Draft

Strategic Plan for NIH OBESITY RESEARCH

A Report of the NIH Obesity Research Task Force

TABLE OF CONTENTS

EXECUTIVE SUMMARY ii

DISCOVERIES AND NEW DIRECTIONS IN OBESITY RESEARCH 1

Epidemiology and Health Consequences of Obesity 1

New Scientific Opportunities, Renewed Commitment to Obesity Research 3

About *The Strategic Plan for NIH Obesity Research* 4

A Multi-faceted Approach to a Multi-faceted Problem 6

OBESITY RESEARCH ADVANCES AND OPPORTUNITIES 7

Discover Biological Mechanisms Regulating Energy Balance 8
Selected Research Advances and Challenges 8
Research Opportunities 9

Understand the Correlates, Determinants, and Consequences of Obesity 12
Selected Research Advances and Challenges 12
Research Opportunities in the Correlates and Determinants of Obesity 13
Research Opportunities in Understanding the Consequences of Obesity 14

Design and Test Interventions to Promote Healthy Weight 16
Selected Research Advances and Challenges 16
Research Opportunities 17

Conduct Dissemination and Implementation Research 20
Selected Research Advances and Challenges 20
Research Opportunities 21

Improve Measurement Tools, Technology, and Methods 24
Selected Research Advances and Challenges 25
Research Opportunities 25

INTEGRATION OF RESEARCH INTO PRACTICE 30

Examples of NIH Efforts to Apply Research Findings in Practice 30

Opportunities for Fostering the Uptake of Research Findings 31

CONCLUSION 32

EXECUTIVE SUMMARY

NOTE: The executive summary will be finalized and inserted after the public comment period.

DISCOVERIES AND NEW DIRECTIONS IN OBESITY RESEARCH

Obesity is a growing threat to health in the United States and around the world. Reducing the prevalence, incidence, and health impact of obesity requires a broad-based effort by many—government, the private and nonprofit sectors, healthcare professionals, community organizations, schools, businesses, and families.

The foundation of such a comprehensive effort is research conducted by a diverse scientific community to illuminate the causes and consequences of obesity, develop and test prevention and treatment strategies, and inform policy making and community efforts. The NIH supports such research with the aim of extending healthy life and reducing the burdens of illness and disability. Consistent with this mission, the *Strategic Plan for NIH Obesity Research* aims to serve as a guide to accelerate research that will lessen the personal and public health burdens of obesity.

Epidemiology and Health Consequences of Obesity

Obesity is a common medical disorder with serious consequences. At a fundamental level, obesity develops because of a mismatch in "energy balance": calories taken in from food and beverage exceed those expended in activity and metabolic functions—including growth in children, with resultant excess adipose tissue (body fat) storage. While obesity is defined as an excess of body fat, it is frequently assessed with the proxy of body mass index (BMI), a measure of weight relative to height that is practical to use in population-wide studies and in clinical and community settings.

A majority of the US adult population is overweight as defined by a body mass index, or BMI, of 25 kg/m^2 or greater, and more than one-third of adults are obese (BMI of 30 kg/m^2 or greater). More than 16 percent of children and adolescents are obese as defined as BMI at the 95th percentile or greater for age and sex*, a prevalence that has more than tripled over the past three decades. Additionally, the prevalence of extreme obesity (BMI of 40 or greater in adults and BMI ≥97th percentile for age and sex) in children has increased precipitously. Although recent data suggest that US obesity rates may be stabilizing in many population subgroups, BMI has increased in the population to such an extent that adults and children within the healthy weight range are a minority. Obesity prevalence rates have substantially increased throughout much of the developed and developing world. In developing countries in particular, obesity and undernutrition often coexist in proximity, especially in urban areas. Once established, obesity is difficult to reverse over the long term, so strategies to prevent its development are essential. In addition, safer, more effective and durable treatments are needed for individuals who are currently obese.

The rise in obesity prevalence has resulted in an increase in the myriad serious medical problems associated with excess body fatness†. For example, type 2 diabetes has increased

* For children and adolescents, the BMI percentiles are based on 2000 CDC growth charts. These revised growth charts incorporate smoothed BMI percentiles and are based on data from NHES II (1963 to 1965) and III (1966 to 1970), and NHANES I (1971 to 1974), II (1976 to 1980), and III (1988 to 1994). The CDC BMI growth charts specifically excluded NHANES III data for children older than 6 years.

† For the purpose of this document, examples of comorbid conditions are used to illustrate current or future research and are not intended to exclude the importance of other relevant comorbid conditions.

dramatically over the past decade: almost 13 percent of US adults aged 20 years and older have diabetes and an additional 30 percent are estimated to have pre-diabetes. An alarming recent development is the increasing number of children and adolescents, especially from racial and ethnic minority populations, diagnosed with type 2 diabetes.

Obesity is an important risk factor for cardiovascular diseases such as stroke and heart attacks and for other cardiovascular risk factors such as hypertension. Certain forms of cancer are associated with obesity. Non-alcoholic fatty liver disease, a consequence of obesity that can progress to cirrhosis, is increasingly diagnosed in both adults and children. Obesity increases the risk of many other disorders, including osteoarthritis and other musculoskeletal disorders, some autoimmune and allergic disorders, gastrointestinal diseases, gallbladder disease, kidney disorders, infertility and other disorders of the reproductive system, urinary incontinence, asthma, sleep apnea, and dementia. During pregnancy, maternal obesity has a deleterious impact on both the mother and fetus, increasing the risk of certain birth defects, gestational diabetes, and pre-eclampsia. Obesity is associated with psychiatric disorders, including depression and some eating disorders. Obesity significantly affects quality of life in children and adults, reducing their mobility and ability to carry out activities of daily living.

Obesity can have an adverse impact on access to healthcare, including preventive services and some diagnostic and therapeutic procedures. These disparities may contribute to the greater health risk conferred by excess body weight. Obesity also may affect the response to medications and other therapeutic interventions.

Not all obese individuals are equally susceptible to these health problems. Recently, a phenotype of apparently “metabolically healthy” obesity has been identified, in which individuals have increased body fat but are resistant to the development of conditions such as insulin resistance and other cardiovascular disease risk factors. Understanding not only which individuals are most at risk for (or protected from) obesity-related health conditions but also the mechanisms by which increased body fatness or body fat distribution does or does not contribute to disease in specific individuals or sub-groups can help target prevention and treatment strategies.

Obesity is more common in certain racial and ethnic minority populations, including African American and Hispanic/Latina women, American Indians/Alaska Natives, and Pacific Islanders. As a result, these populations also experience more obesity-related consequences and comorbidities. In Asians, the BMI underestimates adiposity; diabetes and other complications of obesity are seen at normal or minimally elevated BMI. The relationship between race and ethnicity and obesity is complex and needs to be better understood through untangling biological, environmental, and cultural pathways, as well as differential response to treatment.

Finally, obesity confers important social and economic costs. Weight stigma may contribute to reduced educational and employment opportunities. Socioeconomic status also confers disparate risk for obesity, as those who are poorer and/or less educated are more likely to be obese. The increasing medical costs attributable to obesity-related disorders play a significant role in burgeoning national healthcare costs, and obesity also contributes to lost work productivity.

New Scientific Opportunities, Renewed Commitment to Obesity Research

The pace of discovery in diverse areas of obesity research is rapid and accelerating. . Advances in areas ranging from basic biomedical and behavioral science through clinical and community studies have opened the door to new opportunities for both better targeted and more comprehensive approaches to obesity prevention and treatment. Just a few of the many examples of these advances are highlighted here.

Basic research has led to the development of new animal models, including some in which gene function is changed only in specific tissues, such as brain, liver, fat, or muscle. Using these animal models, scientists are gaining new insights into how genes and the proteins they encode may function and interact with each other in metabolism and weight regulation in people. Results of this research may lead to new therapeutic targets.

Studies of the complex signaling pathways within the brain and between the brain and other organs and tissues, such as the gut and fat tissue, are further elucidating appetite and energy expenditure regulation. For example, recent human brain imaging studies have demonstrated differences in brain structure and activity associated with obesity and weight loss. In genetics, new technologies allowing genome-wide association studies (GWAS) in humans have led to the identification of common genetic variants near or within genes previously unsuspected to be related to body weight. Although such genetic variants may predict only a small degree of variation in body weight, their identification provides new targets for investigations of gene function at both a metabolic and behavioral level. The combination of GWAS with deep DNA sequencing and high-throughput functional assays in areas such as gene expression or metabolomics in humans will lead to a greater understanding of how genetic variation leads to disease risk. Elucidation of the ways in which susceptibility or protective gene variants interact with environmental factors or drugs will provide an opportunity for personalized prevention and treatment strategies. Understanding epigenetic mechanisms regulating metabolic tissues and the role of environmental factors in modifying epigenetic states may lead to important discoveries about potentially preventable contributors to obesity.

