, Metabolism, and Mitochondria: New research in mice has shed light on a biological pathway regulating how a high-fat diet and obesity modify mitochondria in fat cells, disrupting metabolism and leading to fat accumulation. Mitochondria are cellular structures that burn fuel to produce energy, and disrupting this function is linked to insulin resistance, a condition in turn linked to development of type 2 diabetes. Mitochondria naturally modify their structure by elongating, fusing, and fragmenting, which also modifies their function to adapt to the body's needs. During obesity, however, fat cells' mitochondria excessively fragment and burn cellular fuel less efficiently, though why and how has been unclear.

Scientists studying the underpinnings of obesity discovered that production of a protein called RalA was increased in fat cells of obese male mice fed a high-fat diet compared to those of mice on a standard diet. RalA was known to be involved in both glucose (sugar) uptake in fat tissue and in managing mitochondrial fragmentation when needed by cells. To investigate if RalA was a missing link between mitochondrial health and fat cell metabolism, the researchers genetically engineered mice to lack RalA in their fat cells. When fed

a high-fat diet, male mice lacking RalA stayed leaner than their normal counterparts, had better glucose and insulin responses, and were protected from obesity-related liver fat accumulation and inflammation. In investigating the causes of these changes, the scientists found that lack of RalA in fat cells resulted in less mitochondrial fragmentation, leading to improved mitochondrial function and increased energy (calorie) burning. Further experiments confirmed that RalA is a key regulator in a biological pathway that controls the protein Drp1, a molecular switch regulating mitochondrial fragmentation, which affects energy burning in fat cells and, by extension, fat accumulation. Analyses of gene activity in men and women with and without obesity revealed that increased levels of the human version of Drp1 correlated with obesity, further suggesting that RalA and Drp1 are important metabolic regulators.

Researchers found that the protein RalA connects metabolic and mitochondrial pathways in mice, highlighting possible new targets for obesity treatments.

Many questions remain about how RalA and Drp1 function in fat cell metabolism and human obesity. However, these findings provide new insight into how metabolism is repressed during chronic obesity and may yield new targets for obesity treatments focused on controlling mitochondrial function.

Xia W, Veeragandham P, Cao Y,...Saltiel A. Obesity causes mitochondrial fragmentation and dysfunction in white adipocytes due to RalA activation. Nat Metab 6: 273-289, 2024.

Specialized Immune Cells Can Contribute to Obesity-Associated Inflammation and Metabolic Dysfunction: Researchers have discovered a way that certain immune cells work to keep fat tissue healthy, as well as a protein that hinders this process, leading to inflammation and metabolic dysfunction associated with obesity. An increase in fat tissue arising from excessive intake of calories, or overnutrition, is known to activate a normal process whereby specific immune cells are recruited to remove dying and dead fat cells, and this process helps promote formation of new, metabolically healthier fat cells. However, chronic overnutrition can result in obesity and a persistent immune response and inflammatory state without removal of dying or dead fat cells, leading to metabolic dysfunction. The balance between normal fat cell turnover and an abnormal inflammatory response has been poorly understood.

To investigate this complex process, using genomic analysis and other techniques, the researchers identified TM4SF19 as a protein whose levels are significantly increased in specialized immune cells associated with fat tissue from male mice fed a high-fat diet and from people with obesity, compared to their lean counterparts. Further experimentation using laboratory-grown immune cells revealed that TM4SF19 localizes to a cellular compartment called a lysosome that removes dying and dead fat cells through an acidification process. Additional analysis in cells to explore TM4SF19's biological function showed that the protein acts within the lysosome to repress normal acidification. Based on this result, the researchers postulated that TM4SF19 behaves as a brake, hindering clearance of dying and dead fat cells. As anticipated, deletion of TM4SF19 in immune cells increased their capacity to remove dead fat cells. Next, they examined the effects of genetic deletion of TM4SF19 in mice that were fed a high-fat diet. They observed a reduction in fat tissue–associated immune cell accumulation and a restoration of normal fat cell turnover. In addition, they observed decreases in the activity of genes associated with pro-inflammatory responses. In mice fed a high-fat diet, those lacking TM4SF19 gained less weight and were protected from obesity, compared to their normal counterparts on the same diet. Finally, on a high-fat diet, mice without TM4SF19 had improved glucose (sugar) tolerance, insulin sensitivity, and calorie burning compared to mice that had this protein and exhibited insulin resistance, indicating that repressing tissue inflammation by removing TM4SF19 improves metabolic functions.