Our understanding of environmental contributions to obesity is increasing at all levels, from the individual through society. In studies of environmental influences on obesity, technologies such as geographic information systems are now enabling targeted examination of the impact of the built environment on weight or physical activity. In addition, innovative methods to measure food intake and physical activity are allowing better measurement of energy balance in real-world settings. Emerging data on unique aspects of the gut environment suggest that gut microbes and their collective genomes, called the “microbiome,” may play a role in the development of obesity. Expanded knowledge about the microbiome’s role may someday permit prevention or treatment of obesity by manipulating the composition of this environment. Other environmental factors, such as exposure to infectious agents or environmental toxicants and the ambient temperature, have emerged as potential targets of interest in the study of obesity and its complications. Information regarding the impact of the intrauterine or neonatal environment is also leading to research aimed at modifying these environments to prevent later obesity—for example, by preventing gestational diabetes in the mother or by targeting factors to enhance optimal rates of weight gain in infancy and early childhood.

Research findings are yielding new and important insights about social and behavioral factors that influence diet, physical activity, and sedentary behavior. Research regarding social networks, decision making, behavioral economics, sensory input, and sleep patterns as they relate to weight may yield novel targets for intervention.

Advances in statistical and computational methodologies are emerging to help capture and illuminate the dynamic complexity of obesity and test the effects of intervention strategies on individual and societal outcomes. Policies such as mandated BMI screenings of school-age children, enhanced nutrition labeling of packaged foods and restaurant menu items, changes in vending machine options in schools or worksites, and incentives to purchase healthy foods are being implemented in communities across the country, and present a prime opportunity for research to evaluate their effects.

About *The Strategic Plan for NIH Obesity Research*

Given the importance of obesity as a public health problem and its relevance to the mission of most of the NIH Institutes, Centers, and Offices, NIH established an Obesity Research Task Force in 2003 to accelerate progress in obesity research across the NIH. The Task Force is co-chaired by the Director of the National Institute of Diabetes and Digestive and Kidney Diseases the Director of the National Heart, Lung, and Blood Institute, and the Director of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development. The members of the Task Force represent these and many other NIH Institutes and Centers with relevant expertise.

A key element of the initial charge to the Task Force was the development of a *Strategic Plan for NIH Obesity Research,* published in 2004. In light of the rapid progress in obesity research highlighted above and the opportunity to capitalize on emerging scientific discoveries, the Task Force decided to update the *Strategic Plan*.

Like the 2004 *Strategic Plan for NIH Obesity Research*, the 2010 *Strategic Plan* provides a guide for coordinating existing obesity research activities across the NIH. It also encourages the development of new research efforts.

The 2010 *Strategic Plan* is meant not to be all-inclusive or limiting, but to highlight areas of challenge and emerging opportunity. As new scientific opportunities arise from current research investments and accomplishments, the research planning process will build on these areas, thus accelerating research in the most promising directions.

As in the 2004 *Strategic Plan*, this revised *Strategic Plan* was informed by experts external to the NIH, who provide ongoing invaluable research planning advice at scientific meetings and workshops convened by NIH Institutes and Centers. In addition to this external advice, which will continue to inform the obesity research planning process, an initial version of the *Strategic Plan* has been circulated to individuals and organizations outside the NIH, including scientists with expertise in obesity research and leaders of voluntary and professional health advocacy organizations. Their comments have been incorporated into this revised draft. The draft is now posted on the Internet for public comment. The final *Strategic Plan* therefore will reflect the contributions of a wide range of individuals and groups.

Given the complex interaction between biology, behavior, and environment in contributing to the rise in obesity, formidable barriers stand in the way of simple solutions for altering energy balance toward a healthy body weight. Therefore, the *Strategic Plan* encompasses all levels of research, from basic biological and behavioral research through community and population research.

Cross-cutting Issues for Obesity Research

Integral to all areas of the *Strategic Plan* are cross-cutting issues including health disparities; the influence of sex and gender on biological determinants of obesity, diet, and activity; variations in response to treatment; developmental issues across the lifespan; and the needs of vulnerable and at-risk populations, including understudied populations such as racial and ethnic minority populations, older adults, populations with low literacy and numeracy, people with disabilities, rural populations, and those with extreme obesity.

The *Strategic Plan* places special emphasis on the following three areas that are increasingly recognized as essential to a vibrant and successful obesity research effort:

Translational Research

Translational research is a key element in meeting the public health challenge of obesity. Early translational research, sometimes termed "bench to bedside" research (i.e., from test tubes, mouse models, or basic behavioral studies to clinical studies), is crucial for identifying novel behavioral, environmental, social, and biological targets for obesity prevention or treatment and then translating these targets into approaches that can be tested for efficacy in controlled clinical trials. Early interaction between basic scientists and clinicians in developing, planning, and executing translational research may assist in consideration of important issues such as feasibility and potential for uptake in clinical care. "Bedside to bench research," brings knowledge gained in a clinical setting back to the laboratory for further mechanistic exploration that may in turn spur new clinical approaches. Translational research that helps speed these bidirectional and iterative knowledge transfers is important to ultimately improving the public health.

When intervention approaches are proven efficacious in a clinical trial setting, later phases of translational research (e.g., bedside to practice and the community) are needed to examine their effectiveness more broadly—that is, exploring how the interventions could be implemented cost-effectively in real-world populations, clinical practice, and community settings to achieve positive impacts on health. Later translational research addresses issues of feasibility, adaptation, generalizability, adoption, dissemination, implementation and sustainability in environments such as schools, community health centers, and worksites. Community-based translational research is one approach for addressing health disparities issues: for example, through research on culturally competent prevention, early intervention, and disease management strategies for diverse population groups. Community and population-based research also informs new targets for clinical research and practice.

Training

Strengthening and diversifying the pool of researchers who are dedicated to understanding and ameliorating obesity and its many adverse outcomes is a priority for NIH. This commitment includes attracting and training a cadre of researchers with a wide range of knowledge and skills, such as expertise in the basic, clinical, behavioral, and social sciences, epidemiology, cultural competency, measures and methods, interventions, and translation and dissemination. Training in innovative multidisciplinary areas, such as social networks and complex systems, would be useful. As a part of its commitment to supporting diversity in research, NIH will also continue to support and develop new ways to attract and train researchers from racially and ethnically diverse backgrounds.

Transdisciplinary Research

Meeting the obesity research challenges of the future will require transdisciplinary research teams that include the talents of many, such as basic and molecular scientists; geneticists; behavioral, clinical, environmental, and policy scientists; community leaders; industry partners; transportation scientists; and urban design experts. To foster this, NIH encourages integrated, cross-disciplinary thinking and hypothesis generation across the spectrum of obesity research, a commitment increasingly embraced by scientific, industry, academic and healthcare institutions and communities. This type of thinking can inform the ways in which component elements of multidisciplinary and multilevel approaches are integrated to determine best practices for optimal effectiveness of evidence-based programs.

A Multi-faceted Approach to a Multi-faceted Problem

A complicated interplay of environmental, social, economic, and behavioral factors, acting on a background of biologic mechanisms and genetic susceptibility, has fueled the increase in obesity prevalence. An appropriate response must be equally multi-faceted. Although prevention of obesity and its medical complications is the ultimate goal, the *Strategic Plan* recognizes that the current high prevalence of obesity in both adults and children highlights the need for research on treatment as well, including the comparative effectiveness of interventions delivered in settings such as primary care, specialized treatment centers, schools, and community settings.

Research leading to a better understanding of the many contributors to obesity in individuals and populations, the link between obesity and its associated health risks, and development of improved methods for prevention and treatment has the potential to help people to live longer and healthier lives. It is our hope that the *Strategic Plan for NIH Obesity Research* will help accelerate progress toward these goals.

OBESITY RESEARCH ADVANCES AND OPPORTUNITIES

The scope of obesity research across the NIH is broad, encompassing diverse issues, a range of scientific disciplines, and multiple levels, from the genetic and cellular to individuals, communities, and populations. The following sections of the Strategic Plan *include some examples of significant and recent scientific advances and outline opportunities across the spectrum of obesity-related research areas.*

The first two sections focus on research opportunities designed to uncover causes and mechanisms of obesity and identify potential targets for intervention. ***Discover Biological Mechanisms Regulating Energy Balance*** *highlights opportunities in genetics, neuroscience, metabolism, cell biology, and other areas that will improve our understanding of fundamental biologic pathways involved in weight regulation and point the way to novel therapeutic targets.* ***Understand the Correlates, Determinants, and Consequences of Overweight and Obesity*** *moves beyond biological mechanisms to address research into factors that are associated with increases in body weight and the development of obesity as well as the many adverse outcomes resulting from obesity.*

Efforts to change behavior as well as clinical and public health practice and policy are often based on the results of carefully designed and evaluated interventions. NIH currently supports many such obesity-related interventions, and ***Design and Test Interventions to Promote Healthy Weight*** *outlines an array of new opportunities that can further advance obesity prevention and management.*

An important area of research focuses on ways to hasten the translation of research evidence from discovery to intervention and from efficacy to effectiveness and application in clinical or community settings. ***Conduct Dissemination and Implementation Research*** *addresses opportunities in the fields of surveillance, health services, dissemination, implementation, policy, and evaluation research.*

Advances across these areas depend on accurate tools and measurements to enhance understanding of etiology and allow for evaluation of interventions. ***Improve Measurement Tools, Technology, and Methods*** *highlights new opportunities for research to improve measurement of energy intake and output. These tools and measures cover a number of areas, including development of biomarkers; assessment of food intake, fitness, functional status, and thermogenesis; improvements in imaging and body composition technologies; and development of objective measurement systems to better evaluate changes in policy and environments. This section also highlights the need to use emerging methods of analysis and design, which allow researchers to better capture and model the complex relationships in obesity.*

Issues of health disparities, high-risk populations, and critical periods across the lifespan, although not always explicitly mentioned, are viewed as important considerations in all of the research opportunities outlined in the Strategic Plan.

Discover Biological Mechanisms Regulating Energy Balance

Research has elucidated a large number of pathways that participate in the biological basis of weight regulation and the dysfunctions in these pathways that result in obesity. This has led to the identification of potential therapeutic targets to treat obesity and prevent associated comorbidities. Further advances in this fundamental understanding of basic biological mechanisms will yield novel approaches to prevent, as well as treat, obesity and its comorbidities For example, understanding how genes, interacting with the environment, confer risk for obesity should allow investigators to define better targets for drug development, and may also inform other approaches, including lifestyle approaches, for obesity prevention and treatment. Identifying mechanisms whereby obesity causes dysfunction in many organ systems will help target therapies for prevention of comorbidities. The increasing prevalence of overweight in early childhood and increasing evidence that obesity and diabetes during pregnancy have adverse effects on the fetus highlight the need to understand the potential impact of excess energy consumption in the mother on development not only *in utero*, but well into adult life.

Selected Research Advances and Challenges

The decade preceding the first *NIH Strategic Plan for Obesity Research* was a remarkable period in obesity research, and recent advances have continued that high rate of discovery. Much of this is due to improved characterization of the multiple biologic systems that interact to regulate body weight. New technologies, such as cellular and functional imaging, metabolomics and proteomics, gene expression arrays, genome-scale gene knockdown studies in non-mammalian organisms, and powerful transgenic strategies to create complex genetic mouse models have accelerated targeted research with increasing potential for translation to human health. The following observations provide examples of particular insights and define directions for future research.

- The identification of molecules, tissues, genes, and pathways involved in weight regulation continues, and now includes a wide range of gut-produced factors; “tissuekine” hormones produced by fat, bone, and skeletal muscle; and myriad brain regions and peripheral nerves.
- The importance of sleep and the circadian “clock” in obesity development is increasingly recognized. Chronic reductions in sleep time and circadian rhythm disturbance (e.g., shift-work) are commonly experienced by millions of Americans and result in alterations in metabolism-regulating molecular and physiological pathways associated with increased risk of obesity, cardiovascular disease, and type 2 diabetes.
- *In utero* exposure to stress, environmental toxicants, poor maternal diet, obesity, or diabetes confers increased risk of metabolic disease in offspring.
- Understanding of the fundamental role of the brain in controlling energy balance continues to grow. The specific functions of the structures known to be involved, such as the hypothalamus, continue to be elucidated. Human brain imaging studies demonstrate changes in structure and activity associated with obesity and also provide clues to explain failure of normal satiety signals that lead to disordered metabolic states and obesity in an energy-rich environment. Similar functional imaging studies show that the dopaminergic pathways associated with motivation and addictive behaviors also participate in obesity development or maintenance.

- Increasing evidence in animal studies demonstrates that environmental toxicants commonly found in both the food and water supply may contribute to obesity and type 2 diabetes. Many of these toxicants can be found in tissues and blood in the US population.
- The gut secretes a large number of factors that facilitate insulin secretion and regulate eating behavior. The observation that bariatric surgery often leads to resolution of diabetes, before significant weight loss has occurred, provides a model to explore potential mechanisms by which the gut communicates with pancreas, liver, fat, and the central and peripheral nervous systems.
- Gut microbiota, which aid normal nutrient absorption and metabolism, may play a role in obesity. Obesity is associated with remarkable changes in the composition of gut flora, and alterations in gut flora also may have an impact on obesity development.
- Although excess fat is the very definition of obesity, adipose tissue has important beneficial properties that seem designed to protect against adverse effects of excess lipids elsewhere in the body. Fat molecules can be safely stored in adipose tissue, but when the storage capacity of this tissue is exceeded, the resulting deposition of excess fat into other tissues and organs is associated with morbidity. Adipokines, secreted as a function of adipose tissue mass, regulate eating behavior and fat oxidation.
- Brown adipose tissue, a tissue that plays an active role in many species to turn excess nutrients into heat rather than stored fat, was thought to be present only in infancy in humans. Recent work has demonstrated that human adults have significant depots of brown fat, which appears to be metabolically active.
- Obesity is associated with both systemic inflammatory cytokines and inflammatory cell infiltration into fat, liver, and placenta and may activate inflammatory processes in the brain.
- Improvements in the ability to measure differential responses to diet and energy expenditure are confirming that the same exposures do not lead to the same changes in body composition and fat mass in all people.

Research Opportunities

A growing appreciation for the elegance with which the organism adapts to maintain its reserves of energy is giving rise to important questions for future research. How do genes, biological pathways, behavior, and the environment interact to maintain proper energy balance, and what goes awry in an environment of excess calories and reduced energy expenditure to contribute to obesity? The complexity of regulation of energy balance and the relative refractoriness of these regulatory pathways to pharmacologic manipulation suggest the desirability of exploring all possible avenues for sites sensitive to manipulation. Concomitant with support for basic discoveries, NIH must develop paths to translate these discoveries into new diagnostics, new therapeutics, and most important, new strategies for preventing obesity.

Specific opportunities for basic biological research that could provide new therapeutic approaches to obesity include the following:

Specific Roles of Organs, Tissues and Molecules in the Development of Obesity

- Determine the roles of gut microbiota in normal and pathological nutrient absorption and metabolism, including how the disturbance of the biota by different factors might contribute to obesity or weight loss, and explore novel therapeutic strategies to reduce excess nutrient absorption associated with the gut flora or other pathways.
- Determine whether human brown fat plays a major role in energy balance, and explore pharmacologic or environmental (temperature) approaches to manipulate brown fat activity to uncouple excess nutrient intake from energy storage in white fat tissue.
- Elucidate the relationship between excess nutrient intake and physical inactivity on adipose inflammatory processes, define the role of inflammation in obesity-related complications, and explore therapeutic approaches targeting inflammatory pathways.;
- Determine whether mitochondria, the cell's energy factories, are a primary site of dysfunction in obesity or if obesity causes mitochondrial dysfunction resulting in metabolic diseases associated with obesity.
- Identify the brain pathways which integrate cognitive, endocrine, nutrient, and sensory information and the links between these inputs and integrated behavioral, autonomic, and neuroendocrine outputs to regulate energy balance.
- Determine the mechanisms whereby food activates brain reward pathways and association of activity in these pathways with obesity.
- Explore how complex behaviors, such as sleep, patterns of sedentary behavior, and exercise, can influence eating behavior, energy balance, and metabolic health.
- Determine whether specific nutrients, non-nutrient additives, or other dietary components (such as alcohol) have specific bioactivity that would modulate metabolic processes associated with body fat storage and distribution, and thus contribute to the development of obesity.
- Explore the role of neuronal degeneration in brain regions regulating energy balance in the development of obesity.
- Examine potential deleterious effects of obesity on brain function, and define the mechanisms and effects of weight loss and weight gain.
- Study the mechanisms by which different bariatric surgical procedures accomplish weight loss and improve health outcomes as targets for developing new pharmacologic therapies. For example, study patients undergoing bariatric surgery and animal models of bariatric surgery to expand the understanding of the role of gut signaling pathways and secreted molecules in regulating eating behavior, nutrient handling, and energy balance.