These results shed new light on how chronic overnutrition can result in an abnormal and persistent immune response that can lead to metabolic dysfunction. Further investigation is needed to fully characterize TM4SF19's role in this process and potentially develop targeted treatment strategies for obesity-induced inflammation and metabolic disorders.

Choi C, Jeong YL, Park KM,...Lee YH. TM4SF19-mediated control of lysosomal activity in macrophages contributes to obesity-induced inflammation and metabolic dysfunction. Nature Commun 15: 2779, 2024.

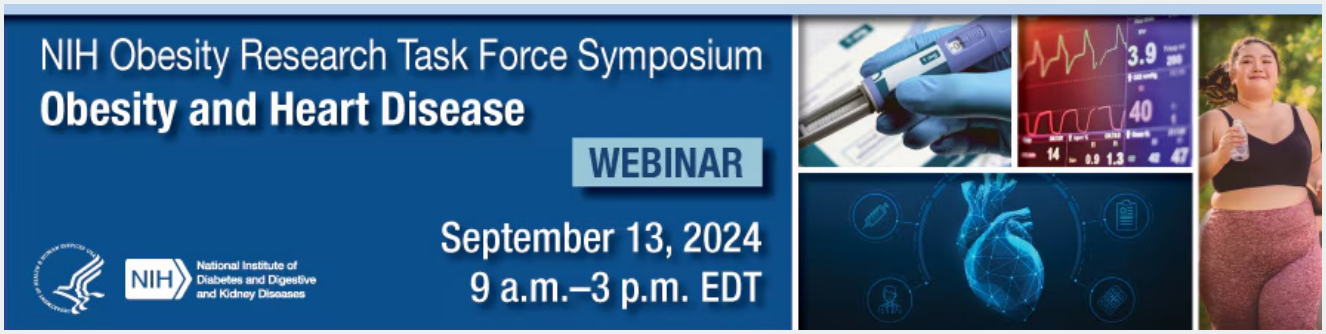
Identification of a Molecular Pathway in Brown Fat That Regulates Metabolic Health: Researchers have discovered a molecular pathway through which a beneficial type of fat called brown fat controls metabolic health independent of its ability to produce heat. The most well-established function of brown fat is

"thermogenesis," or heat production, which increases calorie burning. Studies in rodents have demonstrated that increased thermogenesis is associated with reduced body weight and improved blood glucose (sugar) levels. However, studies in people have shown that while brown fat is protective against type 2 diabetes, this protection is independent of calorie burning or body weight, and the reasons behind this dissociation are unclear. Recent reports have proposed various means by which brown fat affects metabolic health, including levels of molecules called "branched-chain amino acids," or BCAAs. Indeed, there is an association between elevated circulating levels of BCAAs and type 2 diabetes in people. Therefore, the researchers set out to better understand how BCAAs might play a role in brown fat-mediated metabolic health.

Because one of the functions of BCAAs is to be imported into a cellular compartment in brown fat cells and broken down into smaller, beneficial molecules called metabolites, the researchers genetically deleted the carrier molecules necessary for this import, called MBCs, in male mice and measured effects on metabolism. Compared to their normal counterparts, mice lacking MBCs exhibited much higher levels of circulating BCAAs, decreased levels of BCAA-derived metabolites, increased blood glucose levels, and insulin resistance (a condition related to diabetes) without changes in calorie burning or body weight. Further analysis revealed that the livers of mice lacking MBCs in brown fat exhibited reduced insulin signaling and elevated markers of "oxidative stress," which can cause cell damage, compared to normal mice. To determine how obesity impairs BCAA metabolism, the researchers fed normal mice either a standard diet or a high-fat diet and subsequently analyzed proteins in brown fat tissue. They identified numerous proteins involved in the breakdown of BCAAs that were substantially reduced in obese mice compared to standard diet-fed mice. Because exposure to cold temperatures activates brown fat, the researchers also examined how temperature affects the synthesis of BCAA metabolites and found that BCAA-derived metabolites were significantly enriched in brown fat from mice acclimated to cold temperatures, relative to fat tissue from mice housed at warmer temperatures. They also observed similar effects of cool temperatures in some men.