Genes, Epigenetics, and Critical Periods in Human Development

- Identify genotypes that protect against development of obesity in the face of an obesity-promoting environment.
- Identify genetic variants that may contribute to circadian regulation of metabolism and, in particular, those that are associated with variations in eating behavior.
- Examine mechanisms whereby gene polymorphisms in defined loci confer risk of developing obesity or influence development of associated morbidities.

- Define the epigenetic mechanisms regulating metabolic tissues, such as brain, liver, muscle, heart, and fat, and determine whether and when environmental factors (e.g., stress, toxicants, nutrient excess, bioactive nutrients, alcohol, and energy expenditure) can perturb epigenetic states and lead to obesity; determine the plasticity in epigenetic regulation of metabolic tissues.
- Define the biological contribution of the critical periods of susceptibility to the development of obesity during an individual's lifetime.
- Define the contribution of intrauterine exposures related to maternal diet and physical activity, obesity, and diabetes to the subsequent risk of obesity in the offspring.
- Explore the impact of diet composition, obesity, and obesity-associated inflammation on the developing brain and maturation of cognitive functions in children.
- Determine the effect of excess adiposity on normal human development.

<u>Enabling Tools for Basic Research in Obesity and the Translation of Discoveries into Clinical Utility</u>

- Use global approaches (such as genome-wide association studies [GWAS], genomics, metabolomics) to define all the molecules and pathways that participate in regulating eating behavior, physical activity, sedentary behavior, nutrient absorption, muscular response to exertion, and energy partitioning.
- Devise approaches to measure and manipulate tissue- and organ-specific thermogenesis and adaptations to diet, and weight gain or loss. In particular, new means of monitoring brown adipose tissue mass and activity are needed.
- Explore the use of imaging technology for obesity research, including new tools to probe neuronal pathways controlling eating behavior, investigate lipid metabolism and inflammation in tissues, and image energy expenditure.
- Develop tools to monitor mitochondrial function *in vivo*.
- Develop novel screens to identify small molecules that can modulate energy balance pathways.

Understand the Correlates, Determinants, and Consequences of Obesity

This section highlights two research areas critical to understanding obesity—factors associated with the development of overweight and obesity, and the consequences of obesity.

A wide range of factors—biological, demographic, psychological, socio-cultural, organizational, environmental, and regulatory—influence obesity-related lifestyle behaviors and weight gain. These factors span multiple interacting levels, from the individual through societal. Considerable evidence supports a growing list of physical, social, psychological, and economic consequences associated with excessive weight gain. Research in the United States, as well as in international settings which have recently experienced increases in obesity prevalence, can help disentangle the various factors that promote obesity or protect against excess weight gain.

Because obesity is not a single condition, increased knowledge about phenotypes and the various influencing factors and consequences can be used to develop novel hypotheses to be tested or to identify targets for intervention, surveillance, and translational research.

Selected Research Advances and Challenges

Knowledge about the correlates, determinants, and consequences of obesity has expanded significantly in recent years, as illustrated by the following advances:

- Research has emerged suggesting links between obesity and the physical environment. For example, the presence of sidewalks and more street connectivity in neighborhoods is associated with more physical activity and less obesity.
- Several dietary behaviors have been strongly associated with weight gain, including frequent consumption of fast foods, sugar-sweetened beverages, foods prepared outside the home, and larger portion sizes. These behaviors occur in an environment that favors inexpensive, highly palatable, energy-dense food that can be consumed with minimal preparation.
- Sedentary behavior, which occurs in the context of an increasingly automated environment, has been linked to weight gain, possibly independent of low levels of physical activity. It is well-documented that large amounts of TV or video game use are associated with increased risk of obesity in children and adults.
- Sociocultural factors have been associated with a higher risk of excess weight gain, including race/ethnicity, education, low socioeconomic status, and acculturation. For example, obesity co-occurs among persons connected through social networks, although it is unclear how socio-cultural, environmental, and genetic pathways interact to influence these associations.
- Several studies suggest that self-monitoring, such as frequent self-weighing and keeping food and activity diaries, leads to better weight control.
- Excess weight gain during growth and maturation has been associated not only with adverse outcomes during childhood but also with a higher risk of obesity and obesity-related diseases in adulthood. Given that the prevalence of overweight has markedly increased across pediatric age groups, premature onset of obesity-related diseases is

likely to rise. The prevalence of metabolic consequences of obesity, such as type 2 diabetes and metabolic syndrome, is increasing. This is especially true for adolescents in some racial and ethnic groups.

Research Opportunities in the Correlates and Determinants of Obesity

Understanding the independent and interacting biological, behavioral, social, cultural, and environmental correlates and determinants of obesity and how these differ among groups is crucial to identifying new targets for intervention at the individual, community, and population levels.

Several understudied and emerging areas provide opportunities for research:

- Disentangle the roles of and interactions among different aspects of the food- and physical activity-related built, economic, policy, and natural environments in promoting or preventing obesity. Research in this area would be enhanced by the application of theories and approaches from diverse disciplines in longitudinal multilevel analyses.
- Encourage research that includes careful behavioral and biological phenotyping of obese individuals at multiple time points. Because obesity does not have a single phenotype, understanding the various causal pathways and characteristics that promote or protect individuals from becoming obese will likely be important for the development of more targeted and effective interventions.
- Enhance research that evaluates the effects of policy to better inform policy makers. Several priority areas in policy research related to obesity include capacity development, agriculture and food supply, economic research, built environment, and educational policies.
- Identify how psychosocial factors and mental disorders influence weight gain, energy intake, and energy expenditure. Identify factors, such as social support, that may moderate these relationships. Identify how weight gain, energy intake, and energy expenditure interact with high-risk behaviors such as smoking, drinking alcohol, and drug use.
- Encourage research that identifies the reasons for increased risk of obesity in high-risk populations, including racial and ethnic minorities, economically-disadvantaged groups, and people with physical or developmental disabilities or comorbid mental disorders.
- Understand how developmental factors and learning influence the initiation and maintenance of behaviors that promote weight loss or prevention of excess weight gain.
- Understand how individuals interpret and are influenced by messages related to diet and physical activity (e.g., interpersonal, cultural, media, marketing, food labels) through research on learning, cognition, information processing, persuasive communications, and message framing. Explore how traditional and emerging communication channels, such as social media and mobile technology, influence the adoption of these messages.
- Investigate factors related to excess weight gain associated with critical periods and life events, such as fetal exposures *in utero*, infancy, childhood, puberty, adolescence, young adulthood, pregnancy/ postpartum period, workforce entry, marriage, parenting, menopause, and retirement. Identifying factors that may be unique to a specific point in the lifespan could provide important insights for intervention development.

- Clarify the temporal sequence and understand the biological and behavioral relationship between sleep and obesity across the lifespan. For example, conduct studies to clarify the role of chronic sleep time reduction and circadian rhythm disturbance in influencing adiposity or eating and activity behaviors.
- Distinguish the intersecting roles of biological, behavioral, psychological, social, and environmental factors on obesity across the lifespan in longitudinal studies.
- Study how the specific components and characteristics of diet, physical activity, and sedentary behavior interact in contributing to excess weight gain, weight cycling, and weight maintenance across the lifespan.
- Increase the understanding of the role of common drugs/medications, including medications used for the treatment of mental illness, on obesity development.
- Identify how environmental toxicants and other chemical exposures affect the development of obesity in children and adults.
- Explore interactions between genetic and environmental factors related to weight stability, loss, or gain across the lifespan. These interactions, in which environment is broadly defined to include the individual, built, social, economic, policy, and natural environments may help identify new and more personalized targets for prevention and treatment.

Research Opportunities in Understanding the Consequences of Obesity

Research is needed to continue to explicate the relative contributions of excess weight gain, body composition, and body fat distribution to risk factors and disease outcomes, and investigate how the consequences differ for population subgroups, such as those defined by age, sex, race/ethnicity, and life stage. Also important are explorations of the impact of age of onset, duration, and magnitude of weight gain and weight loss patterns on the development of adverse outcomes.

Several understudied and emerging areas provide opportunities for research:

- Document the relationship between obesity and health conditions such as liver disease, osteoarthritis, obstructive sleep apnea, asthma, cancer initiation and progression, and Alzheimer's disease. Elucidate the causal pathways, mediators, and moderators of these associations.
- Identify the mechanisms and behaviors across the lifespan of the "healthy obese" phenotype, as characterized by a favorable cardiovascular disease risk profile despite excess adipose tissue.
- Clarify whether weight gain trajectory, overweight, and obesity lead to adverse consequences among older adults (65 years and older), and whether effects differ by functional status.
- Explore how body composition and fat distribution predict adverse physical and mental health outcomes throughout the lifespan.
- Investigate whether physical fitness can ameliorate specific adverse health consequences of obesity.

- Determine the economic and societal effects of differing levels of obesity across the lifespan and in different subgroups (e.g., by gender or socioeconomic status), including healthcare costs, presenteeism/absenteeism, reduced productivity, earning potential, quality and duration of life, stigma, and discrimination.

Design and Test Interventions to Promote Healthy Weight

This area of research includes interventions to prevent overweight or obesity, avoid additional weight gain or promote weight loss in those already overweight or obese, and reduce weight regain in overweight or obese persons who have successfully lost weight. It also encompasses interventions to examine effects of weight loss on various health outcomes.

It is unlikely that any one approach will address the needs of all individuals at risk for or living with overweight or obesity. As a result, this section includes interventions that address multiple levels (from the individual to societal), various modalities (e.g., medical, surgical, behavioral, environmental, and policy), and across critical or high risk periods throughout the lifespan. Given the tremendous public health burden of obesity, intervention research should, where possible, consider intervention benefits in relation to risk, cost, and feasibility.

Selected Research Advances and Challenges

Recent intervention studies have examined a wide variety of topics including, lifestyle interventions for weight loss, maintenance of weight loss, or preventing comorbidities; diets varying in macronutrient composition for weight loss; increasing physical activity in schools, site-based and community approaches to weight control; bariatric surgery outcomes; and efficacy of weight loss medications. Key conclusions have emerged:

- Both sides of energy balance—intake and expenditure—are important for obesity control.
- Macronutrient composition (i.e., percentage of fat, carbohydrate, and protein) is less important than calorie reduction for weight control after one year or more.
- Modest weight loss in overweight/obese adults (i.e., 5% to 10% loss of initial body weight) can result in significant and clinically important reductions in disease risk factors or morbidity, such as blood pressure level, incidence of type 2 diabetes, and osteoarthritis pain.
- Modest weight loss in adults is achievable with a set of standard behavioral counseling tools, such as goal-setting, feedback, self-monitoring, relapse prevention training, social support, and problem-solving. A “toolbox” approach that allows for multi-component individualized strategies—including lifestyle, meal replacements, and/or support for behavior change—has been effective in relatively long-term weight reduction for up to 4 to 5 years. However, these findings are with intensive interventions delivered in large, well-controlled clinical trials and will likely need adaptation to be used in real-world settings.
- Maintenance of successful weight loss remains a challenge and maintenance strategies are less than optimal. Strategies involving brief, monthly personal contact are modestly effective in maintaining weight over 2.5 years, and more effective than access to an unlimited Internet intervention.
- Environmental and community approaches seem promising, as they can reach large numbers of people, but their effectiveness has yet to be adequately demonstrated.
- In children, there is some evidence that interventions to reduce television/computer use (screen time) and to reduce sugar-sweetened beverage consumption have favorable impacts on overweight or obesity.

- Current weight-loss medications have modest efficacy, but the high drop-out rate in medication studies often makes conclusions difficult and limits their generalizability. Serious adverse effects remain a concern as well.
- Observational (non-randomized) studies suggest that bariatric surgery may have a favorable impact on mortality in those with extreme obesity.

Research Opportunities

Intervention research should be informed by findings from multiple disciplines and approaches including basic biological, behavioral, and social science research; early-phase translational research; epidemiology, pilot, and feasibility studies; and prior intervention studies. In addition to weight and body composition, other outcomes also are important to include in obesity research, including dietary intake and composition, physical activity patterns, quality-of-life, psychosocial and functional status, and health outcomes (e.g., morbidities, adverse effects, and cause-specific or all-cause mortality).

Several understudied and emerging areas provide opportunities for intervention research:

- Examine the effects of diverse approaches (e.g., single- and multi-level, interventions delivered in settings such as schools, primary care, or community settings) to achieving long-term prevention of overweight and obesity across the lifespan.
- Determine the optimal content, dose, and delivery channel of prevention messages delivered within interventions.
- Develop and test the effectiveness of obesity prevention strategies in children, including approaches in the very young (infancy to age 6 years).
- Evaluate the effects of provision, in schools or pediatric primary care settings, of BMI information and parental counseling on children's weight, health, and psychosocial outcomes
- Examine long-term effects of targeted prevention or treatment strategies focused on subpopulations at elevated risk of developing obesity, such as those in disproportionately affected race-ethnic subgroups, of lower socioeconomic status, in rural communities, with physical and mental disabilities, in smoking cessation programs, and in individuals taking medications that can increase body weight.
- Study approaches to weight control associated with life events and critical periods where excess weight gain often occurs (e.g., infancy/early childhood, young adulthood, menarche, pregnancy, parenting, menopause). For example, develop and test interventions to promote healthy weight gain during pregnancy and to facilitate/or return to pre-pregnancy weight after delivery.
- Explore impact of interventions to promote breastfeeding on post-partum weight retention in the mother and weight and body composition in the offspring.
- Test approaches that modify the built environment in ways that are designed to prevent or reduce obesity.
- Examine the long-term effects of treatment modalities (e.g., behavioral, pharmacological, and surgical) delivered in healthcare or community settings on weight loss and maintenance.

- Study long-term effects of various treatment modalities in extremely obese children and adults to determine which approaches are most efficacious, deliver the most improvement in health status, and are safest in these populations.
- Examine effects of weight loss interventions in obese individuals who already have an obesity-related illness to determine effects on long-term control or amelioration of the illness (e.g. obstructive sleep apnea, type 2 diabetes, osteoarthritis, various cancers, or cardiovascular diseases).
- Examine the efficacy of interventions to increase habitual sleep time on metabolic regulation (e.g., reducing body weight, preventing weight gain, regulating appetite, improving glucose tolerance and insulin sensitivity).
- Examine effects of diet composition, including nutrients and bioactive food components, food additives, sensory and hedonic properties of food, and dietary supplements on body weight and body composition.
- Test whether personalized dietary or physical activity approaches based on genotype or phenotype are more effective than non-personalized approaches.
- Design and test novel weight control interventions based on basic behavioral and social science findings. Explore how values, motives, and behaviors from non-health areas may change obesity-related behaviors (e.g., how concerns about the environment may increase active transportation).
- Study ways to enhance adherence to behaviors recommended in weight control programs, such as self-monitoring behaviors, increased physical activity, and reduction in caloric intake.
- Design and test novel weight control interventions that incorporate existing or emerging technologies (e.g., mobile phones, interactive voice response, virtual reality mediums, global positioning systems, social networking platforms).
- Study the effect of media (e.g., advertising, television programming, the Internet, digital marketing) on obesity related decision making, energy intake, and physical activity, and test child- and parent-friendly technologies to support behavior change or deliver effective preventive messages.
- Explore approaches to improve the maintenance of successful weight loss over time in diverse populations.
- Test the efficacy of economic strategies, alone or in concert with other strategies, to promote weight loss or prevention of excess weight gain such as financial incentives, subsidies, taxes, and pricing strategies.
- Develop and test the efficacy of weight management interventions that involve collaborations between healthcare providers and non-clinical settings (such as community centers or commercial weight-loss programs).
- Explore effects of existing and new obesity medications to determine which medications and delivery methods, and what combinations of medication and lifestyle changes are most effective in improving obesity and health outcomes in various population groups over the long-term with an acceptable risk/benefit ratio.
- Determine the short and long-term effectiveness of bariatric surgery as compared to behavioral and/or pharmacologic approaches in adolescents and adults with a variety of comorbid conditions.

- Explore the short and long-term safety and effect on health of bariatric surgery in those with a BMI <35 and significant co-morbid conditions.
- Test prevention or treatment approaches that are designed to better inform policy decisions, including testing the effects of approaches that can reach large numbers of people (e.g., communication strategies such as social marketing, environmental changes, or food and activity related policy changes), as well as interventions in various settings (e.g., home, school, worksite, healthcare, community) that are feasible for broad-scale delivery and sustainability.
- Examine the interacting effects and complexity of multi-level and/or multi-component intervention programs addressing behavior, environment, and policy issues, including home/family, sociocultural, and built environments.

Conduct Dissemination and Implementation Research

Dissemination and implementation research are key aspects of translational research and are the focus of this section. These later phases of translational research encompass such fields as surveillance, health services, dissemination, implementation, policy, and evaluation.