Taken together, these results unveil a previously unknown metabolite-mediated pathway through which brown fat controls metabolic health. Diet-induced obesity impairs the synthesis of these beneficial metabolites whereas cold temperatures increase it. Future research could further examine this pathway in humans and explore ways to increase BCAA breakdown in brown fat as a potential new strategy to treat metabolic disorders.

Verkerke ARP, Wang D, Yoshida N,...Kajimura S. BCAA-nitrogen flux in brown fat controls metabolic health independent of thermogenesis. Cell 187: 2359-2374, 2024.



NIH Obesity Research Task Force Symposium: Obesity and Heart Disease

Obesity rates continue to rise in the United States and worldwide. Obesity contributes to diseases of the heart, including cardiovascular disease (CVD), arrhythmias, and heart failure, which are often refractory to treatment. With increasing knowledge, there is real potential to vastly expand therapeutic options for obesity treatment, allowing for more personalized and effective approaches to heart disease prevention and care. To that end, seven leading scientists highlighted their research on the epidemiology and pathophysiology of obesity-related heart diseases, as well as the role of emerging therapeutics and issues related to prevention, access to treatment, and health equity at a September 2024 symposium organized as part of the NIH Obesity Research Task Force Seminar Series. The research presented was supported by NIDDK, other NIH Institutes, and other sources.

Dr. Sadiya Khan of Northwestern University presented her research on the epidemiology of CVD in persons with obesity. Obesity is a prevalent, costly, and chronic disease with significant disparities due to individual, interpersonal, and structural drivers, including racism. Obesity is associated with cardiovascular disease across the life course with implications for intergenerational transmission of risk and disparities. Dr. Khan discussed the American Heart Association PREVENT™ (Predicting Risk of cardiovascular disease EVENTs) risk calculator, a novel measure that recognizes the pathophysiological interrelatedness of obesity, diabetes, kidney disease, and CVD and estimates the 10- and 30-year risk of total CVD for people aged 30 years and older. The equations are sex-specific and race-free, acknowledging that race is not a biological factor, and can include an index of social determinants of health. Dr. Khan concluded her talk by noting that future directions should include improved assessment of body fat beyond BMI, and prioritizing implementation and policy interventions early in the life course to mitigate disparities and intercept this growing public health crisis.

Dr. Philipp Scherer of the Touchstone Diabetes Center at the University of Texas Southwestern Medical Center presented his work on fibrosis—an inflammatory condition that occurs when tissues thicken, harden, or scar in the context of obesity and other conditions—as a final pathway for cardiovascular-kidney-metabolic disease. GLP-1 receptor agonist drugs are highly effective at producing weight loss. However, even after the weight

is lost, there can be residual tissue fibrosis, which can lead to cardiovascular-kidney-metabolic disease. Dr. Scherer went on to discuss the correlation between a circulating molecule in the blood and fibrosis in various tissues including heart, kidney, and liver—the higher the levels of the molecule, the more fibrosis. Neutralizing the molecule can help reduce disease progression and mortality. This continues to be an active area of research for Dr. Scherer and colleagues.

Dr. Alvaro Alonso of Emory University presented his research on obesity and cardiac arrhythmias, including atrial fibrillation and sudden cardiac arrest. Atrial fibrillation (AF) is an arrhythmia characterized by rapid and irregular atrial activation in the heart, and it is linked to increased risk of stroke, heart failure, dementia, and increased mortality. Sudden cardiac arrest (SCA) is the sudden cessation of cardiac mechanical activity that, without intervention, progresses to sudden cardiac death (SCD). Obesity is an established risk factor for AF and SCA. Dr. Alonso explained that while research shows that weight gain may increase the risk of AF, there is no clear evidence that nonsurgical weight loss altered AF incidence. Interestingly, bariatric surgery, compared with nonsurgical weight management, is associated with a significantly lower risk of AF. There is no evidence that weight loss alters the risk of SCD. In addition, treatment with GLP-1 receptor agonists has no significant effect on arrhythmia risk. Dr. Alonso concluded his talk by citing several knowledge gaps that continued research in this area could help fill, including mechanisms linking obesity and arrhythmia risk and precision interventions to mitigate arrhythmia risk in people with obesity.