Traditionally, once targets for intervention were discovered and efficacy established for individual or population-based approaches, a next step was to translate those results into real-world practice and settings. In the past few decades, the need to build cyclical and externally valid models of research, such as "rapid learning" clinical and public healthcare systems in which research and evaluation infrastructures are built into these systems to allow evidence to be gathered in the context of "real-world practice," has expanded the understanding of translational research as an iterative process. In addition, research evidence documenting the critical role of contextual, environmental, and policy forces on achieving sustained improvement in human behavior has led to a focus on multi-level and systems studies that intervene not just with individuals but also the environments in which they live and work.

Dissemination and implementation research are essential to meet the following aims: 1) Quantify the extent of the problem in order to appropriately direct resources and interventions to the populations with greatest needs; 2) Identify whether interventions proven to be efficacious within the context of controlled randomized clinical trials have the same benefit when they are applied in less controlled settings among populations with different characteristics; and 3) Improve the effectiveness, efficiency, and sustainability of providing interventions so that a large number of people can be reached with limited resources.

Emerging evidence indicates approaches that address multiple levels (e.g., individuals, their families, and the environment in which people live) are likely needed for interventions to have broad reach and for effects to be sustained. Therefore, research in surveillance, health services, dissemination, implementation, policy, and evaluation is increasingly designed to encompass data collected at multiple levels, including the individual, family, and community.

Selected Research Advances and Challenges

Key advances have occurred in recent years in dissemination and implementation research:

- Because surveillance of diet and physical activity has benefited by improved measurement and analytic methods, the extent to which the population's behaviors align with recommendations is now more accurately quantified. Improved methods are illustrating that diets fall short of recommendations in many areas. A significant gap exists between self-report (30% to 40% achieving recommended levels of physical activity) and objective measures (3% to 5% achieving recommended levels) of population prevalence of physical activity.
- Geographic information system (GIS) methodologies now enable linkage across levels of data from individuals to family and community. GIS includes measures of the food and physical activity environments, air and water quality, and access to health-promoting environments, healthcare providers, healthcare access, and policies.
- Automated systems for data collection at multiple levels through electronic health records in healthcare delivery systems, geospatial data on communities and environments, and Internet-based survey methods allow integrated linkage of data on

individuals to their environments and examination of self-report and objective measures of behaviors, biologic characteristics, social networks, medical conditions, pharmaceuticals, and treatment that may influence obesity-related behaviors and body weight or composition.

- The need for evidence to support and ensure high-quality obesity care has been recognized. NIH led the first nationally representative physician survey, the *National Survey of Energy Balance Related Care among Primary Care Physicians*, which provides important national estimates of baseline data on knowledge and practices in this area among providers treating adults and children.
- The establishment of health services and economics research consortia that work within the context of healthcare delivery systems enables expanded collection of meaningful use data on the process and cost of obesity-related healthcare. These consortia are leading to an improved understanding of healthcare practice and outcomes, how they relate to obesity and its comorbidities. They also provide opportunities for developing electronic data and feedback systems that provide real-time clinically relevant information to patients and providers.
- Emerging obesity policy research is developing rigorous approaches for evaluating the influence of public policies to improve food and physical activity environments. Early research suggests that approaches such as reducing sugar-sweetened beverages within schools may have measurable benefits in reducing BMI in school-aged children.
- Methods to estimate the economic costs of obesity have evolved from cross-sectional to longitudinal. This evolution is allowing researchers to examine relationships over time and has improved the estimation of the long-term costs of obesity. Researchers can now quantify the contribution of treatment for comorbid disease to increases in healthcare costs.

Research Opportunities

A critical need in this field is to integrate theories and research approaches from multiple disciplines to ensure appropriate research designs that address the complex and multifactorial nature of successful obesity prevention and treatment in clinical and public health practice. In addition, the development of valid measures appropriate to the specific research question and populations and environments under study is a high priority. In some instances, these measures may be objective, such as medical records data of medications or procedures or coding of environmental variables. In other instances, appropriate and valid measures may be based on self-report. Major advances in automated approaches to capturing both objective (e.g., physical activity monitors) and self-reported (e.g., computerized dietary recall instruments) measures of health behaviors and outcomes are being applied to this field. Advances in GIS-labeled data, methodology, and application are essential to enable linkages across the socio-ecological model of obesity.

A number of specific topics within dissemination and implementation research provide opportunities for investigation:

<u>Surveillance</u>

- Develop infrastructure and methods to integrate surveillance research across individual, family, community, and state and national levels, using valid measures of behaviors,

environments and policies to gain a better understanding of the interplay among behaviors and influencing factors. It is critical that such systems include longitudinal components to capture changes in health behaviors and weight over time, including long-term maintenance of weight loss.

- Increase the use of sampling designs that allow for estimates of obesity and obesity-related behaviors in local and/or underserved populations, such as at-risk populations defined by race/ethnicity, income, age, geography, or other factors that influence obesity. These improved estimations will enhance the relevance of obesity data for public health action at the local, state, or national level.
- Encourage research that examines multi-level questions and promotes innovative approaches to linking local, state, or national surveillance systems to monitor health behaviors with GIS and other environmental-level data.

Health Services and Economics

- Conduct comparative effectiveness, cost, behavioral economic, and cost-effectiveness research to identify effective interventions for obesity prevention and control in diverse populations, for example, evaluating the effectiveness of targeted subsidies on purchases of healthy food through nutrition assistance programs or evaluating the impact of taxes on purchase of less healthful foods.
- Support multi-level research within the context of primary care, using advances in eHealth technologies in combination with electronic medical records (EMRs). This research will allow patients and providers to identify integrated and staged approaches for addressing obesity, particularly among patients with multiple chronic diseases.
- Use research networks within healthcare systems to document obesity outcomes related to implementing processes of care, such as screening for obesity and delivery of obesity care within the healthcare setting.
- Enhance capacity to examine behavior and subsequent health outcomes and costs related to factors such as agriculture, food supply, urban design, and transportation policies. All these factors have an impact on physical activity and food choices.
- Determine economic, behavioral, and social costs and benefits, such as health improvement, disability reduction, time use, convenience, perceived benefit, to individuals of making behavior changes recommended for obesity prevention and control.

Dissemination and Implementation

- Use approaches, such as community-based participatory research, that engage and involve community members in designing, implementing, and interpreting large-scale research in diverse communities to determine the acceptability of environmental and societal changes that might be undertaken to promote healthy eating and activity behaviors.
- Conduct research on appropriate terms, messages, media, and strategies to communicate about weight control with attention to population-specific needs, such as in children or adolescents and their families, women who are planning a pregnancy, or are pregnant, ethnically diverse audiences and those of various cultural or socioeconomic backgrounds, and different levels of general and health literacy.

- Conduct "best practices" research to enhance obesity screening, prevention and treatment in primary care. Use these best practices and other resources to develop, implement, and test messages, clinical guidelines, standardized lifestyle assessment methods, and other tools, procedures, and organizational systems in various primary care settings to increase the prevention, identification, and treatment of obesity in children and adults.
- Test innovative adaptations of evidence-based obesity prevention and treatment approaches that can be disseminated and sustained in families, clinical healthcare practice, and child care, school, or community settings.
- Support research on how electronic applications, such as eHealth applications in mobile phones or on the Internet, can expand reach, tailoring, and rapid dissemination of interventions to large and diverse populations.
- Support research on education and outreach efforts to promote healthy weight gain during pregnancy and to promote initiation and maintenance of breastfeeding through creative approaches, including those that incorporate innovative technologies and communications.

Policy and Evaluation

- Evaluate the influence of policy intervention "natural experiments" on diet and physical activity practices at local, state and federal levels. Examples of this research include examining the influence of price on food choices, the impact of school or worksite policies to support physical activity, or the influence of safe environments on physical activity.
- Develop improved methods for evaluation of natural experiments, such as cost effective, practical, and valid approaches to determine the effect of grassroots initiatives to implement community-wide or setting-specific (e.g., school, worksites) regulation regarding diet or physical activity.
- Engage investigators and stakeholders from diverse disciplines to ensure that policies under investigation have the potential for broad implementation.

Improve Measurement Tools, Technology, and Methods

At each step of the research continuum, appropriate measurement is essential for advancing scientific knowledge and ensuring public health relevance. Accurate measures of body composition, energy intake, and energy expenditure of individuals are essential for understanding the etiology of obesity as well as the effectiveness of prevention and intervention efforts. Many existing measures have limitations with regard to accuracy, reliability, and sensitivity in free-living individuals. Measurement in children and adolescents is a particularly challenging and important area for research.

Three types of self-reported diet and physical activity assessment instruments are widely used: frequency questionnaires to assess nutrient intake, records (or diaries), and 24-hour recalls. These approaches have limitations because individuals do not commonly attend to what they eat or their activities levels, and often cannot accurately estimate usual dietary intake or bouts of physical activity without error or bias.

Various objective measures also are used in diet and physical activity research. Direct observation of dietary intake or physical activity is a useful objective measure but its use is limited primarily to institutional settings. Research and clinical practice would be enhanced by the development of new or improved objective measures that could be used in free-living individuals to measure fitness and functional status. Most current biomarkers of diet cannot capture amount of intake nor distinguish short-term versus long-term intake. For physical activity, wearable monitors do not capture the full range of activities in which people engage, and methods to convert monitor data into measures of energy expenditure are still evolving. For both diet and physical activity, objective measures tend to be burdensome for research participants and expensive.

Body composition measurement has advanced considerably in the past decade. However, many of these measures are too costly, time consuming, and technically challenging to use in clinical settings or in population studies. Although BMI is a good estimate of overall fatness in a population, it is not ideal for understanding individual body composition status or changes and is not sensitive to level of fitness, maturational stage, sex, and race. Thus, the same BMI may represent very different body composition profiles. The capacity to measure body composition accurately in all age groups in clinical settings would allow research studies of the relationship between body composition and clinical features, potentially facilitating translation to medical management in real-world situations.

High-quality environmental measures also are vital components of research on diet and physical activity behavior and the prevention and treatment of obesity. Examples of environmental measures of interest include access to nutritious and affordable food, quality and quantity of sidewalks, and availability of bike lanes. Researchers use a variety of methods to measure food and physical activity environments, including instruments—both self-reported and observed—and methodologies such as geographic information system (GIS). Research that can place individuals within the specific environments that they experience has been facilitated through advances in micro-scale measurements, such as sidewalks, safety, and exact locations of food vendors.

Finally, given the multiple feedback loops involved in the regulation of body weight, innovative methods that reflect and encompass this complexity may provide the greatest opportunities for moving forward. Systems methodologies may help uncover novel, and perhaps unanticipated,

strategies to combat obesity. They may also reveal unanticipated adverse consequences of potential interventions and policies. A transdisciplinary systems approach can be used in a host of research areas, from biological to population systems modeling and the integration of the two. Advances in novel statistical approaches can also be applied to the design and analysis of research studies, as well as to technological innovations for genetics and bioinformatics. All of these applications present new and exciting opportunities for future obesity research.

Selected Research Advances and Challenges

Diet and physical activity tools and measures have improved markedly in recent years, as shown by the following advances:

- Doubly-labeled water, an accurate measure of total energy expenditure over a 2-week period, recently has been used to assess and correct for error in self-reported diet and activity assessment instruments in free-living individuals.
- Recent advances have occurred in the use of relatively inexpensive, automated systems for use in self-reported dietary intake and activity. These include Internet, personal digital assistant (PDA), and mobile phone-based methods to collect data for frequency, recall, and record questionnaires.
- Small-molecule metabolite profiles (serum metabolomic profiles) assessed by HPLC MS-separations, coupled with colorimetric array detection, have been found to accurately identify *ad libitum* fed and energy-restricted rats. These profiles are being adapted for human epidemiology studies to provide insight about energy balance and cancer.
- Accurate measurements of body movements and positions, combined with physiological responses (e.g., heart rate, core temperature, oxygen saturation, and glucose) using accelerometers and other advanced biosensors have improved the capacity of wearable monitors to measure physical activity. Associated technological advances in sensor miniaturization, data acquisition and processing, low power consumption, wireless communication, large data storage, and advanced algorithms have placed objective monitoring within the reach of a growing field of researchers.
- Over the past decade, researchers have developed "first generation" measures of the food and physical activity environments using a variety of methods, including self-reported measures, observation systems, and geospatial data mapping technology (e.g., GIS). Advances in mobile phone technology with integrated global positioning systems (GPS) facilitate collection of data about individual physical activity behavior and context in real-time.
- Advances in transdisciplinary research have brought together public health and medicine with other fields, such as computer science and engineering, to apply systems thinking to obesity research. These collaborations have capitalized on new, high-throughput computing power to integrate complex concepts and data that range from genetics to policy.

Research Opportunities

New diet and physical activity measures with improved accuracy, precision, reliability, usability, and flexibility are needed. Measures with improved sensitivity to change are also needed,

especially in the areas of biomarkers, fitness and functional status, thermogenesis, imaging, body composition, objective measurement systems, and environment. Given the complexity of factors that influence obesity, new systems methodologies also need to be employed in conducting next-generation obesity research.

Biomarkers

- Develop genomic, proteomic, and metabolomic approaches for use in identifying biomarkers of energy balance as well as to assist with understanding specific genes, proteins, and small molecules involved in energy balance that influence the tendency to gain or lose weight.
- Develop nanosensors for quantifying circulating and tissue concentrations of macro- and micronutrients and their metabolites to help improve accuracy and precision of dietary assessment.
- Develop high-throughput, low-cost metabolomic profiling approaches in bio-fluids and tissues to characterize and identify biomarkers involved in the progression of weight gain and loss in animal models and humans.
- Develop mathematical models using metabolic profiles to predict energy intake or energy expenditure.
- Encourage systems biology efforts to harness computing power in a way that can bring together information on proteins, genes, metabolites, and human or animal phenotypes related to metabolism and weight.
- Develop technologies for novel ways to noninvasively assess biochemical indicators of fitness. Also develop assays to monitor measures such as nutritional status, cardiovascular/cardiorespiratory tone, serum biochemistry, metabolic enzyme activity, and epigenetic changes. Combinations of these metrics could provide an overall biochemical measure of fitness.
- Refine existing measures and develop new methods to assess biochemical and physiological indicators related to body composition, particularly adiposity and its type and distribution, muscle mass, and bone health.

Fitness and Functional Status

- Clarify the optimal methods for assessing fitness and functional status in people who are overweight or obese. Improve instruments and equipment to have higher dynamic ranges as well as higher sensitivity to measure acute and intermediate changes due to specific interventions.
- Develop practical and cost efficient methods to assess fitness in the context of a medical visit.

Thermogenesis

- Develop technologies that can be used in free-living populations to measure resting energy utilization of the various body tissues or to evaluate efficiency and heat production to better understand energy utilization under various normal conditions. These technologies might include 3-D imaging of heat production deep within tissues, clothing with wireless sensors to capture body temperature and degree of sweating in

addition to movement, and new methods to non-invasively monitor mitochondrial membrane potential and ATP production.

Imaging

- Use brain imaging approaches combined with neuropsychological and neuro-cognitive assessment to characterize the many interacting roles of the brain in obesity. For example, to improve understanding of the role and response of the brain in hunger and satiety, taste, preference and reward with food and physical activity, the sensory and emotional response associated with eating, food craving in the absence of hunger, decisions surrounding food and physical activity, altered response to food and hormone signals after weight loss or gain, and the central control of peripheral nutrient storage, metabolism and heat generation.

Body Composition

- Develop improved technologies to determine body composition. Although dual-energy x-ray absorptiometry is readily available, easily performed in children and adults, and provides an estimate of fat distribution, it involves radiation exposure and generally has body size limitations. Techniques that could minimize variability, yield site- and tissue-specific fat content, eliminate size limitations, and minimize radiation exposure are needed.
- Develop accurate and reliable tools to measure total and regional body composition across the lifespan that are applicable to clinical and population study settings. For example, develop tools to allow improved and safe measurement of body composition in pregnancy, infancy, and early childhood.

Objective Diet and Physical Activity Behavior Measurement Systems

- Encourage development of improved mobile phone or camera devices that can use digital pictures and image recognition technology to accurately identify foods and portion sizes for purposes of advancing food record dietary assessment methods.
- Develop statistical methods for analyzing data obtained from wearable physical activity monitors. These methods can be used to improve modeling of measurement error and correct misclassification of physical activity, as well as model patterns of physical activity behavior so as to better characterize “usual” activity.
- Develop accurate, reliable, and effective devices to be used in monitoring changes over time and in treating obesity and overweight across the life span, including low-cost field measures that are sensitive to change in different age and BMI groups. This includes engineering tools that integrate self-reported information with biologic and/or sensor measures of physical activity, diet/nutrition, and energy balance/obesity in real time.
- Develop energy balance indicators, such as “smart” clothing, household, or office furnishings, that incorporate sensors, bar codes, or other identifying technologies to calculate energy expenditure, detect motion, identify food characteristics, and assess portion sizes.
- Develop mathematical and computational models for predicting interrelationships between energy balance and weight control or obesity.
- Explore how advances in the application of item response theory methodology can be applied to social and behavioral measurement.

- Develop interactive technologies (e.g., virtual reality) to assist individuals in changing their behavior and affective response when making food and physical activity decisions.
- Incorporate measurement approaches for family history and social networks in studies of obesity and health behaviors.