Dr. Michael Lincoff of the Cleveland Clinic presented his work on GLP-1 receptor agonist-based therapies in the prevention of CVD with a focus on results from the Semaglutide Effects on Cardiovascular Outcomes in People With Overweight or Obesity (SELECT) trial, a randomized controlled trial (RCT) looking at the effects of the GLP-1 receptor agonist semaglutide on cardiovascular outcomes in people with overweight or obesity. SELECT trial investigators found that in people who had preexisting CVD and overweight/obesity but did not have type 2 diabetes, a weekly dose of semaglutide was superior to a placebo in reducing the incidence of major adverse cardiovascular events including nonfatal stroke and death. Moreover, people treated with semaglutide had lower rates of death driven by cardiovascular and non-cardiovascular causes, including from COVID-19 infection. There were no increased risks for serious adverse events with semaglutide compared to placebo. Dr. Lincoff noted that semaglutide is the first weight management therapy proven in a rigorous RCT to reduce the risk of major cardiovascular events in people with CVD, establishing overweight/obesity as a modifiable risk factor for such events.

Dr. Barry Borlaug of the Mayo Clinic presented his research on the pathophysiology and treatment for people with obesity and heart failure with preserved ejection fraction (HFpEF, a clinical syndrome in patients with heart failure and dysfunctional filling pressures in the heart chambers). Obesity is a major risk factor for HFpEF, especially in women; it is increasing in prevalence; and it is associated with a high symptom burden. Dr. Borlaug presented results from a clinical trial that examined the effects of semaglutide treatment in people with obesity and HFpEF. Semaglutide treatment led to larger reductions in symptoms and physical limitations, greater improvements in exercise, and greater weight loss than a placebo. In a similar study, treatment with semaglutide in patients with obesity-related HFpEF and type 2 diabetes led to similar results. Dr. Borlaug concluded his talk by noting that the pathophysiology of HFpEF is complex, and there is evidence demonstrating the fundamental role for weight loss as an effective treatment for patients with HFpEF.

Dr. Imo Ebong of the University of California, Davis, presented her work on the role of obesity on CVD risk in women. Women are disproportionately affected by the obesity epidemic and are at higher risk of developing CVD in the context of obesity and insulin resistance. The prevalence of obesity is higher among non-Hispanic Black women compared to other ethnic groups, and Black women have a higher association of obesity and CVD. Dr. Ebong presented

data demonstrating that excessive weight gain during pregnancy, gestational diabetes, and hormonal changes during and after menopause are all CVD risk factors in women. More body weight and excess abdominal fat predict higher levels of the hormone androgen during menopause, and this is associated with increased CVD risk. Dr. Ebong concluded her talk by emphasizing that obesity causes sex-specific risk factors for CVD in women through mechanisms that are unique to hormonal and reproductive status. However, obesity is a major modifiable risk factor that can be targeted to decrease the risk of CVD across all life stages in women.

Dr. Tiffany Powell-Wiley of the National Heart, Lung, and Blood Institute at the NIH presented her research on health disparities and health equity for patients with obesity and CVD. Dr. Powell-Wiley discussed a socio-ecological framework for cardiovascular-kidney-metabolic disease that considers individual predisposition; behaviors such as physical activity, diet, and sleep; relationships with friends, family, and peers; community, including the built environment and structural factors; and societal factors, including education, social needs, and access to health care. Dr. Powell-Wiley stressed the importance of reducing barriers to obesity treatment access. These barriers include weight bias and stigma that limit referral for treatment and place unnecessary burden on patients, limited insurance coverage for pharmacotherapies, and a limited number of obesity medicine specialists with cardiology subspecialty training. Dr. Powell-Wiley emphasized the need for policy implementation and interventions that address socioeconomic and environmental drivers of obesity in order to move toward equity-focused obesity prevention and treatment that can help mitigate the associated risk of cardiovascular-kidney-metabolic disease.

The symposium concluded with a lively panel discussion among speakers and participants on current challenges and opportunities. Continued research could reveal better strategies to prevent and treat obesity and heart disease.