Environment

- Create measures of the initiation, support, and reinforcement of food and beverage consumption and physical activity practices and factors associated with decreasing sedentary behaviors. Measures should assess determinants of behaviors in multiple settings (e.g., home, daycare, preschool, or other community venues) facilitated by a variety of care providers (e.g., healthcare providers or teachers).
- Develop wearable devices to combine GPS with physical activity and physiologic sensors.
- Develop valid and reliable measures of community food and physical activity environment variables that are applicable to communities at highest risk for obesity.

Systems Methodologies in Design and Analysis

- Employ quantitative approaches, such as mathematical and computational modeling, to provide an infrastructure for systematically linking data and knowledge obtained from different biological scales and regulatory mechanisms in obesity. Computational models can be used to drive hypotheses and experimental design (e.g., inclusion of relevant risk regulators). They also can be useful in reformulating hypotheses to optimally address specific questions or predictions. Systems models may provide insights into the mechanisms underlying the success (or failure) of interventions in a particular context. Virtual (*in silico*) drug trials, for example, would save a tremendous amount of time and cost in obesity research.
- Encourage systems science computational techniques to integrate individual and socio-environmental factors over time to investigate the etiology of obesity and to test intervention strategies in a virtual environment. Applying systems science methods in obesity research has the potential to explain how small changes at the individual level accumulate at the population level to reveal significant shifts in the root causes of disease. Examples of these integrative computational techniques include system dynamics modeling, agent-based modeling, network analysis, Markov modeling, dynamic microsimulation modeling, and discrete-event simulation.

Advanced Statistical Approaches in Design and Analysis

- Incorporate approaches to statistical modeling, such as non-linear quantitative statistics, non-parametric approaches, Bayesian and small n-statistics, dynamic modeling, and time-continuous methodology into obesity research.
- Employ intervention designs that can be adaptive, account for multiple active components, and better balance internal and external validity.
- Enhance innovation in the application of simulation modeling that integrates biologic, genomic, behavioral, contextual, policy, and economic data to identify the best candidates for large-scale interventions among diverse populations.

New Genetics Technology

- Encourage the development and use of next-generation sequencing, which holds the promise of identifying rare variants with large effect sizes. These variants are systematically missed in GWAS and may theoretically account for much of the currently unidentified heritability of obesity. Rare variants may be identified in samples of tens or hundreds of individuals (as opposed to the tens of thousands required to identify common polymorphisms with very small effect sizes).

Bioinformatics and Data Standardization

- Encourage advances in data storage, compression, and transmission technology to ensure that the storage infrastructure continues to support the ever-growing data output of scientific and diagnostic instruments. The scientific data storage infrastructure of the future will need to not only accommodate the enormous amounts of data derived from modern experimental techniques but also have the throughput necessary to make the data available for analysis. It also needs to be secure enough to ensure the long-term integrity of the scientific knowledge stored there.
- Encourage the use of core measures across the individual, family, and community level to enable the results of similar studies to be directly compared.

INTEGRATION OF RESEARCH INTO PRACTICE

On the surface, it may seem that the solution to the obesity epidemic is obvious: help people to eat less and move more. The reality is that this change is very difficult to accomplish and research is critical to address the issue successfully.

Research supported and conducted by the NIH will be a key contributor to the efforts to prevent and treat obesity and associated health consequences. The challenges of today's obesity landscape are daunting, yet the discoveries emanating from research investments offer unprecedented opportunities to help meet these challenges. NIH is committed to supporting basic research, clinical discovery, and translational research to inform practice and public policy. Much of this research is directly relevant to providing the scientific evidence base for developing and implementing national public health campaigns, such as the *Let's Move!* Campaign (http://www.LetsMove.gov), launched by the First Lady.

The NIH, in collaboration with other governmental and nongovernmental organizations, helps to disseminate important research findings to the public, policy makers, and healthcare professionals.

The opportunities for applying research findings in practice are many and diverse. As research opportunities identified in the *Strategic Plan for NIH Obesity Research* lead to effective interventions for prevention and treatment, NIH can serve a critical role in helping ensure that these advances reach the appropriate audiences to promote their rapid implementation.

Examples of NIH Efforts to Apply Research Findings in Practice

- The NIH has taken steps to translate obesity research into "best or promising practices" related to prevention and treatment for community leaders, practicing clinicians, patients, and the general public. Population-based strategies that include national education programs have been an important approach to engage numerous partners and organizations around a common message and evidence-based strategies. ***We Can!™*** (Ways to Enhance Children's Activity and Nutrition) is one example of an evidence-informed national education program. This campaign provides flexible resources and strategies that can be implemented in diverse settings to help families, schools, communities, organizations, and national partners and corporations in their efforts to help children maintain a healthy weight. ***We Can!™*** has an extensive website at http://wecan.nhlbi.nih.gov.
- The NIH develops evidence-based clinical guidelines for overweight and obesity as a way to translate the science into practical recommendations for clinical care. Currently, the NIH *Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults* (http://www.nhlbi.nih.gov/guidelines/obesity/ob_home.htm) are being updated using a rigorous evidence-based approach that involves a systematic review of the literature. The updated guidelines will provide recommendations about measuring overweight and obesity in adults using BMI and/or waist circumference measures, information about the role of additional risk factors in defining the risk status of individuals, and recommendations on various treatment options. The expert panel is taking into account the needs of primary care clinicians and patients, and working to be sure that

the guidelines are clear and focused, without ambiguity as to what providers and patients should do as based on the scientific evidence. Upon the release of the guidelines, the NIH will share tools and resources with key national and international audiences through Web Based communities of practice, where clinicians in primary care or patients themselves can also share ideas and strategies. The update to the obesity guidelines, along with updates to guidelines on blood pressure and cholesterol, will ultimately feed into an integrated Cardiovascular Risk Reduction Guideline for Adults.

- The NIH has developed several obesity-related web-based resources. These include: the Aim for a Healthy Weight website that includes the BMI calculator (http://www.nhlbisupport.com/bmi/) and the Portion Distortion website (http://hp2010.nhlbihin.net/portion), the Automated Self-Administered 24-hour Recall System (ASA24: https://asa24.westat.com/index.htm), Measures of the Food Environment (https://riskfactor.cancer.gov/mfe), Cancer Control P.L.A.N.E.T (http://cancercontrolplanet.cancer.gov), and the Weight-control Information Network (http://win.niddk.nih.gov/). The uptake and dissemination of research advances have been accelerated by collaboration among research funders and national organizations. One example of such collaboration is the National Collaborative on Childhood Obesity Research (NCCOR: (http://www.nccor.org/). The NIH has joined with the Centers for Disease Control and Prevention, the Robert Wood Johnson Foundation, and the United States Department of Agriculture to establish NCCOR in an effort to improve the efficiency, effectiveness and application of childhood obesity research and to halt—and reverse—the increase in childhood obesity.

Opportunities for Fostering the Uptake of Research Findings

Enhanced adoption and uptake of outreach and education programs will maximize the public health benefit of research. The NIH can support opportunities for applying research findings in practice in several ways:

- Support communication and collaboration between researchers and other sectors of the community to foster translation and uptake of evidence-based strategies.
- Support population-based strategies, public education outreach programs, and media campaigns aimed at preventing overweight in at-risk groups, such as children and youth, young adults, low income, and racial and ethnically diverse populations. These strategies should draw on research findings to help direct key messages, promote evidence-based strategies, guide social marketing techniques and policy interventions, and develop the role of new technologies and social media.
- Foster communication strategies that are tailored to diverse audiences, including individuals who are overweight and obese, healthcare and public health professionals.
- Convey research evidence about the causes of obesity and its prevention and treatment in a respectful, appropriate and user-friendly way to the public, healthcare professionals and organizations/practices, and policy makers.
- Encourage healthcare systems to apply evidence-informed obesity screening, prevention, and treatment interventions for both children and adults in ways that minimize barriers to uptake for both individuals and healthcare professionals.

CONCLUSION

Meeting the challenges of obesity and its health consequences in the U.S. and worldwide will require the efforts of many. The NIH is committed to moving research forward to build the scientific evidence base for action at multiple levels. This research will address the multi-faceted contributors to obesity, helping to identify novel therapeutic targets and develop more effective approaches to prevent and treat obesity in children and adults, with steps that can be taken by individuals, families, healthcare providers, schools, worksites, and communities. As the NIH pursues promising avenues and exciting new scientific opportunities, this updated *Strategic Plan for NIH Obesity Research* will serve as a guide to accelerate progress in obesity research, from basic discovery to application and integration of prevention and treatment strategies in clinical practice and community settings, with the goal of extending healthy life and reducing the burdens of illness and disability.